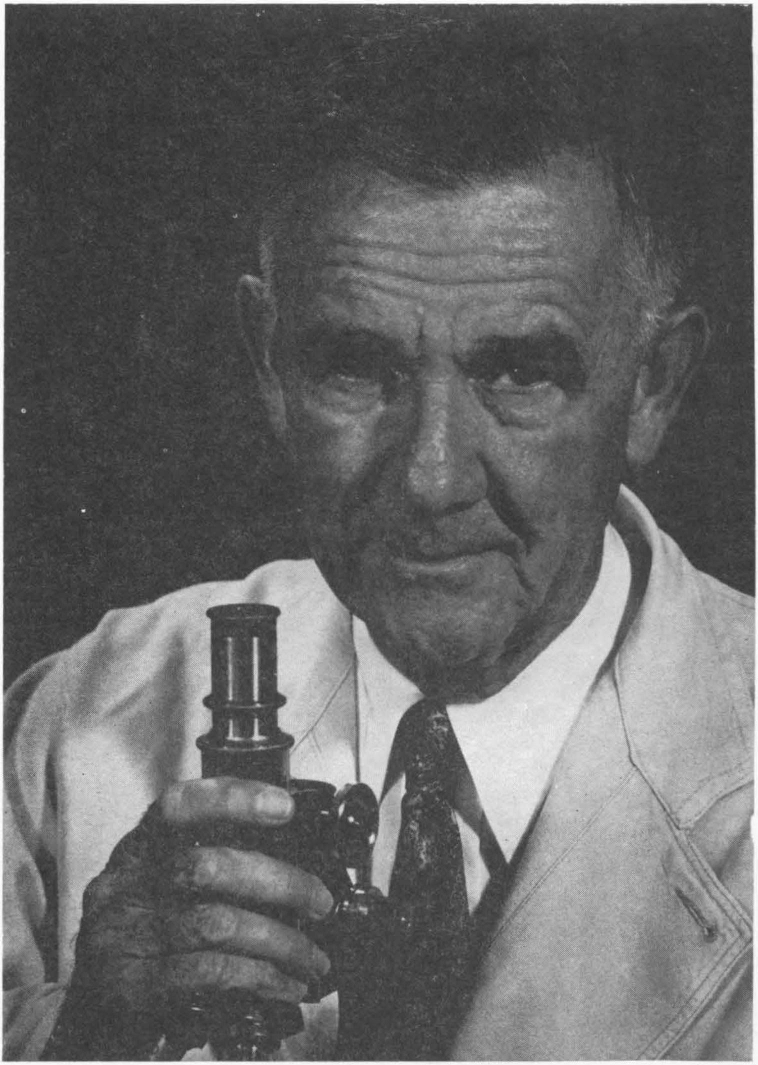
# George Hoyt Whipple and His Friends

CORNER

GEORGE HOYT WHIPPLE

AND HIS FRIENDS



George Hoyt Whipple

Portrait by Ansel Adams, 1955

# GEORGE HOYT WHIPPLE AND HIS FRIENDS

*The Life-Story of a Nobel Prize Pathologist*

*By*

GEORGE W. CORNER

J. B. LIPPINCOTT COMPANY

PHILADELPHIA TORONTO

ISBN-0-397-50092-0

Library of Congress Catalog Card No. 63-20828

Printed in the United States of America

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# PREFACE

GEORGE HOYT WHIPPLE, who in the course of a long lifetime has achieved three-fold success as teacher, investigator, and administrator, feels deeply that among these varied activities it is teaching that gives him the greatest satisfaction. In the concluding lines of an autobiographical sketch published almost a decade ago he wrote, in a rare mood of self-revelation, the simple words, "I would be remembered as a teacher." This wish was already granted long years before he ever put it on paper, for the men and women he has taught—many hundreds of them—during more than a half century in three medical schools and in his research laboratory, can never forget his wise and clear instruction, nor the ideals of the good physician and scientist which he has set before them. To have been a pupil of Dr. Whipple is something his students boast of to their sons, and when they grow old, to their grandsons.

The pride that comes from being the pupil of a great man awakens a desire to know more about the master teacher's own education and training. What forefathers and what parents did such a man have? Where did he get his schooling? What urgencies of life and learning did he face in young manhood when he was acquiring the experience and wisdom that have made him a guide and counselor to another generation? What clues led him through the mazes of scientific investigation? Who were the teachers *he* cannot forget?

George Whipple is not a man who talks much about himself. When, in 1955, at the request of some of his friends he wrote the brief autobiography cited above, he told of many happenings that especially interested him, but far too little of the personal history his friends and students wanted to read. After his retirement from the deanship of the University of Rochester School of Medicine and Dentistry, the medical alumni began to plan for a full-length biography. They entrusted its preparation to one of Dr. Whipple's earlier pupils, one who has known him as teacher, friend, and leader for more than 50 years, and was at his side as a professor when he was organizing the Rochester School.

For the author of this book it has been an unalloyed pleasure to revive the memories of those exciting days and of a still earlier time in Baltimore and in California, to revisit Rochester for long talks with his former chief and to discuss his work with many associates. The story told here, let us hope, will give readers who do not know Dr. Whipple personally some idea of what he is like and what he has contributed to medical science and medical education. Those who have been his pupils or worked with him in the laboratory will find some things that may surprise them, much that they already knew, but they will enrich the reading with their own recollections of an unforgettable teacher.

The book could not have been written without the help of many people. The author acknowledges first of all his great indebtedness to George Hoyt Whipple and Katharine Waring Whipple for the courtesy and patience with which they responded to his numerous inquiries and assisted his efforts to present a clear and accurate account of the events narrated in this book.

Many of Dr. Whipple's friends have helpfully discussed various phases of his career, and have contributed specific information and reminiscences. Particular mention should be made of Mrs. Ashley Whipple Platt (Dr. Whipple's sister), William L. Bradford, Wallace O. Fenn, Edwards A. Park, Harry P. Smith, Frieda Robbins Sprague, Stafford L. Warren. Karl F. Meyer and his colleague, B. Eddie, greatly facilitated the author's use of the Hooper Institute files for 1914-1921.

Other persons who have supplied documents, photographs, information and comment, or have otherwise given valuable assistance, include Walter C. Alvarez, William F. Bale, Elmer Belt, Ruth S.

Belt, Saul Benison, Basil C. Bibby, Ruth A. Boak, The Dean of Bocking (the Rev. S. Duncan H. Bowen), Margaret Bond, Margaret Butterfield, Charles M. Carpenter, William B. Castle, Alan M. Chesney, Henry Clune, Charles F. Cole (University of Rochester, Office of Public Information), Hilda DeBrine, Andrew H. Dowdy, Arthur Drinkwater, Herbert M. Evans, Edna Fairman, Harriett Feary, Clement A. Fitch, Raymond B. Fosdick, William B. Hawkins, Barklie McK. Henry, Jane W. Hill (Memorabilia Collection, Yale University Library), Frank Hinman, Samuel Hurwitz, Albert A. Kattus, Jr., Mrs. Juliet R. Kellogg (Archives of Phillips Academy, Andover, Mass.), Janet Koudelka, Frank W. McKee, Sidney C. Madden, Leon L. Miller, Merwyn C. Orser, Frederic Palmer, Dexter Perkins, Harriet F. Purdy, John Romano, Peyton Rous, John R. Russell, Virginia Sattler, Howard B. Slavin, Francis S. Smyth, Reidar Sognnaes, Roger Terry, Thomas B. Turner, George B. Walden, Mildred A. Walter, Viola Warren, Philip R. White, Angus Wright.

Several present or former associates of Dr. Whipple read and criticized portions of the manuscript dealing with matters with which they are especially familiar. These are Basil C. Bibby, William S. McCann, Frank W. McKee, Karl F. Meyer, Howard B. Slavin, Frieda Robbins Sprague.

The bibliography of Dr. Whipple's publications was prepared by Mrs. Virginia Sattler.

The author's wife, Betsy Copping Corner, made many valuable suggestions as to content and style, and critically read the entire manuscript.

Preparation of the biography was aided by a generous grant to the Medical Alumni Association of the University of Rochester by Eli Lilly and Company, of Indianapolis.

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*There is one way for thee; but one; inform*
*Thyself of it; pursue it; one way each*
*Soul hath by which the infinite in reach*
*Lieth before him . . .*
*Thou hast thy way to go, thou hast thy day*
*To live; thou hast thy need of thee to make*
*In the hearts of others . . .*
*Yea, slake*
*The world's great thirst for yet another man!*

# GEORGE HOYT WHIPPLE

# AND HIS FRIENDS

CHAPTER

# 1

# BORN A YANKEE

NO ONE WHO KNOWS George Hoyt Whipple and has seen his native state can imagine for him any other birthplace. New Hampshire's rugged mountains rise high above wooded valleys and quiet lakes. Having but a scanty seacoast and no capacious port, the state turns its back upon the Old World and looks westward toward the wide American continent it helped to form into a nation. New Hampshire chooses for its symbol of statehood the rock-built, forest-nurtured head of a man that gazes forever from the high cliff above Franconia Notch—maturely wise, imperturbably calm, keeping his own counsel, yielding neither to summer's heat nor wintry storm—a craftsman's sign, said Daniel Webster, hung out by God Almighty to show that here He makes men. Two hundred and fifty years ago this rigorous land gathered to itself settlers hardy enough to win a livelihood in its vales and give it sons and daughters worthy of its soil. With such an inheritance, bred on such terrain, the New Hampshire Yankee at his best has something of the great stone face with something from the green valleys and still waters of his boyhood home.

The man about whom this book is written, who in his own way and in other places would prove himself true to his breeding, was born in 1878 in Ashland, a town in the southern foothills of the White Mountains, near Squam Lake and the western bay of Winnepesaukee. He had behind him nine generations of New England Whipples, five of them New Hampshire men. The family is descended from Matthew Whipple, ?——1647, one of two brothers who settled at Ipswich, Massachusetts, in 1638. They came, according to family tradition, from Bocking, Essex, England, a parish now part of the town of Braintree. Matthew was a man of substance; he held, it is said, some of the chief offices in colonial Ipswich and served on important committees. His brother John's house still stands after more than 300 years, now housing the Ipswich Historical Society. Matthew's grandson James, called "the Deacon," 1681-1766, took a leading part in the foundation of Congregational churches in two villages near Ipswich.

James's grandson Moses Whipple, 1736-1814, was the first of the line to reside in New Hampshire. He and his son Aaron and grandson David lived the obscure life of rural pioneers in the frontier region of Sullivan and Grafton counties. After Matthew, founder of the line, and his grandson Deacon James, the next of the family to emerge from obscurity onto a modest page of local history was a great-grandson of Moses, Solomon Mason Whipple, the grandfather of George Hoyt Whipple. Born at Croydon, New Hampshire, in 1820, Solomon had his schooling at the village of Lebanon, N. H. and later at Norwich University in Vermont, where he was graduated A.B. in 1846. Deciding to become a doctor, he began professional studies, according to the custom of the time, with an experienced practicing physician, and then attended lectures at Dartmouth Medical College and at the University of Vermont, at Burlington. Immediately after he received the degree of M.D. in 1849, he settled at New London, N. H., and began the career of a country doctor. His life-work, said a colleague, was well and faithfully accomplished; born of a hardy race of pioneers, and in early life experiencing the adversity and privation of the frontier, he had a laborious struggle toward local eminence in his profession. Physical weakness of an unspecified nature, presumably chronic asthma, undermined his health but made him a stern and determined man, stoically self-controlled. "If this stoicism," his biographer remarks, "enveloped his character in an ensemble of sternness, its acerbity was only on the surface; beneath it lay the courage and nobility of manhood."

About Solomon Whipple's medical talents we know only that he was considered a good diagnostician and surgeon. One of his former apprentices suffered from a chronic salivary fistula caused by a Civil War bullet. After repeated operations by the celebrated Dr. John Mason Warren of the Massachusetts General Hospital had failed to close the fistula, Dr. Whipple cured this distressing condition by a simple self-devised surgical procedure. This grateful pupil and patient felt that Solomon Whipple had not been sufficiently appreciated by the people among whom he worked, and believed that in a larger, more sophisticated community he might have attained far greater prominence.

Dr. Whipple's colleagues evidently respected and trusted him, for they appointed him to several offices in the New Hampshire Medical Society, and in 1876 elected him its president. Scrutinizing the career of this worthy man for presages of the temperament and talents of his distinguished grandson, one is tempted to think it more than a coincidence that Solomon Whipple's presidential address of 1876 was a plea for better medical education. His specific theme was the need for higher standards for professional qualification and in particular for a state law regulating the licensure of practitioners. With the florid rhetoric of his day he showed how nobly a physician can serve his community, if only his training is equal to the need. The doctors who heard his address scarcely needed to be told that American medical education had declined severely since the beginning of the century, when the few medical schools then existing were all attached to universities. Some of these listeners were graduates of Harvard or Dartmouth, but others had entered medical practice from an apprenticeship supplemented perhaps by a single course of lectures, or on the authority of a diploma from one of the ill-equipped proprietary schools that had sprung up all over the country. Dr. Whipple demanded, as a step toward reform, a law enforcing rigid compulsory examinations for admission to practice. Loyal, however, to his own profession as well as critical of it, he was unwilling to admit that it was at greater fault in such matters than were the law and divinity. Those professions also, he declared, were suffering from low educational standards, and they too must be reformed by better teaching. With regard to schools of religion, indeed, he spoke with a degree of freedom then rare in America. "Let the clergyman," he cried, "drop from his creed the dogmas of a semi-barbarous age, and square his theology to the present standard of scientific knowledge."

On neither of these points, one must admit, were Dr. Whipple's thoughts uniquely original. Compulsory licensing of physicians under state authority was already in effect in two states and agitation for reform was going on in other states as well as in New Hampshire. As for theological instruction, almost 40 years earlier Ralph Waldo Emerson had startled the Harvard Divinity School with a similar demand for nondogmatic teaching. But this was a country doctor, addressing the physicians of a largely rural state—a bold provincial spokesman of the growing professional enlightenment of late nineteenth century America.

Dr. Solomon Whipple's health had begun to fail even before his presidency of the Medical Society. Its meeting of 1876 was in fact the last he attended before he retired from practice. Within two years the New Hampshire legislature enacted the law he had called for, entrusting licensure examinations to the Board of Censors of the State Medical Society. He lived long enough to see his doctor son Ashley Cooper Whipple a member of the Board, taking part—alas, for all too short a time—in the work of reform; and to rejoice in the birth of Ashley's boy, who was destined a half century later, as head of a great new medical school, to educate physicians to a standard beyond his grandfather's highest hopes. On January 16, 1884, Solomon Mason Whipple, eight years an invalid, finally succumbed to the illness he had fought so long.

The doctor's wife, née Henrietta Hersey, bore him three sons. Of these Ashley Cooper, born at New London in 1852, was the eldest. His Christian names perhaps reflect parental admiration of Anthony Ashley Cooper, seventh Earl of Shaftesbury, then at the height of his career as a liberal public servant, philanthropist, and social reformer.

Young Whipple, completing the usual course of secondary instruction at the New London Academy in 1870, chose the medical profession and like his father trained himself for it in the traditional way of a practical apprenticeship followed by lecture courses, a system soon to give place to the modern curriculum of four years' graded study in laboratories and hospital, followed by an internship. Beginning as his father's pupil, he spent the year 1871 as attendant at the New Hampshire Asylum for the Insane, in charge of one of the wards, and during the next year took his first course of lectures at Dartmouth Medical College. In the academic session of 1873-1874 he attended courses at New York University, and upon returning to New Hampshire received the M. D. degree from Dartmouth in 1874. Choosing to settle at Ashland, about 27 miles from his native village, he quickly won the esteem of his people. The scanty record of his life presents a familiar picture of the faithful, conscientious village doctor, working day and night, taking long drives in all kinds of weather, getting no relaxation and neglecting his own health until his friends were constrained to remonstrate with him. Medical colleagues spoke of his sound common sense and discernment. One of them singled out for special comment a notable firmness in maintaining his own opinions, not so much from obstinacy as from conviction based upon careful reasoning. This seems to be a family trait; Dr. Solomon evidently had it, and when in 1939 Ashley Whipple's son George was awarded the Kober Medal of the Association of American Physicians, the spokesman on that occasion emphasized the same characteristic in almost the same words.

Ashley Whipple at first boarded at the village hotel; but the country doctor's life is not for bachelors. In 1876, a couple of years after beginning his practice, he found a wife in the community—Frances Anna Hoyt, beautiful and intelligent daughter of a man prominent in Ashland affairs. The two families had somewhat different backgrounds. The Whipples had been farmers, then professional men in the last two generations; George Hoyt was a business man connected with the Ashland woolen mill and other local enterprises. The Whipples were Baptists—Doctor Solomon perhaps not very orthodox, judging from his address to the New Hampshire Medical Society, but his wife was faithful to Baptist dogma and strict in applying it to everyday life. The Hoyts, Episcopalians, took their religion less intensely, though Anna was always active in parish affairs.

The Hoyt's brick house on Ashland's hilltop, on Pleasant Street near the postoffice, had been designed for two families; in half of it the newly married couple set up housekeeping under the same roof with Anna's parents. Here was born, on August 28, 1878, their first child, whom they named George Hoyt for his maternal grandfather. Less than two years after his son's birth, Dr. Ashley Cooper Whipple, barely 28 years old, contracted an illness diagnosed as typhoid fever. For a fortnight he kept on his feet, seeing patients as best he could, until he was no longer able to work; taking to his bed he died a week later, April 4, 1880. In the following July the widow gave birth to a posthumous daughter, to whom in her grief she gave his name, Ashley. The little family was sadly bereft of male companionship and support. Anna's father had recently died, and Dr. Solomon, though still living, was incapacitated by illness. Ashley Cooper Whipple's brothers were barely beginning to make their way in the world, Sherman as a law student at Yale, Amos in business at New London, N. H.

It was well for the two children that these circumstances did not break up their home. George Hoyt had left his daughter Anna Whipple an inheritance sufficient to support the family modestly, at least while the children were growing up. Now more than ever fortunate in the nearness of her vigorous, competent mother, she remained at the Pleasant Street house with George and his baby sister. Mrs. Hoyt adored her grandson, as did his other grandmother, Mrs. Solomon Whipple of New London, to whom the children, when they were old enough, went for a month or two every summer. It is a wonder that the boy was not completely spoiled, growing up thus among women—two grandmothers, his mother, and a sister who shared the general affection with which he was surrounded, even though she felt sometimes that he was too clearly the favorite. But the grandmothers were both firm disciplinarians—Mrs. Solomon Whipple, in fact, something of a martinet. Anna Whipple, moreover, knew how to give her children not only maternal love but sensible guidance, and as they grew older, high aims.

George grew to be a tall, strong boy, fond of outdoor games and country sports. Ashland is situated at the mouth of a valley through which the swift Squam River issues from Little Squam Lake on its way to join the Pemigewasset just below the village. Wooded hills rise above the stream, and across the valley of the Pemigewasset Plymouth Mountain reaches a height of more than 2000 feet. In country like this a boy learns early in life to handle rod and gun. George's eleventh birthday gift was a single-barreled shotgun. With it he roamed the hillsides, alone when hunting squirrels, or with a friend who owned a dog if rabbits were the game. Sometimes he joined a party of fox hunters out to get valuable pelts. With his rod he took from the lakes such fish as a small boy angles for—sunfish, bullheads and shiners. At Grandmother Whipple's in New London he could try his luck with more sporting adversaries, brook trout. The two grandmothers of course saw to it that the boy's catch with rod and gun appeared on their respective dinner tables. He still remembers the aroma of Grandmother Whipple's rabbit stew. As for other sports, there were always baseball and more casual games with the village boys.

George got through the primary and grammar grades of Ashland public school with no more than the usual ups and downs, until the last year of grammar school. Then a 13-year-old's high spirits and love of mischief got him into a running contest of wits with his teacher. After she had sent him several times to be disciplined by the principal, his mother took him out of the Ashland school and sent him to Tilton, 15 miles away, to which place he travelled daily by train. One of the male teachers there, a friend of the family who had taught for a while at Ashland, took him in hand and with this support he finished the year peaceably and with credit. Out of school he was already showing himself steady and responsible. In the summer of 1890, when he was 12 years old, he helped work his way at the Whipple farm in New London. One of his chores was driving a herd of cows to pasture every morning and back in the evening, trudging a mile each way with a stick in hand to keep off dogs. The next summer, in addition to work on the farm, when his Uncle Amos's stage coach and livery service was short of drivers he sometimes drove a two-horse tally-ho over the hilly roads with a load of tourists.

While still a child George Whipple knew he would follow the profession of his father and grandfather. Although he had no memories of the one and scarcely recalled the other, their honorable service as physicians was a family tradition, to which the boy almost unconsciously responded. No one tried to influence him, nor does he remember ever making a deliberate decision about his career. Yet when anyone asked him, from early school days on, what he meant to do when he grew up, he always replied that he was going to be a doctor. To the astute Anna Whipple, who was fully aware of the rising standards of medical education, this meant a long, expensive course of training in secondary school, college, and professional school. For her son only the best training could be good enough. In the fall of 1892, scraping together all her resources, she moved with her mother, her 14-year-old boy and 12-year-old girl to Andover, Massachusetts, where she entered George in Phillips Academy and Ashley in the nearby school for girls, Abbot Academy.

Anna Whipple enjoyed life in Andover's social and intellectual circles, far wider than the mountain village of Ashland could provide. For her son, one gathers, schooling at Phillips Academy was a chore to be taken head-on without much relaxation or gaiety. For this period of his life—the years of adolescence between 14 and 18 when a boy is peculiarly sensitive to the outer world—there are few records. Phillips Academy has long since discarded the routine scholastic reports of those days, and because George was living with his mother and sister there are no letters home to tell us about the enthusiasms, contentions and diversions that make up a schoolboy's life outside the classroom. As a day scholar with limited means he could take little part in the lighter side of school life. He did not try for the school's athletic teams, but played sand-lot baseball with the town boys. With a trio of schoolmates who were, like himself, day scholars, he frequented the Academy's gymnasium, where the boys learned for themselves how to use the horizontal bars, flying rings, and "horses."

These cronies were Arthur Drinkwater (now a Boston lawyer), Gayton B. Ellis, an orphan living at the home of an aunt, and Frederic Palmer, son of the Episcopal minister in whose parish Anna Whipple had enrolled her family. Palmer, who became professor of physics and dean at Haverford College, was George's closest school friend. The boys went to dancing school together with town girls, Ashley Whipple among them. At Ellis's home on rainy days the four lads often played a surreptitious game of poker, the stakes being ice-cream sodas at the nearby drug store.

" 'Whip,' as we called him," says Drinkwater, "was a tall, slender boy with a long, graceful stride. What remarkably fine, flexible hands he had! He was modest and quiet, but friendly, and attended faithfully to his studies." Yet he was not an outstanding or assertive student; the boys never labelled him a "grind." He found class work, except in the sciences, a tough routine, all the more so because his enrollment in the "Classical Department" of the Academy—to insure subsequent admission to a liberal arts college—demanded thorough drill in Greek and Latin. To a conscientious boy without a strong bent for languages, this meant dogged memory work. Whatever present-day pedagogues may say, George Whipple came in time to feel that his struggles with foreign languages in school and college helped teach him to attack with determination life's many uninteresting but necessary tasks. Science and mathematics he enjoyed and took in easy stride. His one achievement mentioned in the weekly *Phillipian*—which had no occasion to list his name in sports, club events, or dances—was recorded in Commencement Week 1896: graduation with Senior Honors in physics. Evidently his life-long ability to concentrate wholly on what he thought most worth doing was already in full operation. One wonders whether any of his schoolmates and teachers perceived the inner strength of this determined boy, inconspicuous among the social leaders, athletes and elected officers of his class, but the only one among them whose name would some day be known around the world.

After George finished his schooling at Andover, his mother and sister remained there two years longer, until Ashley was graduated at Abbott Academy and went on to Mt. Holyoke College. Mrs. Whipple then moved back to Ashland, but George never returned to the old house to live, except in brief vacations. He spent the summers of 1892 and 1893 working as errand boy and general assistant in a small drug store at New London, owned by his Uncle Amos and operated by a kindly druggist, Will Leonard, who did all he could to make the boy's work instructive. By 1894 Amos Whipple had moved to the Boston area, where he was operating big hotels. At one of these, at Narragansett Beach, he gave George a job as bathhouse attendant; in the next summer the lad was a food-checker in the dining room of the Copley Plaza in Boston. At the end of one more summer, spent as night clerk at the same hotel, he went in October, 1896, to Yale College as a freshman premedical student.

College life, though freer than at Andover, brought for the first two years much of the same scholastic routine. Work for the A.B. degree meant more Latin, Greek, and modern languages, a grinding discipline that George Whipple cordially hated. Mathematics and the sciences—physics, chemistry, and biology—were a different matter; the farther he advanced in those subjects the more he liked them and the better he performed. Yet he gave at first no evidence of exceptional ability. As late as the fall of his junior year his mother seems to have been sufficiently concerned about his work to ask one of the chemistry professors, J. W. Ingersoll, for a confidential report. The reply was not highly encouraging: "To the best of my knowledge your son has no worse fault than carelessness. He is capable and—I believe—well intentioned, and has maintained a fair standing."

George Whipple himself, in his *Autobiographical Sketch,* tells us almost nothing about these first two years in college, and his letters to the family in this period have disappeared. His one appearance in recorded college history at this time (other than in athletics) was in fact not the easiest thing to write home about. One wonders how he explained it to an apprehensive mother. On the night of June 13, 1898, in his Sophomore year, a date known as "bottle night" and traditionally marked by disorder on the campus, the inmates of his dormitory staged a big rumpus in their rooms and corridors, with considerable damage to furnishings and danger to passers-by from water-jugs flying out of windows—hurled by George Whipple among the others. He and his roommate neglected to turn out their lights before opening fire with the bottles, and thus silhouetted in the window were easily identified. The College, having warned the boys against just such carryings-on, took the affair seriously; the known culprits, including George, were banished from the dormitory for the whole junior year. This punishment, though drastic, was not altogether devastating; with his gift for adapting any situation to his own ends, George rented a room in a physician's house less than a block from the library and gymnasium, and during this year of exile from the dormitory, profited by frequent opportunities for instructive conversation with his host about biology and medicine.

During his junior and senior years he had occasion to write home about several events of concern to himself or to the University. A letter to his grandmother Hoyt postmarked October 4, 1899, colorfully describes the campus celebration of Arthur Twining Hadley's inauguration as President of Yale University, and incidentally conveys a gentle hint—quite typical of undergraduates' letters home—about personal financial difficulties:

The big oak in front of Chapel was all full of red lanterns and also the top roofs of Alumni and Dwight Halls. They burned red fire on the towers of Alumni, Phelps, and Vanderbilt which made the whole campus appear blood-color and was very weird . . . In the procession . . . every man had a cap and gown and torch and every college undergraduate was there, with quite a number of graduates. The Seniors wore blue gowns, Juniors green, Sophs lavender, Freshmen yellow, Medical purple and I have forgotten the rest but you can see that the combination of colors was very fine and looked especially well by torch light. Every class had a band and about every man had a revolver with plenty of blanks, so you can imagine the racket that was made. We marched all over town and speeches were made by the Gov., Presidents Dwight, Eliot, and Hadley. The mud was about a foot deep and you can guess how we looked when we reached the campus . . . I spent about all my money paying my last board bill and have a little more than $2.00 left . . .

This cash balance, though alarmingly small, was proportionately not so bad as it sounds today, for the annual tuition fee was then only $155 and George's expenses for room and board amounted to $7.00 per week. Uncle Sherman was helping with the tuition, and Grandmother Hoyt, as the letter suggests, could be relied on for occasional help in emergencies. In March 1900 he told his mother:

I have been offered an election to Beta Theta Pi, a secret society here, at the same time with "Freddie" Blount and we have decided to accept as it will cost but little and if I am ever out West will be a great help to me, for it is the strongest of all the Western societies and also very strong at Harvard and Boston. Things seem to be coming my way this year.

Blount, his fellow "Beta" and a "Y" man in track athletics, was fairly typical of George's college friends, who came from solid but mostly not wealthy business and professional families. Almost all of them had successful careers as business men, lawyers, or physicians.

At Yale there was a good deal of social stratification based on financial standing and status in metropolitan society. Although the class of 1900 included a Rockefeller, a Tiffany and two Havemeyers, these men belonged to the more exclusive residential clubs and a self-supporting student from up-country had little contact with them. Considering that George Whipple became a trustee of three of the most important Rockefeller benefactions, it is an odd fact that he does not remember ever seeing John D. Rockefeller's nephew Percy, his classmate. George's roommate in North Hall was Harry Granville Sanders, son of a Concord, N. H., bookbinder. Their friendship was ended within a few years by Sanders' early death from septicemia, at Johns Hopkins Hospital, where he was taken while George was a medical student there. Three of George's special friends at Yale came with him from Phillips Andover Academy. Frederick W. Allen, captain of the Yale crew, went on to an important career as a banker in Boston and became a trustee of Johns Hopkins University. Horace M. Poynton went back to Andover as a popular and respected teacher of Latin; Herbert G. Williams became a manufacturer in Rochester, New York. Two other friends went into law, Blount as an attorney in Philadelphia and Thomas M. Swan as a professor, later dean of Yale Law School and ultimately a Federal judge. Donald Chappell, whose classmates predicted he would be mayor of his native city, New London, Connecticut, became at least a prominent business man there. Two of George's group of friends entered Johns Hopkins Medical School—William G. Ricker, who subsequently practised medicine in Vermont, and De Witt B. Casler, for many years a gynecologist on the Johns Hopkins faculty. George Whipple had chosen his friends well, yet did not in those days form more than a casual acquaintance with one of the finest spirits in the class of 1900, Edwards A. Park, a New Englander of the Jonathan Edwards line. In later years, when Ned Park had become a distinguished pediatrician and professor at Johns Hopkins Medical School, they found they had much in common through their Yale and Johns Hopkins background, and also through a love of fishing that led to many summer trips together to Nova Scotia to fish for salmon.

George was of course always ready to get exercise playing scrub baseball and other casual games, but deliberately planned his part in more formal Yale sports to further his preparation for medical school. He foresaw that after leaving college he would have to earn money for a year at least before beginning medical studies. School teaching was obviously the surest field for temporary employment, and the combination of science teaching with physical education would qualify him for work in a private preparatory school. In the fall of his sophomore year, therefore, he presented himself as a candidate for the college gymnastic team, and during the winter season made progress sufficient to win a part in the annual exhibition held in March, as a contestant on the horizontal and parallel bars and in tumbling, but did not place high enough to be mentioned in the *Yale Daily News.* With growing experience and strength, in December 1898 he took third place on the horizontal bars, parallel bars and long horse, in points scored running close behind the college champion and the runner-up.

The next year he won first place under trying circumstances. At 3:30 A.M. on the morning of Saturday, December 9, 1899, a fire in North Hall (to which he had been readmitted for the Senior year) routed everybody from bed in suffocating smoke, and forced them outdoors in below-freezing weather. George was up the rest of the night, but in spite of this disturbance and loss of sleep won first place in the intramural gymnastic meeting on Saturday evening. He was judged first on the horizontal and parallel bars and the long horse, and third in rope climbing, winning the all-round championship by a narrow margin. "I have three first place cups coming to me and will bring them home," he wrote, "they are worth about seven dollars apiece and I know, for Patterson and myself did the purchasing." When Yale met Columbia University in a dual contest at New York in March, 1900, George was high scorer for his side, which however was outpointed by Columbia. He won two gold medals, "about the size of a silver dollar, not quite as thick, and they cost between $15 and $20," he wrote his grandmother Hoyt. "After the contest there was a dance until 3 o'clock and I used every one of the 16 dances except the first two when I was changing from my gym suit to my dress suit. There were an unlimited number of very handsome and stylish girls and I enjoyed the whole evening immensely." Another trip of the gymnastic team was not so agreeable socially, but as we shall see helped to get him a good position for the next year. The Yale gymnasts were much in demand as visitors to preparatory schools, where they gave exhibitions. One of these trips took him to Dr. Holbrook's Military Academy at Sing Sing (now Ossining), New York, where, he wrote to his mother,

We were roped into a reception held by the wives of the profs. where we met a lot of old maids and an unusually choice collection of old colonial furniture, etc . . . They fed us on salad and sandwiches with ice-cream and cake, etc., a nice lot of stuff for a man to work on!

At Yale's last meet of his college years, March 27, 1900, he was again all-around champion, taking first in club swinging, and second or third in each of the other events. This victory gave him the imposing title of "The College Gymnast" and the right to wear a varsity "Y" on his sweater.

But indoor exercise in the gymnasium palls when springtime brings its irresistable urge for the out-of-doors, an urge which George Whipple satisfied on Lake Whitney as an oarsman. Too light for the varsity crew, he rowed with one or another crew casually organized to represent various dormitories and with the 1900 class crew. Because of his outstanding height, reach, and steadiness he generally rowed the stroke oar, setting the pace (at the coxswain's direction) for his crew-mates. He enjoyed the sport, with its beautiful timing and teamwork, but remained a scrub oarsman. The *Yale Daily News* recorded no such triumphs for Whipple, '00, on the river as he won in the gymnasium.

As college work progressed, and the required language courses and other academic chores were gotten out of the way, George could devote himself largely to science. His interest in physics, chemistry and biology was reflected in his academic grades. Yale College was still using a picturesque scale of honors coming down from the eighteenth century or earlier when high-ranking students were expected to deliver speeches at Commencement. Appointment to "Philosophical Orations" was equivalent to *summa cum laude;* then came High Orations (*magna cum laude*), Orations (*cum laude*), Dissertations, First Disputes, Second Disputes, and Colloquies. When Junior Honors were announced, George was "appointed to First Disputes," which we may interpret as an all-round "A" grade. During his senior year he took an advanced course in comparative anatomy under Professor Sidney I. Smith, for whom he wrote an honors thesis. This document is now lost and its author has forgotten what it was about, but the work stood him in good stead. In the spring of 1901 when he needed recommendations to medical school, Professor Smith was able to write:

Mr. G. H. Whipple, of the class of 1900 in Yale College, pursued with marked success an academical course in biology preparatory to medical studies and passed all the examinations with very high standing. In addition to the regular work of the course, he did excellent special work, under my direction, in the preparation of a "thesis for honors." I take great pleasure in recommending him as specially well fitted for the work of the Medical School.

The most stimulating science courses available to Yale premedical students were in chemistry, in the Sheffield Scientific School. Founded as an adjunct to Yale College, to supply instruction in science and engineering that was lacking in the time-honored classical curriculum, "Sheff" had its separate funds, instructors, buildings and regulations, though it shared with the College such general facilities as the library and gymnasium. Chemistry was taught in both faculties, the Sheffield courses tending more than those of the College to meet the needs of students of engineering and medicine. An outstanding biochemist, Russell H. Chittenden, had organized in Sheffield the first real laboratory of physiological chemistry in the United States. A few qualified premedical students of the college were admitted to his courses. This branch of chemistry was beginning to be taught in the better medical schools, and in any case need not be studied in college by a premedical student, but George Whipple could not let slip the opportunity to hear Chittenden's lectures and to work in the laboratory under his brilliant associate, Lafayette B. Mendel. Then only 27 years of age, Mendel—a born teacher—was inspiring many of the best students by his whole-hearted enthusiasm and unselfishness. His temperament George Whipple could easily understand, for what Chittenden says of Mendel equally describes this particular pupil: "Always friendly, he had little time for general conversation. He rigidly adhered to a simple mode of life to avoid distractions. Self-denying, he acquired self-control." Mendel is the only one of his Yale teachers George Whipple singles out by name in the *Autobiographical Sketch*. "An unusual man," he says, "who exerted a strong influence on me. Work with him was exciting and never to be forgotten." Mendel, then in an early stage of his lifelong research on the chemistry of digestion, was investigating the path of absorption of proteins from the intestine. Thus Whipple saw him at work in a field which he was himself long afterward to cultivate.

Whipple's work in biology and in the physiological chemistry course was undoubtedly the major factor in his election to the Sigma Xi honorary scientific society in February 1900. Excellent grades awarded him by S. I. Smith, Chittenden, and Mendel brought his general college record high enough to win at his Commencement in June 1900 Senior Honors with the rating of "Orations," equivalent to an A.B. *cum laude*.

Throughout his college years, George Whipple earned a large part of his living expenses by working on steamboats on New Hampshire lakes during the summer resort and camping season. Between his freshman and sophomore years he was coal-passer and freight handler on a boat on Lake Sunapee, whose waters permitted the use of a vessel of deep draft carrying 100 or more passengers, and manned by three or four men. In subsequent vacation seasons he had a more responsible post as pilot on waters close to his boyhood home, Squam Lake and its tributaries. Squam Lake, filled during the ice age by boulders and gravelly glacial till, is shallow, dotted with islands and encumbered by reefs and hidden rocks. Before the day of automobiles a standard route to the lake ran by stage coach from the railway station at Ashland to navigable water on the Squam River, a mile or so from the village. From there a shallow-draft boat could steam up the river, across Little Squam Lake's lovely pool buried in the forest, and through the narrows at Holderness into wide Squam Lake, open to the sky and bordered in the distant northeast by the gray-blue Sandwich Mountains. The run out and back, in and out of numerous coves, with 20 or more stops at the hotels and camps, was about 30 miles long and took six hours. George's little steamer, the *Chocorua,* 45 feet long, named for the boldest of the Sandwich peaks, was operated by himself, an engineer, and a "utility boy." She carried the mails, 30 passengers and their luggage, express parcels, groceries and meat for the hotels and camps. Work began at dawn of the long summer days and ended at dusk. George had not only the exacting task of piloting on the treacherous lake, but served also as ticket collector, supercargo and deckhand. These were busy days, but they gave the young pilot more than money—sunlight and mountain air, experience in dealing with people, self-control gained by responsibility for the passengers' safety and comfort.

During the summer after graduation from Yale George had a different post. Looking to the year after college which he would have to devote to teaching in order to finance his medical course, he applied to several private schools for an appointment to teach science and athletics. This was a superfluous step, for he shortly received a spontaneous offer from Dr. Holbrook's Military School, where he was already known. He had visited the school twice, once on the occasion previously mentioned, and again as judge of the boys' annual gymnastic contest. The pupils were, as George had observed, a rather tough lot of lads, sent there for discipline as much as for schooling. Dr. Holbrook could well use a strong, big-framed man who would be respected by the boys for his athletic abilities and capable also of handling the science courses. To prepare himself further for this post George got a summer job in 1900 as "tuition clerk" at the famous Chautauqua Lake Assembly in Western New York. It was only a cashier's job with a salary of $60 for the season; but there was a better recompense: Yale's gymnasium director, Dr. William G. Anderson, was in charge of athletics at Chautauqua during the summer; he could provide postgraduate training, so to speak, in gymnastics, and also the opportunity to row in a four-oared crew.

The year at Dr. Holbrook's School was easier than George had expected it to be, though he wrote home about the grinding monotony of school teaching, and said he had to work overtime brushing up his trigonometry to keep ahead of the class. Coaching the football team was a weighty responsibility, but baseball in the spring was good fun because the School considered it less important to have a winning team in that sport. During the winter George led all the gymnastic work and instructed a special class of eight boys in boxing. With another junior teacher, one North, he took his turn in charge of dormitory inspections and the general maintenance of order. On the whole, schoolmastering did not interest him, because it did not keep his mind on the stretch, and he felt that if he kept it up more than one year he might begin to get lazy. However, he must have been quite successful as a teacher, for the Holbrooks urged him to remain at least another year. Recommending him for admission to medical school, Henry C. Holbrook wrote:

Mr. Whipple has been an instructor in our school for the past year and we value his services very highly. We take pleasure in commending him, to those with whom he is to be associated, as a man of tact, courtesy and decided ability both as a teacher and as a disciplinarian.

Some years later, having heard from George through the latter's friend North, he wrote: "North says you are the same good fellow you were when you were at Ossining. I have always felt grateful to you for your year's work with us. We shall look for great things from you." Perhaps when George Whipple left for medical school, the scholastic world lost a great headmaster.

Ossining was near enough to New York to make week-end theater going and social recreations readily possible. After mid-year George was away to the city almost every time he was off duty on a Saturday evening or could get his colleague North to take his place "in charge." Writing to his mother he said that after entering medical school he would have no time for society and intended to make the best of his opportunities while he could. His letters home are full of visits to friends in Manhattan and Brooklyn and to his cousins the Brewers in northern New Jersey. These week-ends usually included dancing and the theater. Sometimes he went with a male companion to a vaudeville show, sometimes with a girl friend to an operetta or a serious play acted by the stars of the day. He saw performances of "Floradora," "When Knighthood was in Flower," and the popular melodrama "Under Two Flags," Nat Goodwin and Maxine Elliott in "When We Were Twenty-one," and Julia Marlowe in a play he failed to name.

Dancing was an exciting pleasure both at Ossining and in New York. George, a good dancer himself, took pains to fill his card with the prettiest and most graceful girls. A letter to his mother after a party at a girls' school in Ossining shows ruthless efficiency in getting the best partners:

I had a very good time at the Sem. dance in spite of the fact that my dance card was a blank when I got there and most of the fellows' cards were made out in advance. By dint of hustling round I managed to get every dance with the good dancers. Whenever I saw a girl whom I knew, standing round waiting for her partner at the beginning of a dance I stepped up with all my brass and told her I thought it was my dance. It worked almost every time as the girls didn't know lots of the fellows very well.

He had to be careful in writing to the home folks about all this gaiety, for Grandmother Whipple, it will be remembered, was a strict Baptist. "I wrote an expurgated edition of my doings last vacation," he told his mother; "I hope she will not be shocked." With Anna Whipple he could be frank. She received full accounts of his party-going, with rhapsodical comments on girls who attracted him, each, it seems, more attractive than the last. Had she not known that his heart was firmly set on going to medical school, with serious romance far in the future, she might have been alarmed by his admiration of this succession of belles of the ball, among them a Miss G——, "a Brooklyn girl and very good-looking, also full of the dickens"; Miss M——, "a large queenly-looking girl full of fun and life"; Miss J——, "the most beautiful girl I ever saw without exception"; and a Miss S——, "as near my ideal as any girl I ever met."

George's zest for dancing helped, unfortunately, to aggravate an injury that ultimately limited his participation in the more active recreations. Late in May, 1901, playing baseball with the Holbrook boys in an intramural game, he severely wrenched a knee sliding for second base. In spite of some pain he finished out the game and spent the evening dancing at a friend's house. That evening the swelling increased sharply and he lay awake all night, unable to move without excruciating pain. The next day he had to stay in bed and for days to come could only limp about the schoolhouse. He seems to have recovered normal motion before long, but the knee remained permanently susceptible to similar injuries.

George stayed on at the school through June to help some of the boys get ready for college entrance examinations. His uncle Amos had offered him for the rest of the summer a job as night clerk at the Nottingham Hotel (now the Copley Plaza) in Boston, but he was very reluctant to take it, however much he needed money. His social successes of the past year had brought a lot of invitations to all sorts of good times with young friends, including a house-party in Maine. "I shall earn $50 and miss $100 worth of fun," he wrote to Anna Whipple. The outcome was that he went to Boston, worked a month at the hotel, and then found himself very tired and ill with a cold. Throwing up the job he recovered quickly enough to enjoy outdoor life and sociability the rest of the summer. One of the good times, however, almost ended in a tragedy. In early September he spent some days on Newfound Lake with a cousin. As a local paper reported:

During the high wind a few days ago Orton Brewer and George Whipple, guests at Cottage City, ventured on the waters of the lake in a canoe. When about midway between Mayhew Island and the mainland the canoe was upset. After remaining in the water about an hour their plight was discovered by parties on shore, and Wm. H. Marston and Fred Kelly went with a rowboat to their assistance. Had not both Mr. Brewer and Mr. Whipple been expert swimmers the result might have proved more serious.

It should be added that the two young men had the sense to stay by the canoe. Both were thoroughly chilled, but a stout glass of whiskey cured that and there were no further ill-effects. At the end of the season, refreshed by almost two months of outdoor sport and social life, George Whipple, once more in serious and determined mood, began his studies at the Johns Hopkins University School of Medicine in Baltimore.

CHAPTER

2

# WORK, THE MASTER WORD IN MEDICINE

THE MOMENTOUS QUESTION, where George Whipple should go for his professional training, had been settled in favor of Johns Hopkins by the spring of 1901, after much reflection and consultation with his mother and his uncle, Sherman L. Whipple. In those days the prospective medical student could choose a school for himself; if he met the entrance requirements, he need not, as he must today, run the gauntlet of deans' offices and faculty admissions committees struggling with excessive numbers of applicants. Most Yale men who entered medicine before the turn of the century went to the College of Physicians and Surgeons of Columbia University, or to Harvard or the University of Pennsylvania. Some of them remained at Yale, although its school of medicine (now first-class) was then by no means as good as these others. More and more of them, however, were being attracted to the Johns Hopkins University School of Medicine, opened in 1893, the first medical school in the United States comprising all the elements of a university medical faculty. This school possessed adequate laboratories, manned by full-time teachers capable of investigation in their respective fields; an excellent library; and a hospital for clinical teaching under complete educational control and staffed according to university standards. The school was, moreover, the first to require the B.A. or B.S. degree as prerequisite to admission.

From the first Johns Hopkins enrolled some of the best Yale graduates—three in its first class—and by 1897 the dean, William H. Welch, was able to boast that it was getting more Yale men than was the College of Physicians and Surgeons. Five members of George Whipple's college class, in fact, went to the Baltimore school in the fall of 1900. To loyal Yale men there was perhaps special merit in the fact that Welch, its outstanding leader, was a fellow alumnus of Yale College, class of 1870. In favor of Harvard, on the other hand, in George Whipple's case, was the tempting circumstance that his uncle Sherman, one of Boston's most successful attorneys, could make life much easier for him there.

On this matter of selecting a medical school, Anna Whipple had definite opinions. Her son's choice of Johns Hopkins, he tells us, was strongly influenced by her continuing concern that his education should be the best available. She had read much about the new school in Baltimore. Impressed by its advanced program, exceptional faculty, and modern equipment, she repeatedly urged George, while an undergraduate, to keep Johns Hopkins in mind and to plan his college course so that he could meet its requirements for admission, which were more stringent than those of the other schools.

These high requirements he could easily fulfill. Johns Hopkins demanded, in addition to the B.A. or B.S. degree from a recognized college or scientific school, an acquaintance with Latin including grammar and four books of Caesar, a fair reading knowledge of French and German, one year of biology and one of physics in college and at least one year of chemistry. George Whipple's application listed readings in Caesar, Cicero, Virgil, Horace, Ovid, and Nepos; two years of French at Andover, and two years of German at Yale. He had accomplished more than the required work in biology; a year of college physics following honors work at Andover amply met the requirements in that subject, and Chittenden's course in biochemistry gave him special standing in chemical studies. With this record, and recommendations from Professor Sidney Smith and Principal Henry C. Holbrook, his acceptance by Johns Hopkins Medical School was a matter of course.

Financial considerations, however, still weighed heavily. His mother's income, never large, had been reduced by the failure of some ill-advised investments. More than ever George must be self-supporting, and first of all some way must be found to supplement his small resources during the school year. For this his best asset was his knowledge of biochemistry. Thanks to the exceptional training provided by Chittenden and Mendel, Yale premedical students were as far advanced in that subject as medical students ordinarily were at the end of their first year, and were qualified to assist in teaching or in research rather than repeat the subject in medical school. Hearing that John J. Abel, professor of biochemistry at Johns Hopkins, had a student assistantship at his disposal, Whipple asked Chittenden to recommend him. Chittenden was himself a Yankee, of the Connecticut breed, not given to exuberant praise. If George could have read his former teacher's cautious letter, he might have given up hope;

I write you in his behalf, merely saying that, as far as my experience went with him, he is a good man. He had a fairly good training in physiological chemistry while with me, and I think I am safe in recommending him for a position of this kind.

Abel, knowing his New Haven colleague's cautious temperament, rightly took this for praise and gave Whipple the appointment. The pay was $150, half the year's tuition fee. George's Yale classmate and friend, Bill Ricker, had written to say that he was getting along well enough at Johns Hopkins on $500 a year. With an assistant's stipend, his savings from Holbrook, and a legacy of $2000 he had received from his grandmother Hoyt, George could make out for the next four years.

By his choice of Johns Hopkins, he had placed himself in the best environment America could then provide for a medical student gifted for research. With its faculty of recognized distinction and its mature student body, Johns Hopkins had set an example of scientific education that would not be matched for many years to come. Had George Whipple gone to any of the other schools chosen by his Yale classmates, he would have been taught to practice medicine adequately by current standards, but would not have found a spirit of research pervading the whole institution from the senior faculty down to the students, some of whom at Johns Hopkins were publishing research papers even before they were graduated. Rufus Cole, student at Johns Hopkins a few years before George Whipple, wrote that when he joined the school he

> entered a new world, a world in which everyone seemed to be inspired by visions and to be working with feverish intensity to prepare himself for sharing in the great new developments in medicine which the new hospital and the new school seemed to promise. . . . Most of the students, even those coming from the best colleges, apparently realized for the first time the importance of working for the highest objectives; they became serious students, not merely carrying out the tasks set for them. . . . The professors made little or no effort to urge them to work. The example of the perfectionists who founded and organized the school and of those who were then directing its activities, seemed to be a sufficient stimulus.

When in 1901 George Whipple became a medical student, this early enthusiasm had by no means diminished, but had actually been strengthened and solidified by the general awareness of faculty and students that Johns Hopkins had taken the lead in medical education. The historian of the Johns Hopkins medical institutions, Alan M. Chesney, declares that at the beginning of the twentieth century the school had passed the experimental stage and, as he puts it, had come of age. All the original department heads were now in the prime of their careers. William H. Welch, professor of pathology, was already a recognized national leader in medical education; William Osler, whose departure for Oxford was in 1901 still four years in the future, was the country's foremost internist. Every one, in fact, of the senior professors was a man of the first rank in his special field. Among the younger men—some of whose names will come up as we follow George Whipple through his Johns Hopkins years—an extraordinary number would achieve professional eminence. As for the students, their quality was unsurpassed. Many a man who entered the school in its golden age, looking back upon the earliest days and weeks of his first year, recalls a feeling almost of awe at the knowledge and talents of the young people among whom he found himself—a concentration of ability far beyond even the best college classes. Each one wondered how he could face the competition and yet was proud to belong to such a *corps d'élite*. Almost threescore students entered with George Whipple in 1901; 54 were graduated in 1905. In retrospect, they included one man beside himself who won world-wide fame, Peyton Rous, and another outstanding pathologist, David Marine; the dean of a first-class medical school, Henry S. Houghton; an able scientific editor, Donald R. Hooker; a pioneer in blood-vessel surgery, Bertram M. Bernheim; a prominent ophthalmologist, Frank H. Constantine; and professor of anatomy (Arthur W. Meyer), gynecology (Edward H. Richardson), medicine (William L. Moss), and physiology (John A. E. Eyster.)

The life of the medical students in East Baltimore was very different from student life on a college campus. The neighborhood is one of quiet streets lined by the characteristic Baltimorean three-story row-houses with white marble stoops. There were no dormitories, and only two or three medical fraternities provided living quarters for their members. Most of the students rented rooms in private houses near the school, and took their meals with the family or at similar houses where some neighborhood housewife ran a students' dining room. Hard work was the order of the day and half the night as well; on Broadway, Fayette Street, and Jackson Place (where George Whipple lived) the gaslights burned late every evening in third-floor rooms where solitary students bent over their textbooks. The quiet of a winter night was occasionally broken by a student shouting from the sidewalk to a friend upstairs to toss down the door-key so that he might come in for a conference over some difficult point in his reading. Even on hot nights in May and June, when the local families were sitting outdoors on their cool marble steps, the students, getting ready for examinations, stuck to their rooms.

Some of the young men were a bit unconventional for that period; they went about the streets hatless or otherwise eccentrically garbed and once in a while even staged a public rumpus. One spring evening an hilarious dozen of them went splashing half-naked in the Jackson Place goldfish basin. George Whipple was certainly present on that occasion, although (he says) not in the fish pond. East Baltimoreans sometimes spoke of the neighborhood as a "Latin Quarter"; but it really had nothing of the gaiety, romance, or youthful abandon that novelists have seen in Paris student life. Most of the men followed William Osler's advice that a medical student had better keep his heart on ice. The few women students were if anything more serious than the men. Married students were unheard of. There was little time for sociability with Baltimore girls of the better class and philandering at a lower level did not obtrude into the school's neighborhood.

For an occasional evening downtown there was music at the Lyric concert hall or the Peabody Conservatory, and good entertainment in the theaters. In those pre-movie days, Baltimore had three legitimate playhouses, and for the jaded medical student as well as the tired business man there were several vaudeville and burlesque shows. On Saturday afternoons a walk in Clifton Park or the suburbs provided what little physical exercise most of the medical students got. Those lucky enough to make friends with the well-to-do Maryland families might visit country estates or be taken on a week-end cruise on the Chesapeake. The more athletic—of whom George Whipple was one—went downtown to the Y.M.C.A. for handball and in the fall and spring got outdoor exercise by taking part in Johns Hopkins collegiate sports. At that time graduate students with athletic experience were welcome to play on college teams. Not expected to spend time practicing, they simply turned out for Saturday games. For several seasons George Whipple played baseball in this informal way, getting about to many pleasant campuses, including Princeton University and the United States Naval Academy at Annapolis, as well as to country clubs where ex-college men kept up the game. To eke out its scanty funds, the Johns Hopkins team once rashly took on top-flight Holy Cross College in Baltimore's professional ball park. However George may have performed in that game —he claims not to remember—he generally got good press notices. Reporting a game with a small college near Baltimore, the Baltimore *Sun* said:

For Hopkins Whipple was the bright particular star. In the fifth inning he took McKnight's place in the box, and from that time out Rock Hill was not in the game. In three innings he struck out seven men, and kept the home team well under hand.

Two of his medical classmates also played in this game, Philip Gilman at first base and David Marine in left field. Against Georgetown University Whipple "pitched some balls that were very annoying" though Johns Hopkins lost that game 24 to 1. He also played football for Johns Hopkins, including at least one game against the legendary Carlisle Indian School team, but another injury to the knee originally hurt at Ossining in the spring of 1901 forced him to give up the game for good.

But work, as Osler said, is the master word in medicine, and in the daily work George found himself at home and happier than ever before. His impressions of the school in 1901-1905, recalled in his *Autobiographical Sketch* of 1959, throw an instructive light upon his interests and attitudes as a student and help us understand his thinking when he became the leader of a new medical school. It is something of a surprise, for example, to find so disciplined and systematic a student enjoying the Johns Hopkins courses in anatomy, which many of his classmates thought ill-directed and much too casual. At the time anatomy in its main divisions—dissection of the human body, microscopic and neural anatomy—took practically all the students' working hours from October until March of the first year. Traditionally, dissection was accompanied by formal lectures and recitations that made the work chiefly a test of memory, but Franklin P. Mall, the Johns Hopkins professor of anatomy, was a radical opponent of the old method. Study of the human body, he felt, should be an exciting exploration, not a guided tour. To illustrate his pedagogical ideas the students invented a story that Mall, asked by his wife how to bathe the baby, replied "Just put her in the tub and let her work out her own technique." For his medical students this principle meant in the first place excellent working facilities—small, quiet rooms instead of the large, often disorderly dissecting-halls of older schools—and the daily example of instructors doing research under the same roof. These were men of superlative ability; Mall and three of his young staff members, Charles R. Bardeen, Ross G. Harrison, and Warren H. Lewis, were all headed for election to the National Academy of Sciences and each of the four would be called to the presidency of the American Association of Anatomists. Mall gave each student a place at a dissecting table and after a brief demonstration of the use of scalpel and forceps left him alone except for a daily visit from an instructor, who asked a few searching questions and might give a minimum of advice. There were no lectures in gross anatomy, no class recitations and no assigned textbook lessons. Choice of reference books and independent reading was left to the student.

One of Whipple's classmates, Bertram Bernheim, in his *Story of the Johns Hopkins,* recalls his resentful feeling that Mall had abdicated the responsibility to teach—and then pays an unconscious tribute to the method by confessing that in his despair he smuggled part of a cadaver to his home and during the summer vacation studied it by himself, thus doing exactly what Mall hoped his students would learn to do during the course. Students who got the idea more quickly found Mall's laboratory inspiring. George Whipple, with self-confidence gained by largely supporting himself through school and college, by advanced work at Yale, and by studying Gray's *Anatomy* while at the Holbrook school, had no difficulty in making his own way through the maze of anatomical detail. He did so well that in his second year Warren Lewis made him a student instructor. Mall subsequently offered him an opportunity (which he did not accept) to do research on pathological embryos. Whipple's understanding of Mall, gained by association with this subtly original man, no doubt contributed in later years to his own liberal ideas about the training of professional students.

Whipple did not much enjoy the course in physiology. Although the professor in charge, William Henry Howell, was an able investigator of international reputation, and one of his associates, Joseph Erlanger, was a future Nobel laureate, the atmosphere in the physiological laboratory, for George Whipple at least, was not highly stimulating. Howell's lectures, perfectly prepared and delivered without notes, in English so polished that they could have gone directly to a printer, were instructive rather than provocative. He was, in 1902, writing his notably clear and precise textbook for medical students (published in 1905), which reflected this quality of the lectures. No medical student was ever disappointed by Howell's teaching, but few were excited by it. To advanced research students who worked closely with him, on the other hand, Howell was a stimulating leader, as George Whipple was to discover a few years later. Meanwhile the most useful part of the course for him was the ample laboratory practice in current experimental methods of investigating the circulation, respiration, and nerve and muscle functions.

In biochemistry Whipple was on a special footing because of his student assistantship. Although John J. Abel, renowned for his pioneer work on the chemical structure of adrenaline, supervised the course in biochemistry as well as that in his personal specialty, pharmacology, instruction in biochemistry was largely in the hands of Walter Jones. To this odd character George Whipple reported as assistant. Jones, product of a stodgily evangelical Baltimore environment against which he was in bitter lifelong revolt, was physically lean and mentally tense, alternately morose and excited. In the class laboratory he paced about loudly complimenting or castigating the students according to their individual capacities and his own current mood. His assistant's even-tempered courtesy must have been balm to unlucky youths who failed to crystallize a batch of creatinine or spilled a beaker of beef extract. On the lecture platform Jones was a dramatic performer, making his points by witty exaggeration and over-emphasis. When, each year, he reached his favorite topic, the purine bases, upper-class students used to return to his lecture room, thronging the back seats to hear again his annual denunciation of a German chemist with whom he held a chronic controversy. Well aware that he was expected to put on a good show, Jones once began the lecture in silence by writing his opponent's name on the blackboard, then shouted with sardonic emphasis, "The gentleman whose name I have just indicated—I cannot bring myself to pronounce it—has erroneously declared . . ." and he was off on an hour's vivid exposition of an intricate chemical problem.

On the principle of the attraction of opposites, Walter Jones and George Whipple liked each other. Whipple was allowed to assist his chief in an investigation of certain nucleoproteins and their derivatives. The chemistry, he says, was above his head, but at least he provided a good pair of hands and a good listener to his voluble colleague, in return for advanced training in biochemical analysis. When the investigation was published, Jones treated him as co-author and thus the name of George Whipple appeared for the first time at the head of a scientific paper, in the *American Journal of Physiology,* Volume 7, 1902.

This assistantship gave Whipple the privilege of joining the departmental staff now and then at afternoon tea in Professor Abel's office. Most of the students knew Abel only through his lectures (if so formal a term may be applied to his delightfully rambling, almost conversational talks) and from the experimental course, over which he presided with an absent-minded sort of distinction, winning the amused affection of his pupils. At the staff tea hour George Whipple saw Abel at his best—the cultivated, cosmopolitan man of science, a living link between the great nineteenth-century German biochemists and the rising American workers. Charmingly reminiscent, giving freely of his experience to the young men about him, he inspired them by his enthusiasm and skill in research.

Whipple's introduction to pathology, which was to be his life's work, and his first association with William Henry Welch, the preeminent pathologist who would long and deeply influence his career, came at the beginning of the second year of medical studies. Welch, head of the combined departments of bacteriology and pathology, was now in the full tide of his career as America's leading medical statesman. By 1900, says his most recent biographer, Donald H. Fleming, Welch was "the leading Influential of American science in succession to Benjamin Franklin and the elder Benjamin Silliman—by far the greatest Influential that the biological sciences had yet known in America." When George Whipple's class began to study pathology, Welch had just been elected president of the Association of American Physicians and president of the Board of Scientific Directors of the Rockefeller Institute of New York, then being organized. He was at the call, for counsel and guidance, of every new enterprise for the advancement of medical research and education. These demands upon his time, willingly accepted, had brought his own researches to an end, but he continued to lead his Johns Hopkins department and to give superb lectures. Appearing weekly, when in Baltimore, before the second-year class—rotund, ruddy, with closely cropped white beard, so fatherly in appearance and manner that his staff as well as the students called him, behind his back, "Popsy"—he spoke with effortless grace and unfailing memory, about everything in medical science from Hippocrates to such moderns as Koch and Cohnheim, with whom he himself had studied, until the windows of his classroom seemed to open not upon the drab roofs of East Baltimore, but upon the whole scientific world.

Every one of Welch's six associates who helped him teach George Whipple's class in the fall and winter of 1902 was, or would become prominent in American medicine—William G. MacCallum, destined to be professor in Columbia University and then Welch's successor at Johns Hopkins; Eugene L. Opie, already well started on a distinguished career as teacher and investigator which took him to professorships in Philadelphia, St. Louis, and New York; Harry T. Marshall, afterwards professor of pathology at the University of Virginia; John H. Yates, pathologist and physician of Detroit; a talented young woman, Dorothy Reed; and Norman T. Harris, later a leader of public health research in Canada. With aides like these, Welch could carry on his increasing outside activities and yet keep the teaching of pathology at Johns Hopkins on the highest level of intellectual and scientific distinction. George Whipple found everything in the pathology course superlative. In the autopsy room, where the lesions of mortal disease were exposed to study and comparison with the clinical findings, and in the laboratory of histopathology, where the microscope revealed cellular changes in diseased tissues, a thousand problems cried for further research. Whipple could even help toward solving one such problem, for W. G. MacCallum gave him spare-time work dissecting from autopsied bodies the tiny, inconspicuous parathyroid glandules, to be used in microscopical and chemical studies that led MacCallum a few years later, to the discovery of the relation between the parathyroids and calcium metabolism.

George Whipple thinks that his freedom from serious illness, through all the years of close study and exposure to disease to which a medical student is subjected, resulted in large part from his habit of spending as much spare time as possible in open-air sports and from healthy outdoor employment in the summer vacations. This he managed to keep up all through medical school. In the summer of 1903 he was tutor and outdoor companion to the children of L. J. Loree, president of the Delaware and Hudson Railroad, at their summer home on Long Island. For the next two summers he was councilor in a private boys' camp in the northern Pennsylvania mountains, operated by a Baltimore schoolmaster, where he was athletic coach and medical officer, looking after minor ailments and giving first aid to the injured.

In the third year the students moved on to clinical studies, working in the out-patient department of the Johns Hopkins Hospital. At noon, six days a week, they attended a lecture or a demonstration clinic by one of the professors or some other experienced physician. In internal medicine, of which William Osler was the senior professor, they were at first instructed chiefly by his associates, relatively young but already outstanding physicians, including William S. Thayer, Thomas McCrae, Thomas B. Futcher, Louis Hamman, Henry M. Thomas and Campbell P. Howard.

In the fourth and last year the students served as clinical clerks in the wards of the hospital, taking the patients' histories, keeping records of medical examinations and the course of illness, and doing chemical analyses, blood counts, and other routine tests. Following the visiting physicians or the Resident on their rounds, they watched them study the patients, heard expert discussions of the diseases, and observed the prescribed treatment. George Whipple's class was the last to study internal medicine on the wards under William Osler, for just before their senior year started the great internist accepted the Regius Professorship of Medicine at Oxford, to begin in the autumn of 1905. To their successors, disconsolate at missing Osler's instruction, the class of 1905 boasted that he was being graduated with them. In the previous year George had heard "the Chief" every Saturday, at one of his famous clinical lectures which the two upper classes attended. These Saturday clinics were admirably clear and wise, but Osler had said that the only epitaph he wanted was "He taught medicine at the bedside," and there he was incomparable, dazzling the staff and students by his rich experience and diagnostic acuity, and incidentally charming everyone present, patients, students, nurses, and staff alike, by the warm sympathy and insight through which he made suffering and sorrow easier to bear. He often went to the autopsy room to witness the postmortem examination of a patient whose illness he had followed to the end, and there too, with his excellent knowledge of pathology, he put himself at the center of an animated clinical discussion. To George Whipple, already as a fourth-year student leaning toward pathology, Osler's command of that subject was not the least of his merits. Like everyone else at Johns Hopkins Whipple surrendered to Osler's charm, influenced for life by the Chief's love of teaching and enthusiasm for the art of medicine.

William Stewart Halsted, professor of surgery and America's most thoughtful surgeon, a teacher of teachers *par excellence,* made little impression upon beginning students, except as a great and distant figure. He left ward rounds to his Resident, was uninspiringly painstaking and silent at the operating table, and limited his attention to students to a weekly diagnostic clinic in the surgical amphitheater. On these occasions he usually put a couple of them on the rack before their classmates by making them diagnose a difficult case under his own critical quizzing. Thereafter he drifted off into a mumbled, scarcely audible reverie upon some subtly technical question, such as the problem of "dead spaces" in an operative field, or the choice of ligating or not ligating the veins when a major artery was tied. These talks, too deep for the students, constituted an impressive postgraduate course in surgical principles for the resident staff. The students learned more from Halsted's senior associates, the practical, affable John M. T. Finney, earnest, plodding Joseph C. Bloodgood, and scintillating Harvey Cushing. George Whipple, thinking at the time that he might become a surgeon, was lucky enough to get into Cushing's class in experimental surgery, so popular that students had to draw lots to gain admission. From this work he not only gained a valuable introduction to surgical methods, but saw in action a remarkably original and effective teacher who more than compensated for his chief's aloofness. The course, however, dispelled Whipple's thought of surgery as a career, for he found himself interested in its physiological problems and diagnostic puzzles, but not in the manual procedures, and feared that with his turn of mind he risked enslavement to the mechanics of the work and the endless ritual of asepsis.

Whipple found the work in gynecology a total loss as far as he was concerned. Howard A. Kelly, the professor in charge, was one of the most dexterous and resourceful surgical operators of his time. This skill the students were permitted to observe; but unlike Osler, who made students feel like colleagues, Kelly made them merely an audience. Students were not in those days admitted to his wards; Kelly did not try to overcome the difficulties involved in giving them practical training in pelvic examination of ward patients. He seems, moreover, to have been just then in an acutely evangelistic mood, talking to the students, Whipple tells us, more about religion than medicine. Many of them were critical of his self-conscious showmanship, and his great talents were apparent only to those who were specially interested in gynecology and gynecological pathology, of which he and his colleague Thomas S. Cullen were masters, or in old medical books, which he collected with scholarly enthusiasm. Obstetrics under J. Whitridge Williams, on the other hand, appealed to Whipple because Williams and his staff were obviously interested in their pupils. The wards were open to students and a well-organized outside obstetrical service gave them practical experience. George Whipple's awareness of this difference between the two clinics no doubt influenced him twenty years later, when the new school at Rochester, in a major break with the Johns Hopkins tradition, reunited obstetrics and gynecology under one professor.

As he studied the several main branches of clinical medicine, George Whipple like most other students became interested in each, and successively thought of devoting himself to surgery, medicine, and pediatrics. It may seem odd that in his *Autobiographical Sketch* he does not mention the course in children's diseases nor name any teachers of that subject. Pediatrics was at the time included in Osler's department of internal medicine, and was taught by competent local practitioners. If Whipple had come along a few years later, after Clemens von Pirquet came from Vienna to organize a first-class pediatric clinic and hospital (the Harriet Lane Home) on the Johns Hopkins grounds, he would have found the subject much more stimulating and might have made it his life work.

George's special friends among his classmates included Edward H. Richardson, the future Baltimore gynecologist, and Douglas Vanderhoof, a promising student whose marriage, soon after graduation, to a rich wife tempted him away from the career his classmates expected of him. Closer than these were Philip K. Gilman, an extroverted youth with a fine singing voice, and the more serious Henry S. Houghton. Both these men began their professional careers, after graduation, in the Far East. Gilman, expected by his friends to become Halsted's Resident, a sure way to success as a consultant or professor, gave up his chances by marrying a nurse. Since married men were never appointed to the resident staff, he took his bride to Manila and went into practice there until 1917, when he settled in San Francisco. Houghton went to China as a medical missionary and became dean of Peking Union Medical College; when the Japanese overran China he too came back to his homeland, to the deanship of the University of Iowa's Medical School. The class of 1905 at graduation included Peyton Rous, whose international fame as a pathologist was to rival George Whipple's, but the two were not intimate when fellow students. They were, in fact, not classmates until Whipple's last year in school. Rous had entered with the class of 1904, but had to drop out for a year because of illness. Their one year of association at this time was marked by sharp disagreement on many topics. The two were temperamentally unlike, "inherently contrasting types," Rous said years afterward; "George had a granitic aspect and repose, whereas I was overactive and a volatile talker, and we just did not understand each other." In middle life they still for a time agreed to disagree, over the interpretation of their respective research results, but finally learned to respect and admire each other's work and became warm friends, united not only by scientific interests, but also by comparing notes on their respective experiences as trout fishermen.

In Whipple's fourth and last student year he was elected a member of the Pithotomy Club, a dining club formed early in the history of the school by congenial and sometimes ribald spirits. Its name, so its members aver, is derived from Greek words meaning "keg-opening." One of the favorite amusements was poker, at which George Whipple, gifted with a natural "poker face," showed himself an expert. Nevertheless the club had its serious side, and provided good company and good talk at mealtimes. With some of its members George enjoyed a number of week-ends duck-hunting on the Chesapeake or cruising in the oystermen's fast centerboard sharpies. While still a student he was on friendly terms with several faculty families, two in particular. Henry M. Thomas, Quaker physician of selfless devotion (brother of Mary Carey Thomas, formidable president of Bryn Mawr College) and his wife made him almost a member of the family. George was always welcome, too, at the home of

Harvey Cushing—"Keen, high-strung Cushing of the chiseled features"—whose record as a Yale varsity baseball man no doubt added to his attraction for George Whipple, as did Mrs. Cushing's charm and the company of their delightful children.

These faculty friends and his classmates saw George as a tall, handsome young man, respected by all his acquaintances. He made friends slowly but kept them for life. "I cannot vaunt you as a gay and genial cavalier," said one who knew him then, "but I can as a hard-headed, honest, forthright man." With his reserve and plain speaking went fair dealing and courtesy. His kindly attentions, at a student dance, to Peyton Rous's two shy young sisters won the enduring gratitude of that most critical of his classmates. That George could and would stand up for his own opinions, then as now, we know from a story told by one of his instructors in internal medicine, Louis Hamman. Reviewing with his pupil the latter's examination of a patient suffering with lobar pneumonia in an early stage, Hamman, an expert diagnostician, was surprised to find George disagreeing with him on the chief site of inflammation in the lungs. Hamman predicted that the impending consolidation would occur in the right lower lobe, George said the left, and amicably but stubbornly stuck to his opinion. The two could only await the outcome as the disease progressed. George, as it turned out, was right and his instructor wrong. The importance of this incident, said Hamman long afterward, was the light it shed on George Whipple's character and the temper of his mind. He held his own views without vanity or arrogance, but with tenacity, and was not to be jostled from his place by authority, but would yield only to clear demonstration and proof.

During the final year, medical students have to make plans for the next year or two which in many cases determine the course of their lives and work. For George Whipple the problem was whether or not to take an internship as an introduction to a career in pediatrics, the branch of medical practice that most appealed to him. Although the Johns Hopkins Medical School never divulged students' grades, it gave out each year a list of the upper section of the graduating class in order of standing, and permitted each man in sequence to name his choice among the 12 available appointments to the house staff, of which four were in medicine (then including pediatrics), four in surgery and four in gynecology and obstetrics. On this list in the spring of 1905 George Whipple's name was fourth in the class of 53, and he could therefore claim one of the highly prized internships in medicine. The prospect was however not highly tempting. Osler was leaving the Hospital, to be succeeded by Lewellys F. Barker, an excellent anatomist and pathologist but untried as yet in clinical medicine. Since the pediatric service was for the time being to remain a relatively undeveloped part of the clinic of internal medicine, Johns Hopkins had little to offer in comparison with New York, where Abraham Jacobi and L. Emmett Holt were rapidly building up pediatrics into an independent specialty based on research in pathology, bacteriology, and the chemistry of nutrition. It might be better to get further experience in the pathology of children's diseases before going on to clinical work. Discussion of this possibility with his teachers led to an offer from W. G. MacCallum (acting for his chief, Welch) of an assistantship in the department of pathology, with the understanding that George could devote his time largely to pediatric pathology. After a year spent thus he could be reasonably sure of a pediatric residency in New York. George needed but little time for reflection before accepting MacCallum's proposal. Welch's kindly interest in the young man his colleague had thus recruited for the department is shown by a letter to Dean Howell, dated May 25, 1905:

I have told Mr. Whipple that I do not anticipate any hitch in his appointment as assistant in Pathology to succeed [*W. W.*] Francis. Will you kindly see that he is notified when the appointment is made? I wish very much that his salary could be made $600. instead of $500., and I asked Mr. Coy [*the Registrar*] to bring the matter to your attention. He has supported himself, and cannot do so on $500. Will you not bring the matter before the Executive Committee?

Final examinations in the heat of late springtime in Baltimore can be trying, but a student who had cleared all but this last hurdle and had in his pocket an appointment to Welch's department, had little to worry about. At Commencement on June 13, 1905, George Whipple received his diploma from the hands of President Daniel Coit Gilman. His mother did not attend the ceremony. The trip would have been expensive, and the Baltimore weather, at this season often uncomfortably hot, would be especially trying at the crowded ceremony in the old Academy of Music, on Howard Street. George Whipple confesses that he and several of his classmates seated that June day at the rear of the platform, out of sight of the audience, slipped away backstage during the formal address, threw off their caps and gowns, and cooled off lying on the floor. But Anna Whipple, at home in Ashland, undoubtedly took note of the hour when her son became a doctor of medicine, and with a mother's affection and perhaps a few proud tears thought not only of him, but of his father, dead at 28 of illness contracted in the line of a physician's duty, and of his grandfather, who in 1876 had pleaded before the New Hampshire Medical Society for high standards of medical education in America.

CHAPTER

3

# PATHOLOGY, THE SUPREME COURT OF DIAGNOSIS

GEORGE WHIPPLE spent the summer of 1905 in Baltimore, giving up all thought of the mountains and his beloved Squam Lake. Although he was not taking the usual year-long internship, he could at least get some experience of hospital work by substituting for interns who were on vacation. For three months he lived in one of the plain, uncarpeted, almost monastic rooms in the Administration Building, in the quarters reserved for the house-staff, under the famous cupola of the Johns Hopkins Hospital, three flights up and no elevator. He spent his days on Ward F of the medical service, examining incoming patients and checking his findings with those of the Resident and the visiting physicians, following the course of the illnesses, doing blood-counts and urine analyses, supervising treatment, and keeping records. The intern's days are long and tiring, filled with ever-changing duties, but rich in experience and responsibility. Far more than in student days he is burdened with the needs of suffering people and their relatives. This is training in humanity as well as in medicine, and even if the doctor spends the rest of his life over a microscope or at the chemical bench, the memory of his days on the wards will keep him at heart a physician.

In September, 1905, shortly before school opened, Whipple began work in the department of pathology. The staff that year included, besides Welch and MacCallum, W. W. Ford, a pleasant, easy-going man in charge of bacteriology; Charles H. Bunting, afterward professor of pathology in the University of Wisconsin; and a young Canadian assistant, Ernest K. Cullen, brother of the gynecologist Thomas S. Cullen. Whipple's duties were numerous and varied. In the first place he assisted MacCallum and Bunting in the performance of autopsies in preparation for taking over his share of that duty later. Laymen repelled by the idea of searching the bodies of the dead for evidence of the diseases that laid them low, may not appreciate the fascination such work has for the physician. In one of his letters George tried to give his mother some idea of what it meant to him. Reading his words one must picture the scene in the autopsy room of a teaching hospital: the little knot of white-gowned experts gathered around the still, recumbent figure of the dead, and the attentive, always somewhat awed students in the stands; the careful, systematic exposure of the viscera; the play of keen minds as pathologist and clinician discuss the lesions in comparison with the signs and symptoms during life; the test of diagnostic skill and, perchance, the revelation of diagnostic errors; above all, the endless urge to find out more and more about the human body in health and disease. Fresh from such a scene he wrote:

> Any medical man will tell you that you can do nothing for a man until you have some picture in your mind of the diseased parts of the body. . . . In post-mortem work you see the groups of changes in the various organs which are found together in a given case and depend on some primary cause (which you find out and perhaps the clinician was unable to do). You can readily tell what symptoms would arise from such diseased organs and you hear the history of the case read and talked over. Dr. Osler says the Pathology Department is the supreme court of appeals in diagnosis.

A few days after each autopsy came the examination, under the microscope, of sections of the diseased organs, and once a week another session of the "supreme court," at which Dr. Welch reviewed the reports of his staff and from a vast experience gave the final judgment. In addition to the sections from autopsies there was a stream of specimens from the surgical operating rooms to be examined, sectioned and diagnosed. Thrice a week for a half-day during the fall and winter months, the assistants took part in teaching the second year class in the laboratory of microscopic pathology. They also gave elementary lectures on pathology to pupil nurses.

At the end of a year George Whipple, happy in this work, asked for a second appointment, which Welch gladly granted, with promotion to the rank of instructor. Another year, he told Whipple prophetically, would anchor him to pathology for life. During the second year, Bunting and Cullen having left, two new men joined the department, one of whom, Henry F. Helmholz, of the class of 1906, was already George's good friend. In frequent discussions of their plans, Henry had talked of making a career in pathology and George of pediatrics; but in the end shifting interests, not unusual in young men finding their way in the profession, led Whipple to stay in pathology, whereas Helmholz soon gave it up and went to the Mayo Clinic, where he became chief pediatrician.

The other new man, Marshall Fabyan, went at the end of the season to the University of Virginia as professor of pathology, and ultimately to Harvard, where he succeeded the celebrated bacteriologist Theobald Smith as professor of animal pathology when the latter was called to the Rockefeller Institute.

The assistants were expected to undertake research in descriptive or experimental pathology. Whipple's first original investigations began at the Baltimore City Hospital (Bay View) where the younger Johns Hopkins pathologists were sent to gain experience by doing autopsies on their own responsibility. Bay View, since thoroughly modernized, was then hardly more than a lazaretto for paupers and the insane. To its filthy autopsy room came bodies of numerous inmates dead of advanced ulcerative tuberculosis. Looking back upon his work at Bay View George Whipple wonders how he escaped infection, and conjectures that he must have been rendered immune in childhood by a small lesion, since healed. At any rate what he saw at Bay View awoke his interest in tuberculosis. In his first paper he answered a recently raised question about the spread of the disease through the body from the first focus of infection, by showing from examination of 24 cases that the bacilli from active tubercles may get into the lymph stream as well as into the local blood vessels, and may thus reach the general circulation by way of the thoracic duct. He read this paper at a meeting of the American Association of Pathologists and Bacteriologists at Baltimore, May 18, 1906,—his first appearance as a scientific speaker. In a second paper he dealt with the question, then being debated, whether tubercle bacilli may infect the body by way of the intestinal canal. By analysis of all his cases, now numbering 47, in which tubercle bacilli were found in the thoracic lymph duct, he showed that the intestinal canal is a possible but far less frequent portal of infection than the lungs. Another report, based on 23 autopsy cases, revealed the frequency of focal necrosis of the pancreas in various acute infectious diseases and suggested that this may be a cause of subsequent diffuse pancreatitis. These early papers are written in a style presaging Whipple's later publications—straightforward, unadorned, carefully explanatory and definite as to the conclusions. It was his fortune to autopsy two very rare cases, one in 1906 and another in the following year. The first of these (typhoid nodular colitis) need not be reviewed here. The other at once put Whipple's name into the literature of pathology as the discoverer of a previously unknown disease. On May 9, 1907 he did an autopsy on the body of a physician, 36 years old, whose illness had puzzled an all-star group of Johns Hopkins specialists, William S. Thayer, Lewellys F. Barker, William S. Baer, and Rufus Cole. Thayer's diagnosis was either sarcoma or Hodgkin's disease of the mesenteric lymph nodes. At autopsy Whipple found an extraordinary accumulation of granular cells in the walls of the intestine and in the mesenteric lymph nodes, *i.e.* in regions where fat is normally stored. Applying microchemical staining tests for fatty substances, he found fatty acids but no neutral fat in these cells. This led him to suppose that the condition involves a breakdown of fat storage. Recognizing its uniqueness, he published the case in the Johns Hopkins Hospital Bulletin, suggesting the name of *intestinal lipodystrophy*. Medical writers, however, dubbed it "Whipple's disease" and it is usually called by that name. Pathologists alerted by Whipple's original description have since reported about 100 cases in various parts of the world, almost all of them fatal. Beginning about 1949 there has been a wave of increased interest in Whipple's disease, especially since cortisone has been found useful in treating it. The cause and classification of the disease, however, remain enigmatic. Progress is being made in analyzing the chemical nature of the tissue damage, and minute objects thought to be microorganisms have been observed in the affected regions. Microscopic slides and alcohol-preserved tissues of Whipple's first case, stored at Johns Hopkins Hospital, have been subjected to chemical analysis which confirmed the correctness of Whipple's chemical description as far as methods available at the time allowed him to go. The investigator who in 1961 reported these tests remarked that "the original description by George Whipple of the disease that bears his name stands as a classic of clarity, objectivity, and completeness."

In the spring of 1907 Colonel William Crawford Gorgas, heading the medical and sanitary work of the Panama Canal Commission, asked Dr. Welch to find a young man to assist, for a year, Samuel T. Darling, chief pathologist of Ancon Hospital. At Welch's suggestion the post was offered to George Whipple. Ancon was the largest of several hospitals in the Canal Zone. Construction work on the canal had brought thousands of American and European workers under the protection of Col. Gorgas's skilled health organization. Yellow fever had been kept out and malaria greatly reduced, but a good deal of tropical disease was inevitable. Ancon offered an unusual opportunity to study it under favorable conditions. The salary, moreover, was several times George's pay of $800 as instructor at Johns Hopkins. In a year he could save enough, he thought, to finance a trip to Europe.

His report of this offer to his mother surprised and alarmed her. In turn he was badly upset by her reaction. Many a young physician, interested at that period in a career of medical research, faced in some degree a similar family crisis. The very idea of full-time research was unfamiliar to parents knowing nothing of the new scientific currents in American medicine, who naturally expected their sons to go into private practice, and like Anna Whipple had made sacrifices to that end. If they had heard anything at all about research they pictured it as precarious, ill-paid, even chimerical. Anna herself, though by now somewhat better informed, still thought of her son's work in pathology as further training for the practice of medicine. Another year of laboratory work, and in the tropics at that, looked to her like very poor preparation for practice in the north. She wrote him an urgent plea to give up the idea, settle down somewhere as a general practitioner, earn a good income, and get married.

His reply, here condensed from a long, heart-felt letter written April 7, 1907, reveals both the hopes and the uncertainties of a young man thinking out his future.

I have done nothing the past week but think about that Panama job, and have talked it over with many of my best friends and very competent advisors. . . . You know times have changed since my father was at his work. . . . With my training I should never consent to become a practitioner in a small town, as you would not wish, I am sure; if I went into medicine I should strive to become a consultant. . . . You have always advised me to set my ideals high and I am sure your ideals are as high as my wildest dreams. I will tell you that my ideals are Drs. Osler, Welch, and Barker. . . . They all began medicine as pathologists—Dr. Osler five years, Dr. Barker three years *here*. Dr. Welch didn't switch to medicine as they did. So you see that a man (as I have said many times) doesn't waste any time by staying in Pathology no matter what branch he follows out. Now about getting into practice—you know that just as soon as a man does that and is so busy that he has no time for research work and teaching at some school, he begins to fossilize and ceases to develop. You have only a slight conception of the value to a man of associating with men who are so much his superiors in learning etc. and who act as stimulants for his work and help him to develop. Just at my time of life all this, I think, is most important and means all the difference between an ordinary narrow-minded person and a broad-minded man as I hope to become. You say you wish me to make a home etc. and I have every desire. Perhaps fortunately I have never seen the girl who made me sure that she ought to be Mrs. W. and if that occurs I don't know how it would influence my course of work. But there is no need of worrying about that until the right girl comes along. Do you think that many practitioners make over $4,000 without working themselves into an early grave? . . . A professorship brings $4,000-$5,000,

which in the average town, except New York, is a comfortable income even for a family man. . . .
Dear Mother, a man's worth is just the estimate of his coworkers and associates and I assure you that in the minds of his fellow doctors a pathologist (if of any ability) is held in the highest respect and honor. It seems to me that the great thing in life is to know the great men in medicine, become acquainted and form friendships with them and gradually win their respect, perhaps praise and admiration. . . . I assure you that I have lost considerable sleep and many hours of work thinking about all this matter and it is at best a very complex problem. . . . I will tell you frankly that I will only stay in Pathology if I find that I am making good and can get one of the good places that are coming along in the next few years. . . . I hope in a few years to have some definite course mapped out and be of some financial aid to you.

He took the Panama job. It is good to know that Anna Whipple lived to see her son a Nobel laureate.

George left New York August 27, 1907, on the steamship *Dunnotar Castle,* bound for Colon, and the next day spent his 29th birthday at sea in perfect weather. The five-day voyage was a good rest after two years' hard work. "I have done scarcely any reading on this trip," he wrote his mother, "I just sit around doing nothing. . . . There are few single young ladies aboard and none of them rouse any curiosity on my part." No wonder this; whether or not he was willing to admit it, he had left his heart at home. Although on April 7 he had told his mother, in all sincerity, that he was still fancy-free, he had already met, a few weeks before, a girl whose charm was beginning by August to make him suspect that she "ought to be Mrs. W." He first met Katharine Ball Waring at a students' dance at the Medical School. Katharine, a pretty, vivacious redhead, was one of five or six girls from Charleston, South Carolina, attending Goucher College (then called the Woman's College of Baltimore) who were introduced to medical school society through Thomas P. Sprunt, a popular Charlestonian student and a friend of George's.

Goucher College, a Methodist institution, at that time did not permit the girls to attend dances, but their friends and relatives in the city found ways to evade the prohibition. Katharine's great-aunt, Mrs. Augustin Taveau, lived in Baltimore and it was from her house that she went to Johns Hopkins dances. There were Sunday supper-parties, too, at hospitable Mrs. Taveau's, where young university men were invited to meet the college girls.

Katharine came from one of those families of Carolina landed gentry whose fortunes were irreparably reduced by destruction of their homes and property in the Civil War. Such families kept up as well as possible the old Southern way of living. The Warings had a Greek Revival house in old Charleston, furnished with heirlooms, and kept two or three Negro servants. If, behind a cultured front they had to practice rigid economies, so did everyone else in that brave aristocracy where breeding outranked wealth. Katharine, youngest of Thomas Malbone Waring's seven children, had a long Southern ancestry, going back to Benjamin Waring, member of His Majesty's Council of South Carolina, who arrived in the colony in 1683. Her social grace and gaiety made an immediate impression upon George Whipple. Reserved, plain-speaking men, to whom small talk does not come easily, often specially enjoy the company of people who make them comfortable by easy manners and good conversation. Many of George's male friends were of that type; Katharine combined the same gifts with feminine charm and a Southerner's lively interest in people and personalities. She had a good soprano voice that appealed to George's real though seldom displayed liking for music. Their friendship did not for some time lead to an engagement, but already on the eve of his departure for Panama signs of a romantic attachment were obvious, at least to an observant friend who mailed to George at Ancon some doggerel rallying him on his attentions to "Katie the gay" at a party at Mrs. Taveau's on August 19.

The year at Ancon was as profitable as George could have hoped. He had a comfortable room in bachelors' quarters on the top of Ancon Hill, among the royal palms. At the hospital he could observe tropical disease in many forms—amebic dysentery, malaria, beriberi, filariasis, and all sorts of parasites, internal and external—in the wards as well as in the autopsy room, where he performed 420 postmortems in his one-year stay. Hookworm disease, then of deep concern to health authorities in the southern United States, was prevalent in the Canal Zone also, and Gorgas's sanitarians needed all the information about it they could get. In an article on the incidence of hookworm disease in the Canal Zone, Whipple reported on 232 autopsies, finding hookworm in about a third of them. Because of the diverse national origins of the Zone's population, he saw both the old-world and new-world species of hookworms, both occurring together in 25 cases. In this and a subsequent paper he studied the anemia from which practically all hookworm patients suffer. Several investigators had suggested that it is produced by a blood-dissolving substance (hemolysin) emanating from the worms. Whipple confirmed the presence of a hemolysin, but found it too weak to attack the patient's blood, and showed that the anemia results from loss of blood through mechanical and inflammatory damage caused by the parasites.

The most important of his three investigations at Ancon dealt with an often fatal disease, blackwater fever, which gets its name from the presence of large quantities of blood pigment (hemoglobin) in the urine. It had been variously thought to result from poisoning by quinine given as a malaria cure or preventive, or to be a peculiar kind of malaria, or even a distinct disease caused by an unknown parasite or virus. Whipple began his study suspecting the latter guess to be correct, but his careful analysis of 17 autopsy cases convinced him that an attack of blackwater fever is always preceded by malarial infection and is, in essence, malaria plus an unknown factor, probably a toxin resulting from a reaction of the tissues to the malarial parasites. To the present day this is all that is known about the nature of the disease. Whipple's report, published in 1909 in the short-lived international journal *Malaria,* brought heart-warming praise from a distinguished foreign reader, George Alexander Gibson, physician to the Royal Infirmary of Edinburgh:

> Your valuable paper on Blackwater Fever and Pernicious Malaria in Panama reached me a couple of days ago, and I have been reading it with the greatest interest. I should like, if I may, to offer you my most sincere congratulations upon a beautiful piece of work, one of the greatest importance to all of us who belong to the two great imperial countries.

The histological description of the lesions of pernicious malaria and blackwater fever given in Whipple's paper were the best available for many years. Since *Malaria* ceased publication after only two volumes, the paper was unavailable in most medical libraries, and

Whipple was asked to reprint the descriptive part of the article in 1927 in the *American Journal of Tropical Diseases.*

George's ambition "to know the great men in medicine, become acquainted and form friendships with them" was again fulfilled by the opportunity Ancon gave him to see a good deal of Colonel (later General) William Crawford Gorgas, leader of the immense work of sanitation and disease control without which the American canal builders would have failed as did the French under De Lesseps, defeated by yellow fever and malaria. Gorgas was friendly and generous to the young men of his staff, not only in the field and the hospitals, but also in his home. Fond of evening horseback rides, he was often accompanied by his daughter and some of the younger medical men. Watching him, George could learn how a high-minded executive wins the loyalty of his juniors, and how he carries on against obstacles, even against the resistance of the high military command to some of his scientific control measures. Gorgas, George observed, could win over any group of local officials to his way of thinking, and get them to do what he wanted while believing it was their own plan. This too was a useful lesson for the future head of a medical school closely tied in with the city government.

In the tropics, outdoor exercise is a necessity. Ancon provided ample facilities for tennis, riding, and swimming, and to George Whipple's special satisfaction, called him to an unanticipated brief career as a semi-pro baseball player. Among the morale-building diversions arranged by the Canal Commission for its thousands of workers was a baseball league representing the principal towns and construction camps in the Canal Zone. As outfielder, first baseman, and occasionally pitcher for Ancon in the Isthmian League he was in fast company, for some of the players were out-and-out professionals from minor leagues in the States. The details of his individual record are not available, because the *Canal Record* printed only team standings; but the figures show at least that he did well at the plate. Ancon led the league that season, and Whipple was the team's leading batter. The record reads: Whipple, at bat, 33; hits, 15; percentage 454. When the season ended in June, 1908, George returned his salary as a ball player to the Ancon club's meager treasury, to be applied to the pay of his young professional teammates.

Toward the end of his year in Panama George suffered two blows, both painful in very different ways, but fortunately curable. Late in the summer of 1908 he took a month's vacation in the States, and on his way back to Panama to finish out his service, stopped over at Charleston to visit Katharine Waring. She had returned to Charleston for lack of funds to continue at college, and was studying music and at the same time earning money by tutoring and singing in a church choir. While George was at Ancon she had made her debut, in the highest Charleston tradition, at a St. Cecilia ball. George's visit was not a success. He was not versed in Southern gallantry, and Katharine, miffed by some of his unadorned Yankeeisms, broke off their engagement, or understanding, whichever it was at the time, and sent him away to Panama in despair. In September, while at sea *en route* for New York, he came down with a sharp attack of malaria, probably caused by latent organisms which suddenly began to multiply in his blood as a result of the change of environment. When the ship docked at New York he went immediately to the Presbyterian Hospital, affiliated with the College of Physicians and Surgeons. The intern in charge of his treatment was Allen O. Whipple, future professor of surgery there. The two men adopted each other as "cousins" and have been friendly ever since.

The personal ailments of a pathologist are medically interesting in the light of his occupational hazards. Whipple has had relatively few major illnesses. In his third year at Phillips Academy he was confined to bed for a month with "catarrhal jaundice," probably infectious hepatitis. A case of mumps early in 1907 during an epidemic among the Johns Hopkins doctors and nurses—no light matter for an adult—and the malarial fever of 1908 were the only illnesses directly attributable to exposure to infection in the line of duty, in more than five decades of professional activity. As we have seen already, his work had constantly exposed him to infection with tuberculosis, against which he believes he possessed acquired immunity. Frequent references to colds in his letters between 1910 and 1914 hint at a weakness of the upper respiratory tract perhaps related to the allergies that have long plagued him in one form or another. In retrospect, the earliest sign of sensitivity to pollens was an irritation of the skin occurring only in late spring and early summer, first noticed while he was on the Johns Hopkins staff.

Other illnesses will be mentioned in the course of our narrative.

Welch had written to Whipple in Panama in May, 1908, to say that MacCallum was considering the offer of a good position elsewhere: "If he goes you would be my mainstay, and I should expect you to take his position." As it turned out, MacCallum stayed one more year as associate professor and resident pathologist. Meanwhile Whipple was appointed assistant resident pathologist, with living quarters in the Hospital. When MacCallum finally left in mid-1909 to be professor of pathology at Columbia University, College of Physicians and Surgeons, Whipple succeeded him not only as the senior member of Welch's staff, but as resident pathologist also. He now stood high enough in the Johns Hopkins Hospital staff to have a commodious room in the Residents' wing on the second floor of the Administration Building. Although he was not at once promoted to the rank of associate professor, but only to that of associate (the Johns Hopkins equivalent of assistant professor), he had full charge of instruction in pathology, under Welch's nominal direction. Next in rank was Milton C. Winternitz, assistant resident pathologist and associate on the teaching staff, and therefore Whipple's most intimate professional colleague for the next six years. The two were as unlike as they could possibly be, and yet were to have very similar careers. "Winter" was a small, dark, bright-eyed man, exceedingly quick of speech, and quick-tempered as well. Students liked him, even under the lash of his sharp, bantering tongue, for they recognized his enthusiasic devotion to teaching and research. After MacCallum left, Whipple and Winternitz conducted the daily work of the department, not without occasional ruffled tempers, but with respect for each other's talents and mutual desire to support and please Dr. Welch. They had full responsibility for the autopsy service, and also frequently lectured as understudies for Welch, who expected one or the other of them to take the weekly lecture whenever he went out of town, sometimes on short notice. Finding it impossible to predict these emergencies, they divided the whole series between them, each preparing half the talks. When Popsy turned up, they had the instructive experience of hearing him present impromptu, and beautifully, what had cost them hours to prepare. "This," says Whipple in his dry way, "improved our technique and kept us free of any feeling of superiority as teachers."

An imaginative student fortunate enough to have studied pathology under this extraordinary trio might have seen them as typifying three aspects of medical science. Welch, portly and bearded, stood for the hieratic tradition in medicine—its long history, its Hippocratic image of the father-physician, its intellectual dignity. Winternitz represented the ever-youthful curiosity of science, its prying search, its excitement in discovery; Whipple the steady, solid accumulation of observed facts, and the deductions and analysis by which they are put to use.

A group of men who were in fact Whipple's pupils at this period, talking about him years later, tried to free their minds of subsequent impressions and recall him as they had known him about 1910. The picture thus called up was that of a quiet and reserved young man, but not without a sense of humor; a careful, factual lecturer, and in the students' laboratory always courteous, answering every question with a definite, well-reasoned explanation. Unlike his volatile colleague Winternitz he did not make a vivid impression upon students not particularly interested in pathology who knew him only in the class laboratory. If such pupils had never seen him after the course was over, nor heard him spoken of, they might have remembered only that he was a sound teacher. It took more than a few hours or weeks of sporadic acquaintance to perceive the depths of his mind and character.

George Whipple told Simon Flexner, Welch's biographer, that Welch had taught him tolerance toward students. Each year when Whipple brought in a list of students graded as "failed," Popsy insisted on going over the papers and generally found reasons for passing them. "This happened again and again each spring," said Whipple, "although I learned each year to be a little more reasonable in my demands upon students. . . . If it had not been for Dr. Welch's influence at that time, I might have been pretty hardboiled and unreasonable relative to students' shortcomings." Thus he had learned from Mall not to spoon-feed medical students, from Osler to treat them as if they were professional colleagues, and from Welch not to despair of them.

Welch, however, was not infallible. Whipple had to take a stand against at least one of his proposals. Sir Almroth Wright, celebrated bacteriologist of St. Mary's Hospital, London, had called attention to substances in the blood called opsonins, that enhance the power of the leucocytes to attack bacteria. Obviously the concept had important implications for the treatment of infectious diseases. Lectures given by Wright at Johns Hopkins in the spring of 1909 deeply interested Welch, who told Whipple that their laboratory ought to follow up the subject and asked if he would like to take it on. This was almost a royal command, but after thinking the matter over for a couple of days George told Welch that he had become interested in another problem to which he wanted to give all his available time and energy. If he were ever to develop independence in research, he said, he had better begin at once. Welch took this in his usual genial way and said nothing more about it. One of Whipple's friends in the hospital staff, William L. Moss, soon afterward began work on opsonins, but neither he nor investigators elsewhere were able to develop practical use of Wright's rather nebulous ideas.

Through his promotion Whipple now commanded good facilities for experimental research. The Johns Hopkins Medical School had built in 1905 a plain two-story building known as the Hunterian Laboratory, designed for experimental work on animals by the departments of surgery and pathology. Harvey Cushing was in charge of the surgical floor, where he was conducting the pioneering experiments on removal of the pituitary gland of the dog, on which his early fame rested. MacCallum's departure left Whipple in charge of the pathology floor, with adequate space, equipment and technical assistance for his work. As he had told Welch when discussing the opsonin problem, he had already begun on his own initiative a study of disturbances of liver function resulting from damage to the tissues of that organ. Late in 1908 he heard an interesting lecture on acute chloroform poisoning by two visitors from New York, John Howland and A. Newton Richards, who pointed out that one of the specific toxic effects was focal necrosis of the liver. At that time the cause of cirrhosis of the liver was a great puzzle to pathologists. It occurred to Whipple that by repeated poisoning with chloroform he might produce cirrhosis experimentally in dogs, and thus not only help to solve the riddle, but also secure material with which to study the deranged liver function characteristic of cirrhosis. This hope was in vain. He and a co-worker, John A. Sperry of the gynecology staff, found that the liver damage produced by chloroform was promptly repaired by regeneration of the tissues, leaving no scars to block the circulation and produce cirrhosis. As so often happens, however, when good work is done on an erroneous hypothesis, the effort was by no means wasted. Whipple and Sperry's report gave pathologists a noteworthy description of liver necrosis and its repair by natural processes.

Early in July, 1909, Whipple left Baltimore on his long-planned trip to Europe. Half the Johns Hopkins medical faculty must have been abroad that summer. In Paris he met two colleagues from his own department, John H. King and Henry Helmholz, with whom he visited the Louvre. They ran across Rufus Cole and just missed Welch and Halsted. At Heidelberg Whipple and King met J. Whitridge Williams and saw the Castle with him. Settling down in Heidelberg as boarder at a house on the Uferstrasse, Whipple took German lessons and began attending the lectures of Ludolf Krehl, professor of pathology. In the laboratory he joined P. Morawitz, Krehl's capable senior associate, in some of his experiments on anemia in rabbits, produced by bleeding. Whipple's assignment to that topic was purely a coincidence; the work had no direct bearing upon his own later research. Neither Morawitz nor he could have dreamed that his greatest achievement in research would depend upon a similar method using dogs. His stay was too short for significant accomplishment, but gave him a chance to see a first-rate European laboratory in action. While he admired the scientific talents of Krehl's staff, he could not help comparing the rigidity of a German institute, evidenced by the domination of the senior men over the younger, and by regimentation of the use of apparatus and supplies, with the freedom given the younger men in Welch's laboratory.

For recreation Whipple joined the University boat club and rowed on the Neckar every evening in a two- or four-oared shell with some of the older German students. Undergraduates, he commented, took little exercise except fighting duels, some of which he witnessed with more curiosity than distaste. An exhibition of gymnastic work by visiting "Turners" was better than he had ever seen in America. There were concerts twice a week, and once a grand illumination of the Castle. With John H. King he visited Strasbourg, Frankfurt, and Mannheim. At Heidelberg they called upon the great biochemist Albrecht Kossel, a friend of Abel and Welch. After King left for Vienna early in August, Whipple went with other friends to Basel, where he enjoyed the art museum's Holbeins, and, somewhat surprisingly, the romantic, brooding fantasies of Arnold von Boecklin. His 31st birthday was spent in Nuremberg; then on to Luzern, which afforded a base for the ascent of rocky Mt. Pilatus (7000 ft.) from whose slopes he sent his mother a little collection of wild flowers. The homeward journey took him by way of Brussels and Amsterdam to London. At Oxford, like almost every other traveler from Johns Hopkins, he called upon William Osler, who presented him with a textbook of pathology by some old Heidelberg professor, giving it special value for his loyal pupil by inscribing his name and the date on the flyleaf. At Edinburgh George was met by a Scottish friend, Hugh Stewart, who had once worked in Welch's laboratory. Tired of sightseeing in cities, he passed up Edinburgh and went to Pitlochry in the Highlands for a brief stay at Stewart's home, then sailed for New York on September 18 on the Anchor Line steamer *Columbia.*

Once back in his own laboratory he took up research where he had left it in July. Some of the dogs he and Sperry treated with chloroform had died with uncontrollable hemorrhages in the abdominal cavity and elsewhere. What was the reason for this? With a medical student, Samuel H. Hurwitz, he found that chloroform poisoning interferes with the clotting of blood, and hence promotes hemorrhages, because it inhibits the production of fibrinogen, the protein that forms blood clots. The amount of fibrinogen in the blood goes down proportionately with the extent of liver damage. Just where fibrinogen is formed had been a mystery; these experiments indicated beyond reasonable doubt that it is produced in the liver or through action of that organ. Eighteen years later, when methods had been perfected for total removal of the dog's liver with survival for two or three days, Douglas R. Drury and Philip D. McMaster of the Rockefeller Institute, and F. C. Mann of the Mayo Clinic, confirmed and strengthened Whipple's deductions of 1911 by fully conclusive experiments.

Another feature of chloroform poisoning is jaundice. Somehow the bile pigments, which normally are secreted by the liver into the intestine by way of the bile ducts and gallbladder, get into the blood when the liver is damaged—a fact dismally apparent in the cases of infectious jaundice which have become so common of late. The same contamination of the blood with bile pigments, showing up as jaundice, happens when the bile is dammed back into the liver by obstruction of the bile ducts. Two possible pathways for this diverted flow had been suggested: bile forced out of its proper channels into the tissue spaces of the liver, by obstruction or cell-damage, must either pass directly into blood capillaries or into the lymphatic channels. Whipple and his collaborator, John H. King, studied the question by tying the common bile duct in dogs, thus obstructing it, and tracing the subsequent appearance of bile pigments in the blood stream, body fluids and body cavities. Their findings completely excluded the lymphatic system; the extruded bile passes directly into blood capillaries.

In April, 1910, Whipple happened to see an announcement of the Warren Triennial Prize of Massachusetts General Hospital, an award endowed in 1867 in memory of Dr. John Collins Warren by his son J. Mason Warren (the same whose unsuccessful attempts to cure a salivary fistula had been bettered by George Whipple's grandfather). It was one of those old-fashioned competitions in which essays were submitted under a pseudonym to avoid prejudicing the jury, which in this case was a committee of the Massachusetts General Hospital staff. Any topic in medicine, surgery, or pathology was eligible. With only a week before the deadline, he wrote in great haste a paper "The Pathogenesis of Icterus" which he submitted with no great hope, thinking it incomplete and too brief. Three months later he received notification of the award and a check for $500. Giving his mother the news, he wrote

> Dr. Welch was told of it by Dr. Thomas, who told me that Popsy was more pleased about it than anything he had ever seen. Dr. W. saw me last Friday at Dr. Thomas's and was very nice—said it was the most noteworthy prize given in the country in medicine. When I think how much of an accident it was that I did send anything, it seems like nothing but luck. However, it is about the best thing that has happened to me—like being recognized in the enemy's country.

On December 26 of that year he sent the amount of the Warren

Prize to Anna Whipple as a Christmas gift, to be used for a trip abroad the next summer. The prize essay was not published, but the findings were included in a paper by Whipple and King in the *Journal of Experimental Medicine.*

Baltimore society has the reputation of being slow to accept newcomers, but a good-looking, discreet bachelor is a social asset to any hostess. George Whipple quickly made friends in well-placed Maryland homes, including those of Blanchard Randall and Richard Janney White, trustees of the University and Hospital respectively, and George Gaither, an eminent lawyer. As early as 1906 he was invited to attend one of the Monday Germans, exclusive assemblies at which Baltimore debutantes were introduced to society. He deepened his friendships with some of the most important faculty people also. After returning from Panama he must have told his old friends the Thomases about his blighted romance with Katharine Waring, awakening in Mrs. Thomas the matchmaker's instinct that every happily married woman is said to possess. Learning that Katharine was coming to Baltimore in June, 1909, for the graduation of her Goucher class, Mrs. Thomas invited the young lady to stay at her house, and seized the opportunity to impress her guest with the merits of the tall, shy, serious New Englander whom she had impetuously rebuffed some months before. The lesson must have been taken to heart, for Katharine gaily accepted the role of guest of honor at a large dinner party at the Thomases', to which Dr. Welch, the Barkers, the Finneys, the Futchers, and the Thayers were invited, to meet "the girl to whom George Whipple was *not* engaged."

In the spring of 1909 George's week-ends, faithfully reported in letters to his mother, included tea and supper one Sunday with the Cushings, a call on Mrs. Thomas, and supper with the Barkers. Dr. Welch asked him to dinner at the Maryland Club to discuss plans for a new autopsy room to be added to the Pathology Building, a pet scheme of George's now on the eve of fulfillment. To dine with Popsy meant the best of Maryland food as well as a feast of good talk. In April George journeyed again to Charleston. The time had come for a formal visit to the Warings; he found the family circle ready to accept even a Yankee if Katie really wanted him. Back in Baltimore, a few weeks later he was calling on the Thayers, and visiting the Gaithers and the Whites. On December 25, 1910, he was with the Thomases for Christmas dinner and the Cushings at an oyster roast in the evening.

There was no longer any question in Whipple's mind about staying in pathology. Welch's encouragement and the wide outside recognition of his research assured him that he was on the right path. A story has gotten about that he suddenly gave up the idea of being a pediatrician because of overwhelming distress when he had to autopsy a child of his friend Lewellys Barker. This is manifestly over-simplified. George Whipple was certainly fond of children and sensitive to their sufferings. The laboratory scientist is of course spared much of the personal association with ill and dying people and their kin to which a practitioner of medicine is exposed. A conscious or unconscious wish to have less to do with people's troubles and griefs than does a practicing physician may well have been a factor in his decision; but he was too determined and too logical to seek escape from mental trauma by a deliberate leap from the frying pan into the fire. As a pathologist he would obviously be exposed to repeated distress when people he had known came to his autopsy table; as a practitioner he might expect a happier outcome in most of his cases. Actually his interest in pediatrics had begun to fade as his research program prospered. He had come to realize that he did not care to deal personally with the treatment of the sick; the cause and diagnosis of disease alone attracted him. Pathology offered plenty of such problems without the distractions of practice.

Further evidence of his success as a pathologist came in the form of two calls to professorships. About the end of May, 1910, President Benjamin Ide Wheeler of the University of California telegraphed Whipple, asking for a conference in New York. When they met, Mr. Wheeler remarked that when he was a boy, he had known George's grandfather. After an accident Dr. Solomon Whipple had removed a lot of burnt gunpowder from his face and saved his features. Coming to the point after this anecdote, he offered George Whipple the chair of pathology at the University of California. Whatever attraction the offer might have had was overbalanced by disadvantages; the medical school was only then being brought up to national standing, and was unfortunately divided, with some of its preclinical departments in Berkeley and the rest of the school in San Francisco with only a small hospital in its immediate vicinity. Less than a fortnight after Whipple declined Wheeler's call, the University of Pennsylvania also made him an offer. Its chair of pathology, distinguished by the former occupancy of Simon Flexner, Welch's cherished pupil and friend, and of Richard M. Pierce, was again vacant through Pierce's transfer to a different department of the school. Welch, who was continually being asked to suggest candidates for vacant posts, and always unselfishly named his own men, proposed Whipple for Pierce's place. The Dean at Philadelphia was apparently not quite sure that Whipple was ready to follow men of such distinction. With an excess of caution he offered an associate professorship for two years with a promise of promotion to the chair of pathology at the end of the period if everything went well. Whipple countered this naive proposal with the remark that if he must be kept on trial for a full professorship he preferred to continue his probation on familiar ground in Baltimore. That ended the negotiation. In the academic world, however, nothing succeeds like success. Welch had not been enthusiastic about either of these offers, for he thought that still better ones were in the offing. Moreover Welch really needed Whipple's continuing help. The two calls created the necessary leverage to secure George's promotion, in 1911, to an associate professorship at Johns Hopkins.

Since Whipple's return from Panama his investigations had turned more and more from pathological anatomy, that is to say description and classification of the changes produced by disease, to physiological pathology, the analysis of abnormal states by the methods of physiology and chemistry. Such an approach was relatively new in America. Although investigation of this kind had begun in Europe about 1850 under the lead of Ludwig Traube, Friedrich Theodor von Frerichs and Claude Bernard, Americans could undertake it only when the medical schools began to turn out men thoroughly prepared in physiology and biochemistry as well as in pathology. Christian Herter had applied physiological methods to problems of disease in his private laboratory in New York before the turn of the century and so had Eugene Opie at the Rockefeller

Institute a few years later. W. G. MacCallum was actually designated a physiological pathologist when Johns Hopkins, trying to hold him in 1909, at Welch's suggestion created a chair of that subject for him. Whipple too must be counted one of the pioneers. There are of course no sharp lines between pathology, physiology, and biochemistry; the study of normal functions merges with that of the abnormal. The problem is the important thing; a good investigator will attack it by any promising method. Great advances are usually made along the borders between established fields of science. To get on with his inquiry into disturbances of the liver and the intestinal canal Whipple needed new technical methods. These could be learned only in Europe, and one of the best centers of experimental physiological chemistry was Hans Meyer's Institute of Pharmacology at the University of Vienna. Whipple had heard Meyer give the annual Herter Lectures at Johns Hopkins in 1905, on "The Contributions of Pharmacology to Physiology," and knew that his outlook was relevant and his techniques applicable to the problems under investigation in Baltimore.

Whipple left New York on March 11, 1911, bound for Europe by the southern route, which offered a long, restful voyage with plenty of sunshine. For about three months he had been ailing with a vague sort of lassitude, occasional low fever, and considerable loss of weight. Looking back, he now supposes that this was brucellosis; at any rate decades later when a colleague studying the incidence of that disease in the Rochester area tested his blood for brucella antibodies, the reaction was strongly positive. At the time, however, he thought he might have tuberculosis, and worried about himself for months without ever having his lungs examined, for fear of being ordered to quit work and go to Saranac for the cure. The lassitude fortunately wore off in time for him to profit fully by the trip. At Vienna he roomed in a household where nobody spoke English, with much benefit to his use of German. He enjoyed some of Vienna's excellent concerts and operas, visited Munich and Budapest and went up the Danube by boat. By the end of August he was in good health once more, and back to normal weight at 176 pounds. On a tour to Cortina and the Dolomites he had sufficient energy to climb an 8000-foot peak.

Hans Meyer was hospitable and his associates P. Wiechowski and

Alfred Froelich were very helpful, inviting Whipple to witness their teaching and assist in research. A young instructor, E. Jaeger, taught him a new simplified technique for making an Eck fistula in the dog—a communication (anastomosis) between the portal vein and the vena cava, by which the blood coming from the stomach and intestines flows directly into the general circulation, completely by-passing the liver. This instruction was extremely useful a few years later when Whipple's experiments depended upon constant use of the Eck fistula.

After his return in the fall of 1911 Whipple's section of the Hunterian Laboratory was more than ever productive, and the main lines of his lifelong research program were becoming apparent. In the three years 1912-1914 he with his co-workers published 21 research papers. Although their topics may at first sight seem rather diverse, actually all of them fall under four general headings—liver function, blood coagulation, pancreatitis, and intestinal obstruction. A gifted, independent scientific investigator takes up specific problems by a combination of chance and hard thinking. A problem may first present itself in various ways: a hint from a teacher with whom he was trained, a puzzling observation of his own, a colleague's query, or something heard in a lecture or read in a book. If the question puzzles him sufficiently he goes to work on it. Sometimes he gets nowhere and lets the matter drop. Sometimes he finds an answer that seems to lead no farther; he had better drop that problem too and follow a more productive lead. Sometimes he reaches a satisfying solution, but this always means he has opened up a new lot of questions. The born scientist, who never ceases to ask questions and never stops working on them, sooner or later breaks through into an unexplored field that lies wide open to his talents.

In George Whipple's case we can trace at least some of his leads and see how his training and experience fitted him to follow them up, and why he chose to put some of them aside and concentrate on others. Three of the 1912-1914 papers explore a curious situation he had encountered when studying chloroform poisoning. Chloroform was widely used as an anesthetic in childbirth, and doctors asserted that pregnant women were less liable than others to bad effects from it. Whipple studied its effects upon pregnant bitches, and found their livers as susceptible as those of the nonpregnant, but to his surprise the fetuses, and also newborn pups up to three weeks of age, suffered no liver damage. Ingeniously conjecturing that this immunity is somehow related to the presence of nucleated red blood cells in the blood-forming spaces of the fetal liver, he and a student tested various animals whose red blood cells are nucleated in adult life—pigeon, frog, and terrapin—and found, as his hypothesis predicted, that their livers too were immune to chloroform poisoning. There he left the matter, as one of the numerous facts of unknown significance that science files away for future consideration.

The work on experimental damage of the liver suggested an investigation of various methods of detecting impaired liver function in human disease and measuring its extent. This resulted in several papers published jointly with Paul W. Christman, Beekman J. Delatour and Vergil P. Sydenstricker, medical students destined to become prominent internists, after which he left that field to the clinicians.

Jaundice resulting from chloroform poisoning posed a particularly important question. It was generally thought that the bile pigments are derived solely from the hemoglobin of red blood corpuscles, and that this transformation occurs, under normal conditions, only in the liver. From his previous experiments Whipple had reason to doubt this, and could now attack the problem by use of the Eck fistula technique he had learned from Hans Meyer in Vienna, by which blood from the intestines is shunted past the liver. In this study he first had the collaboration of an able medical student, Charles W. Hooper, who was to work with him for some years to come, sharing in his most exciting investigations. By combining an Eck fistula with ligation of the hepatic arteries, they could exclude practically all the blood from the liver, yet hemoglobin injected into the circulation was converted into bile pigments within an hour or two. Even if the circulation of the spleen and intestines was also cut off, a similar conversion of hemoglobin to bile pigments still occurred, evidently by the breakdown of hemoglobin in the bloodstream. Whipple and Hooper noted, however, that a dog with both an obstructed bile duct and an Eck fistula will develop jaundice to a much less degree than a dog with similarly obstructed bile duct and normal blood circulation through the liver. In other words, although the formation of bile pigments from hemoglobin can occur under experimental conditions without the aid of the liver, under ordinary conditions of life the liver must have a constructive role of some sort in forming bile pigments, as well as the accepted eliminative function which depends on the destruction of red blood cells containing hemoglobin. We shall find Whipple and Hooper continuing to study this subject in future years. It was, in fact, directly on the line of progress toward the work on hemoglobin production that won a Nobel Prize.

Whipple's interest in the strange phenomenon of coagulation of the blood stemmed from three roots—his autopsy work and experiments in Panama on hookworm anemia and blackwater fever, the hemorrhagic lesions he had observed in chloroform poisoning, and autopsies of several persons who died of hemorrhagic diseases. To understand what had gone wrong in these cases he had to study the complex chemical mechanism of coagulation. This took him to the laboratory of William H. Howell, the Johns Hopkins professor of physiology, who was then studying intensively the normal physiology of coagulation. Generously admitted to work with Howell in his private laboratories on Sundays, when they could be free of interruptions, Whipple gained from Howell all the inspiration he had missed in his classes as a student, and learned to admire and adopt his simple but very accurate laboratory procedures. Whipple's three papers on clotting factors in hemorrhagic disease, published in 1912-1914, attempt to answer the problem in terms of Howell's theory of the coagulation mechanism.

One of the most distressing of the diseases Whipple studied is *melena neonatorum* or hemorrhagic disease of the newborn, in which intractable bleeding occurs from the whole lining of the intestines and other vascular surfaces of the body. Describing his findings in a case of melena neonatorum, in a paper published in 1913, Whipple was the first to show that this disease is characterized by a serious deficiency of the clotting factor prothrombin. His discovery, which for a long time attracted no attention from pediatricians, received due credit in 1939 when Hendrik Dam, discoverer of vitamin K, and other workers found that prothrombin deficiency results from a lack of vitamin K. Putting together the facts observed by Whipple and by Dam, pediatricians now treat hemorrhagic disease of the newborn successfully with vitamin K.

In 1911 two thoughtful Baltimore surgeons, Harvey B. Stone and Whipple's classmate, Bertram W. Bernheim, came to him with the story of a baffling experience they had when trying to help a biochemist who wanted to obtain pure pancreatic juice and duodenal secretions of the dog for chemical studies. To this end they isolated a loop of the duodenum between ligatures, so that the desired fluids would be free from contamination by intestinal contents. Although they restored the continuity of the intestinal canal, by-passing the isolated loop, the dogs died, for no known reason, within 24 hours. If, however, they made an opening from the closed loop to the surface of the body, so that the fluids drained freely, the dog survived. The two surgeons knew that in human patients intestinal obstruction high up toward the duodenum is fatal if not relieved by operation. Since in their dogs the intestine was not obstructed, the dogs must have died from some cause connected with the closed loop, presumably a toxin formed in its lumen. They deduced therefore that death from high obstruction of the human intestine also results, not from mere blockage, but from a toxin formed in the blocked canal. Six papers published by the team of Whipple, Stone and Bernheim presented a skillfully planned step-by-step attack on this important problem which need not be detailed here. The experiments showed that fluid drawn from an isolated loop will kill another dog when injected into its bloodstream. Further experiments proved that the toxin is produced in the mucous lining of the intestine. Workers elsewhere were also investigating intestinal obstruction, some of whom sharply opposed the toxin theory, claiming that loss of water is the fatal factor. Whipple's group continued their experiments far enough to establish beyond doubt the existence of a toxin. Whipple himself was on the point of identifying the toxin when his work in Baltimore was ended in 1914 by events shortly to be narrated.

By 1913 all this work was bringing Whipple wide recognition. Well entrenched at Johns Hopkins as associate professor under a distinguished chief who depended upon him for executive direction of the department, with a highly productive research program in progress, and getting a fairly good salary by the standards of the time, he was content to stay in Baltimore unless a very desirable post developed elsewhere. At last he felt secure enough to get married. Katherine Waring was in easy reach for consultation on this important question, for since 1911 she had been teaching in New York City and studying singing at Walter Damrosch's Institute of Musical Art (now the Juillard School of Music). Their engagement was announced on Easter Sunday, 1914, and the wedding day was set for the following June. George was already negotiating for an apartment in which to set up housekeeping, when he was startled by a letter from President Wheeler. The University of California was planning to establish a department of research medicine in its medical school in San Francisco, with funds given by Mrs. George Williams Hooper of that city in memory of her late husband, a lumberman and forest-land magnate. George Whipple was invited to organize the Hooper Foundation and to become its director with the rank of professor in the University. At first he was reluctant to make so radical a change, but the opportunity to develop a research-oriented department outweighed his objections. Katharine's enthusiasm about going to California to live helped to settle his mind.

They were married at the Waring home in Charleston on June 24, 1914. The official temperature that day reached 101°, but half a hundred guests in the sitting room and hallway, and the negro servants peering through a doorway, saw the bride composed and beautiful in her wedding dress overlain by fine old rose point lace which had belonged to George's Grandmother Hoyt, and ornamented with three antique topaz brooches worn 100 years before by Katharine's great-grandmother Bentham. By George's own report he had "paralysis agitans of his knees and a husky voice." Incredible as it may seem, this was the first wedding he had ever attended; a deep-seated dislike of solemn ceremonies had kept him away from all such rites. The best man was Tom Sprunt of Johns Hopkins, who had first introduced the couple. Among Katharine's wedding presents was an etching from Dr. Welch and another from seven members of the Johns Hopkins department of pathology. Letters of congratulations came from every place where George had worked; from Yale and Johns Hopkins classmates, from William C. Gorgas and Samuel T. Darling, Milton Winternitz and Richard Pierce; from friends in Baltimore society and the Hugh Stewarts at Pitlochry;

from Hans Meyer, Wiechowski and Froelich, Simon Flexner and Benjamin Ide Wheeler.

The wedding tour took them to Savannah and thence by S. S. *Nacoochee* to Boston, where Anna Whipple, who had not ventured into the heat of Charleston for the wedding, was eager to meet the wife that George had chosen. George's uncles, Sherman and Amos Whipple, anxious to know his charming bride and to welcome her to the family before he took her to the far west, did the honors of Boston and vicinity most hospitably for several days. The rest of the honeymoon was spent camping on the shore of Lake Winnepesaukee. Resuming their travels, George and Katharine were in Boston August 4, where Harvey Cushing, now professor of surgery at Harvard, won Katharine's heart by presenting her with orchids. At New York, the next day, Peyton Rous took her and a friend to a roof-garden restaurant while George visited friends at the Rockefeller Institute. In Baltimore there was a grand reunion of the wedding party, followed by hasty packing of George's effects; at night the newlyweds sat outdoors on the Johns Hopkins Hospital "bridge" in the warm summer air, looking at the full moon. On August 8 they left for Chicago to catch the Overland Limited for San Francisco.

CHAPTER

4

# WESTWARD, LOOK, THE LAND IS BRIGHT

HOUSEHUNTING in San Francisco is likely to be a distracting business for newcomers from the East, dazzled by the extent and variety of the city's residential quarters and the magnificence of its setting; but by October the Whipples found a pleasant, small apartment at 2298 Baker Street, on a hillside overlooking the Golden Gate, with Mount Tamalpais as the distant backdrop of a spectacular vista over the Marin peninsula and San Francisco Bay. Below them in the foreground lay the northernmost part of the city, to which the Panama-Pacific Exposition, then under construction, added a bright and busy scene. It was a good time of the year in which to begin home life in California. September and October are San Francisco's summer. In this blessed season the chilly ocean fogs which had hidden the sun during most of the Whipples' first months in the city, no longer pushed, every morning, through the Golden Gate and over the mountains to the north and south. The hillsides of Marin County were bone-dry, browned by seven rainless months, and would not turn green again until the rains began in November. Yet, looking from their sitting-room windows across the water to the canyons of Tamalpais and its foothills, the Whipples could see live oaks, manzanitas, and bay trees in narrow tongues of green shade pointing upward from the valleys, and tempting outdoors-loving folk to long rambles in the redwood aisles of Muir woods and on to quiet Bolinas Lagoon. But such outings were for week-ends only; on working days, while Katharine was about the wifely business of making the apartment into a home, George was getting acquainted with the University of California and sizing up the task he had undertaken.

Mrs. Hooper's gift of the Hooper Foundation, whose laboratories he was to organize, had been stimulated by personal experience of the need for research on disease and of its potential benefits. In his later years George Williams Hooper suffered from myxedema, a chronic disease resulting from deficient activity of the thyroid gland. The nature of this ailment had only recently been recognized; Mr. Hooper's case was in fact one of the first in California to be correctly diagnosed and treated. Thyroid tablets were not yet available; Hooper's very competent physician, Dr. George H. Ebright, had to supplement his patient's diet with fresh sheep thyroids from the slaughter-house. When the doctor informed him that he owed the relief thus obtained to recent discoveries in endocrinology, Mr. Hooper, who had no heirs but his wife, began to think of dedicating his fortune to the advancement of medical research. After his death in 1912, Sophronia Hooper offered to give the University of California redwood timberlands conservatively valued at $1,000,000, the income from which was to maintain an institution defined as a "school of medical research." The George Williams Hooper Foundation, she further stipulated, was to be located in San Francisco and conducted as a department of the University of California.

That the projected institute was described as a school reflects the principal weakness of medical education in San Francisco at the time, for such a designation implied that the clinical division of the University's medical school, situated in that city, was not itself a center of medical research. This implication was indeed correct; for neither in the rather imposing building of the medical school, erected in 1897 on windy Parnassus Heights, nor in the small hospital that stood beside it, were there any facilities whatsoever for experimental investigation. At the time of Mrs. Hooper's gift, the medical faculty was in a curiously divided and unbalanced state. The elevation of medical education to full university status, which the Johns Hopkins University had achieved at one stroke by creating a new medical school, was for the University of California a slow process, begun about 1898, far from complete in 1913-1914, and fraught with difficulties resulting from its history. Its medical school had grown out of a small privately owned institution, founded in 1864 by a pioneer doctor, Hugh H. Toland, which the University took over in 1873. University affiliation, however, had very little effect on clinical teaching. The San Francisco part of the school largely conducted its own affairs, and kept the chairs of medicine, surgery, gynecology and obstetrics filled by members of the local medical profession in active private practice. On the other hand, the preclinical subjects (anatomy, physiology, biochemistry, pharmacology, and pathology) which had been taught by men of the same type, were gradually taken out of their hands early in the twentieth century. The University administration, presumably looking forward to concentrating its medical school on the main campus at Berkeley, began in 1899 to build up preclinical departments both in Berkeley and in San Francisco, under full-time investigators and teachers chosen, as in other fields of learning, because of demonstrated experience and competence measured by national standards. Alonzo E. Taylor, later distinguished as a nutritional chemist, was professor of pathology and physiological chemistry at San Francisco from 1899 to 1910, when he left for the University of Pennsylvania. A brilliant teacher, much appreciated in the University, he did not influence the clinical men among whom he worked. Joseph Marshall Flint, who had worked under Mall at Johns Hopkins, was professor of anatomy from 1901 to 1907. In 1902, President Benjamin Ide Wheeler brought Jacques Loeb, a pre-eminent experimenter, to the Berkeley chair of physiology, built a seaside laboratory for him at Pacific Grove, and held him until 1910, when he joined the Rockefeller Institute for Medical Research in New York.

After the San Francisco earthquake and fire of 1906, the teaching of all preclinical subjects except pathology in San Francisco was discontinued, and thenceforward all the medical students took their preclinical work in Berkeley. Frederick P. Gay, Alonzo Taylor's successor, a Johns Hopkins medical graduate with postgraduate training under Simon Flexner at the University of Pennsylvania and in Jules Bordet's laboratory at Brussels, taught bacteriology and an introductory course in pathology, which was continued in San Francisco by members of his department. When George Whipple began his association with the University as a member of the San Francisco group, the Berkeley division of the medical faculty included Samuel S. Maxwell, who had come from Harvard to succeed Jacques Loeb, and T. Brailsford Robertson, one of Loeb's California Ph.D's, in charge of biochemistry and pharmacology. Flint had left to become professor of surgery at Yale, but within a year after Whipple's arrival, President Wheeler secured for the chair of anatomy a native son of California, Herbert McLean Evans, most brilliant of Mall's pupils. Under these able men and their small but well-chosen staffs, teaching and research were carried on concurrently.

In San Francisco, on the other hand, the busy physicians who constituted the clinical faculty were content with teaching only; they had neither time nor inclination for advancing medical knowledge by experimental investigation, and even if they had, there were no facilities at hand for such research. The most that the best of them could do was to publish case-reports of unusual or specially instructive illnesses, and to tabulate and review their practical experience in print. This is not to say they were not excellent physicians and surgeons, nor unprepared to teach the current practice of their respective specialties. Several of them were highly cultivated men, notably the dean and professor of internal medicine, Herbert C. Moffitt, a high-minded, aristocratic San Franciscan whose native intelligence and Harvard training equipped him to understand and foster the spirit of research that George Whipple brought to the school on Parnassus Heights. Moffitt was aware of the limitations of his clinical faculty, and had begun to build it up by bringing in a professor of obstetrics from Johns Hopkins, J. Morris Slemons, and a professor of pediatrics from Harvard, William Palmer Lucas; but two such appointments were merely a step in the right direction.

Such was the environment in which George Whipple began to organize the Hooper Foundation laboratories. On one hand, he had the opportunity to build in his own way, in an unoccupied field; on the other hand, he would lack the daily moral support of kindred spirits and the friendly intellectual competition that the University's scientific center, ten miles away in Berkeley across San Francisco Bay, could have provided for him and his fellow-workers.

The Hooper Foundation was one of the earliest institutes for general medical research to be founded in the United States. Its only predecessor with equally broad scope was the Rockefeller Institute of New York, chartered in 1901. Two other institutes with similar but less general aims were founded a little earlier than the Hooper Foundation—the now defunct McCormick Memorial Institute for Infectious Diseases (1903) in Chicago, and the Otho S. A. Sprague Memorial Institute (1911), also in Chicago. Among these four pioneer organizations, the Hooper Foundation was unique in being part of a university. John D. Rockefeller's advisers had, in fact, deliberately avoided any such affiliation of the Rockefeller Institute because in 1901 there was no medical faculty in New York City qualified to control a research institute. In planning the Hooper Foundation, President Wheeler's medical advisers, it is said, were William H. Welch, president of the Rockefeller Institute's board, and Simon Flexner, its director. Doubtless it was their shrewd counsel that placed the Hooper Foundation under a separate board of trustees, appointed by the Regents of the University and directly responsible to them. The board consisted of the president of the University *ex officio,* and six other individuals, including the director of the Foundation and at least three other persons of standing in medical science or medical education. George Whipple's board actually included Regent Arthur D. Foster, President Wheeler, Dean Moffitt, Dr. Welch, Dr. Henry S. Pritchett (president of the Carnegie Corporation of New York), and Mr. E. E. Conolley, a lawyer representing the Hooper estate. The Hooper Foundation was thus an independent unit of the University of California, reporting directly to the Regents through the president of the University. Before accepting the directorship, however, Whipple stipulated that he was to be made a member of the medical faculty with the title of professor of research medicine. Through this appointment he became automatically a member of the Advisory Board (i.e. executive committee) of the medical faculty and was able to speak there on matters of joint concern to the School and the Foundation. This arrangement, which kept him safe from domination by the medical faculty, yet assured him stability and support through the University, lasted long past the time of his directorship. Not until 1958 was the Foundation placed under the control of the medical school, by that time a far more sophisticated organization than in 1914.

For the time being the Foundation had a fixed annual income of $50,000 per annum, to which the Regents had committed themselves by certain extraordinary provisions of a joint Declaration of Trust signed in 1913 by them and Mrs. Hooper. The redwood lands that constituted the endowment were remote and isolated, not yet developed for timbering operations, and consequently were producing no income at all. Moreover, they were encumbered by a mortgage of $307,500. The Regents, accepting an optimistic estimate that the lands, nominally valued at $1,000,000, were actually worth twice that sum, agreed to assume the mortgage and not to sell the lands at less than the stated value during the next four years. Meanwhile they undertook to provide from University funds, in lieu of the potential income from the endowment, $50,000 per year (5% on $1,000,000,) for the operating expenses of the Foundation. These payments and the costs of the mortgage were to be charged against funds receivable from future sale of the lands, subject to 5 per cent interest on the money thus advanced. This agreement meant plenty of trouble in a not too distant future; meanwhile, however, under the Regents' pledge George Whipple could budget his expenses adequately for an indefinite period. He was given a building, moreover, in which to set up his laboratories, for the Regents' agreement included the provision of suitable housing. Behind the Medical School building on Parnassus Avenue, against the wooded hillside, stood a substantial three-story brick building, about 90 x 40 feet in ground plan. It was originally erected for the School of Veterinary Medicine, but had never been used because the veterinary faculty was started at Berkeley in 1908 instead of at San Francisco and was afterward transferred to the College of Agriculture at Davis, California. With some alteration this building would serve very well as a medical research laboratory.

Meanwhile the most important consideration was the creation of a staff. Whipple had definite ideas about the fields of research to be cultivated. His own investigations of the physiology and pathology of the digestive tract, including the liver, and of blood formation, were of course to be pursued and expanded, and for these he must recruit assistants. The first of them he brought with him from Baltimore, Charles W. Hooper (not related to the donors of the Foundation), who, as told in the previous chapter, had taken part in Whipple's studies on the bile pigments while still a medical student. Taking his M.D. degree in June, 1914, he joined the Hooper staff that fall, to George Whipple's great satisfaction.

Whipple's outlook, however, was naturally now far wider than his own area of research, for Mrs. Hooper and her advisers had included in their stated aims the whole of medicine and hygiene. Considerable delimitation of these broad fields was obviously necessary. Since the Rockefeller, McCormick and Sprague Institutes were intensively studying the common infectious diseases, the Hooper Foundation need not enter that field. Tropical and exotic diseases, on the other hand, offered inviting opportunities. San Francisco is by no means a tropical city, in spite of the palm trees on some of its streets, but it has a warm hinterland. Because of its geographical situation, it had developed extensive trade with the Orient and the South which made it a likely port of entry for tropical and oriental diseases. Malaria was endemic in certain areas of the Bay region. In 1899 bubonic plague had broken out in San Francisco's Chinatown. The Hooper Foundation was evidently in a strategic position to take up investigations of the bacteriology, pathology, and public health aspects of such potential invaders.

A man ideally adapted for such a task was already at work in Berkeley. Karl Friedrich Meyer, born at Basel in 1884, and trained at several European universities, had spent a couple of years in South Africa as pathologist to the Transvaal Department of Agriculture. Coming to the United States he rose rapidly to a professorship in the University of Pennsylvania's School of Veterinary Medicine, and was then called by F. P. Gay in 1914 to the department of pathology and bacteriology at Berkeley. Whipple's invitation to Meyer to join the Hooper Foundation and to do his research there while continuing to teach at Berkeley, as might have been expected won only reluctant consent from Gay, but gave Whipple a stalwart, alert, wide-ranging colleague of inestimable value to the new enterprise. Within a few years Meyer gradually dropped his Berkeley connections, spending his whole time at the Hooper laboratories. Another competent man, Ernest A. Walker, Chief of the Biological Laboratory of the Phillippine Bureau of Science, wrote from Manila asking for a place in the Hooper Foundation, and on the strength of his Harvard training and long experience in bacteriological work in Boston and Manila, was promptly appointed.

These four men, Whipple, Meyer, Walker and Hooper, constituting the whole staff at the start of the academic year 1914-1915, busied themselves getting the laboratories ready and starting experimental work. They represented two main fields of research, physiology and physiological pathology under Whipple's leadership on one hand, bacteriology and tropical diseases, under Meyer, on the other. These remained, as long as Whipple was at the Hooper Foundation, the major areas of investigation. As the staff grew larger, newcomers (except for a few guest investigators working on problems of their own) attached themselves to one or the other of these divisions. Whipple felt that medical chemistry also should be well represented in the laboratories. Aiming high, in September, 1914, he offered a senior appointment to Donald D. Van Slyke, assistant to Phoebus A. T. Levene at the Rockefeller Institute, but Van Slyke's promotion just at this time to the post of chief chemist to the Hospital of the Rockefeller Institute held him in New York, where he has had a distinguished career. Rudolph A. Kocher, a biochemist trained at Johns Hopkins Medical School, joined the Hooper staff in its first year, but left after a year or two. Subsequent efforts to find a promising biochemist were not highly successful and biochemistry never acquired a major place in the Hooper Foundation, although of course its methods were applied in many investigations.

Karl Meyer recalls that when George Whipple first took him through the old veterinary building, Whipple shuddered at the thought of all that had to be done to adapt it to its new use, but the building eventually proved more suitable than it first appeared. Whipple removed an outside double stairway leading to a main entrance on the second floor, substituting a plain door at ground level. Whatever sacrifice of architectural values this change occasioned, it saved space formerly occupied by the entrance lobby for valuable use as a library. For the postmortem pathological work he meant to undertake, Whipple installed an autopsy room at the west end of the ground floor, as near as possible to the hospital. To the east he set aside space to be used by junior research workers he was planing to recruit. A large room at the back, occupied by horse stalls, relics of the veterinary school, was converted into a cage room for small animals. A small new building to house dogs was constructed on the slope back of the main building. The second floor housed a chemical laboratory and a small pathology museum to be filled with instructive specimens from the autopsy room. For the research laboratories—the heart of the institute—Whipple chose the top floor, which was a kind of attic. This he cut up into laboratory rooms, separated by partitions which could be no more than seven feet high because of overhead skylights. Whipple felt, however, no concern about the open space above the partitions, through which all the sounds and smells created by a dozen busy experimenters drifted into their colleagues' rooms. In his view scientists, young and old, should work together in harmonious intimacy, and if they had their minds on their work need not give vent to thoughts or emotions too private for general circulation. These rooms, simply furnished but amply equipped with research apparatus and instruments, adequately met the needs of workers in physiology, pathology, bacteriology and parasitology. Whipple took the east rooms, Meyer and Walker the west end of the floor.

During the construction of the laboratory building George Whipple had his first experience of the restrictive practices of labor unions. Carpenters at work in the building threatened to strike because one of them noticed an animal caretaker saw off a piece of board and nail it to the wall as a shelf for drinking cups. Under advice from the Buildings and Grounds office of the University Whipple had to order his own employees not to touch the fabric of the building with carpenter's tools while the union men were about. This experience awoke all his individualistic Yankee spirit and left him with a critical attitude toward union labor that flared up again a few years later when he was presiding over an infinitely larger construction job.

By the first months of 1915, when the building was ready for occupation, the First World War was making laboratory apparatus and chemicals very scarce. Karl Meyer remembered that F. P. Gay's storerooms in Berkeley contained surplus chemicals left behind by Alonzo Taylor, and that many pieces of glassware and apparatus used by Jacques Loeb remained in the attic of Brailsford Robertson's laboratory. Rummaging through these deposits, Whipple and Meyer came away with treasures that went a long way toward supplying their needs. The Hooper Foundation of course reimbursed the Berkeley departments, but Robertson, who seems to have been away at the time, wrote Whipple a pained letter protesting the irregularity of the proceedings, nor did Gay, though always a courteous gentleman, fully relish the new institute's requisitioning of his reserve chemicals as well as of Meyer, his right-hand man.

By the spring of 1915 the senior staff men had their work under way. Whipple resumed his study of intestinal obstruction, with the aid of several new associates recruited locally. With Samuel H. Hurwitz, who had worked with him as a Johns Hopkins medical student, and William J. Kerr, who came from Harvard on a Sheldon Traveling Fellowship, he began to look into the formation of the proteins of the blood plasma. Above all in importance, as it turned out, he and Charles Hooper took up again their studies on the bile pigments, which were soon to open up leads of great significance. These investigations of Whipple's immediate group will be described fully in the next chapter. For the present let us continue the general story of the Hooper Foundation, how it was built up and what it accomplished as an organization.

Karl Meyer lost no time in beginning work of immediate service to the public health, when he and Ernest Walker at the request of the California State Board of Health made a brief field survey of the incidence of malaria in the upper San Francisco Bay area. In the laboratory, helped by several Fellows and other collaborators he made a long series of studies of disease-causing organisms of the typhoid and paratyphoid groups, and of *Brucellae,* a group of organisms one of which causes contagious abortion in cattle and another Malta fever in man. His great opportunity for public service came in 1920, when extensive outbreaks of a most dangerous kind of food poisoning, botulism, occurring in various parts of the country, were traced to canned ripe olives processed in California. There will not be space here to narrate in full Meyer's successful effort, at the invitation of the Canner's League of California, the National Canners' Association, and the California Olive Association, to stop this disastrous food infection and prevent it in the future. Not much was known about the physiological characteristics of the infecting organism, (*Clostridium botulinus*); for example, what conditions of oxygen tension and acidity-alkalinity balance favor its growth; how to time the sterilization in order to prevent the survival of spores, and similar questions. By prompt and thorough laboratory research Meyer worked out these problems basic to the manufacturing process, then with the assurance founded on this hard-won information, and with great political skill and determination, secured legislation necessary to enforce bacteriological control in processing olives. Even after these regulations were set up he had to inspect the canneries to make sure the more recalcitrant packers were obeying them. J. C. Geiger, an experienced officer assigned by the U. S. Public Health Service to aid Meyer, took an active part in both the bacteriological research and the field work. The standards they laid down were applicable to the protection of other foods, besides olives, from botulinus infection. As a result of Meyer's work public health authorities were able in 1940 to state that since 1925 no outbreak of botulism had been caused by factory-canned foods processed in the United States.

This was the beginning, for Meyer, of a distinguished and most useful career as a public health bacteriologist of national standing, which brought him many honors and greatly helped to establish the reputation of the Hooper Foundation. A number of bacteriologists, including especially the competent Hilda Hempl Heller, worked alongside of Meyer on problems related to his own. Among these were two or three dentists, whose rather elementary investigations no doubt helped to make George Whipple aware of the need for dental research, to which he afterward at Rochester gave great impetus. A pediatrician, C. Charles Fleischner, who assisted Meyer in the work on *Brucella,* did a great deal to win the confidence of local pediatricians and dentists in the Foundation's bacteriological researches.

Ernest A. Walker was a quiet, diffident, rather restless man, given to working alone. He devoted himself largely to the bacteriology and parasitology of certain tropical diseases, including leprosy, leishmaniosis, and amebiasis. His thorough familiarity with amebic dysentery made his counsel useful to physicians. Walker, disappointed by the scarcity of cases of tropical disease, suitable for his studies, in California, made a long visit to the Amazon basin in 1916-1917. Returning to the laboratories, he carried on an extensive study of the therapeutic action of chaulmoogric acid derivatives in leprosy and tuberculosis, based on folk-knowledge of chaulmoogra oil as a treatment for leprosy; his results, though more or less promising, were rendered obsolete by the introduction of effective antibiotics.

To make a beginning in biochemical research, even though he could not tempt Van Slyke to join him, Whipple appointed two medically trained biochemists from Johns Hopkins. Rudolph A. Kocher made a promising beginning with a chemical study of cancer tissue. Unfortunately the newspapers exploited this work because of some over-hopeful accounts of it that got about. Later he did good work on protein metabolism, but after a year left the Hooper Foundation in pursuit of a war-time project for making alcohol from sawdust. The other appointee, Alice Rohde, also stayed but a short time, working on protein metabolism. The most significant contribution to biochemistry from the Hooper laboratories was that of Carl L. A. Schmidt, of the Berkeley department of biochemistry, for whom Whipple set up a fellowship for several years, enabling him to conduct extensive investigations of a varied nature related to Whipple's interests and those of F. P. Gay and T. Brailsford Robertson.

In 1916 the Hooper Foundation acquired an enthustistic and loyal worker when Walter C. Alvarez, a medical graduate of Stanford University, with postgraduate training at Harvard and a varied experience as a physician in Mexico and California, asked for the privilege of working in the laboratories on a problem of his own. Deeply interested in diseases of the digestive system, Alvarez had given much though to the physiology of the contractions of the intestines, and had developed a hypothesis explaining the action by which the small intestine keeps its contents effectively in motion. He supposed that there is a gradient of various physiological properties, of highest activity at the upper (duodenal) end of the canal and lowest at the ileal end, where the small intestine enters the colon.

Granted an assistantship, Alvarez divided his time between laboratory work in the morning and his medical practice in the afternoon. Rising to an assistant professorship, he remained at the Hooper Foundation for several years. Keeping to the one general problem, and aided by a couple of younger men holding fellowships, he demonstrated by careful experiments the existence of gradients of rhythmicity, irritability, susceptibility to contraction-inducing drugs, and several other measurable properties of the muscular wall of the intestine. His results have become part of the common stock of knowledge about intestinal movements. Undoubtedly the opportunity George Whipple gave this alert, persistent young man to try out his ideas contributed greatly to Alvarez's career as an outstanding gastroenterologist and medical counselor.

Samuel Hurwitz, after a couple of years as a full-time worker in the laboratories, began to devote part of his time to the practice of medicine. Having a special interest in hemophilia, he was very useful to the San Francisco medical profession as a consultant on the diagnosis and treatment of that difficult disease. Other scientifically minded practitioners of medicine and surgery, realizing that at last a place was available in San Francisco where they could carry on research, joined the group as volunteers. Jean Valjean Cooke, pathologist to the University of California Hospital, and William J. Kerr, previously mentioned, worked with Whipple's group; Frank Hinman, Johns Hopkins-trained urologist, with Whipple's and Karl Meyer's advice tried out various ideas of his own about hydronephrosis, a common problem in urological practice.

As soon as the Hooper Foundation laboratories were in running order, George Whipple began to take an active part in the advanced teaching of pathology in the medical school. At Berkeley, F. P. Gay's department had no facilities for postmortem examinations, but certain hospitals in Berkeley, Oakland, and San Francisco allowed autopsies to be done before a class. The 75-bed hospital on Parnassus Heights provided a meager autopsy service under Glanville Y. Rusk and Jean V. Cooke, members of Gay's staff assigned to the University Hospital, who were glad to turn over some of their autopsies to the Hooper Foundation. The opening of the large new University Hospital in 1915 considerably increased the postmortem service. Whipple was thus able to conduct a weekly clinical-pathological conference of the kind with which he had been familiar at Johns Hopkins since his student days. At such meetings, held in the autopsy room, the pathologists and the clinicians jointly discuss some of the more instructive or more puzzling cases which have come to autopsy during the past week. One of the hospital physicians, usually a member of the resident staff, opens the proceedings with an account of the signs and symptoms of the disease and the results of whatever special examinations and tests were made. He exhibits relevant charts and x-ray films. Finally the diagnosis, as made on the ward, is stated, and if there were doubts or disagreements about the nature of the case, each physician who examined the patient may, if he chooses, explain his diagnosis. The clinicians having committed themselves, the pathologist who performed the autopsy reports his findings. The diseased organs which he has preserved under refrigeration are exhibited. The true state of affairs having thus been revealed, there is a free-for-all discussion which brings out the instructive features of the case and if the medical diagnosis was incorrect or incomplete, points to the reasons for error. The pathologist who conducts these "CPC's," as they are called in hospital jargon, must be very sure of himself and a master of tact, for he may at any time face the embarrassing necessity of challenging his clinical colleagues before their own interns and students. Medicine being after all not an exact science, even the professors are sometimes puzzled, sometimes wrong. George Whipple had learned how to conduct a CPC from an authoritative performer, William H. Welch, and adding his own canny skill to that of his former mentor, managed to avoid placing blame for mistakes on any one person. Once when his autopsy had proved the Dean himself badly in error, he saved the situation by gently remarking "Well, Dr. Moffitt, it looks as if we were on the wrong track this time." His clinical-pathological conferences, thus skillfully conducted, were not only highly instructive to everyone concerned, but helped to bring the practitioners and the scientists together and to build up a stronger spirit of inquiry in the hospital staff.

George Whipple's boldest innovation at the Hooper Foundation was his creation of student fellowships. He very soon began to miss teaching medical students and the satisfaction, which he had found at Johns Hopkins, of initiating some of the best of them into research. At San Francisco he could not hope to interest students in the same way, because they began pathology in Berkeley, and when they came to San Francisco were at once immersed in a clinical atmosphere which provided neither inspiration nor opportunity to inquire into the basic problems of disease. As a result they never saw pathology as a unified science, combining gross and microscopic studies with experimental research. Those students who in a unified medical school might have chosen pathology as a career, were not attracted to it under the prevailing conditions. Yet the school ought not go on indefinitely recruiting all its professional pathologists from outside. "We must get the younger generation from the Medical School," said Whipple to his colleague Karl Meyer, and to this end invented the student fellowship plan. In October, 1916, having secured the consent of President Wheeler and Dean Moffitt, and having overcome a number of difficulties caused by university regulations, he announced the creation of two fellowships of $600 each, open to students who had completed one and a half years of medical study (which included the regular course in pathology), and tenable at the Hooper Foundation for one year, after which the Fellows would resume regular medical studies with the succeeding class. They would receive advanced training in human pathology including postmortem examinations, and would be expected also to undertake experimental research under a senior member of the Hooper Foundation. The year's work would be accepted in lieu of the internship required in California in qualification for the M.D. degree. Thus for a man intending to go directly into laboratory work after graduation the student fellowship would not lengthen his training.

Successful launching of this plan depended upon its reception by the class then studying pathology at Berkeley. Many faculty members doubted whether any students would risk a venture which meant a radical departure from the traditional curriculum, the breaking of class ties, and for those who meant to practice medicine and must have an internship, lengthening of the curriculum by one year. On the other hand faculty members—especially in the anatomy department—who came from schools where student research was encouraged, and who understood Whipple's aims, supported the plan. The upshot was that several students applied for the fellowships, three of whom—Elmer Belt, Charles C. Hall and Harry P.

Smith—were so highly recommended that Whipple added a third fellowship in order to take all three.

Joining the Hooper staff in the spring of 1917, these young men took on responsible duties as assistants in Whipple's experimental work and after suitable instruction performed autopsies. They attended the clinical-pathological conferences and the weekly staff seminars of the Hooper Foundation, and were—in short—accepted as colleagues in its group of experienced medical scientists. In 1918 Nelson C. Davis, Daniel P. Foster and Irvine McQuarrie were appointed to student fellowships; in 1919 Hubert R. Arnold, G. D. Delprat, Jr., Francis Scott Smyth and Stafford L. Warren; in 1920 Beatrice Carrier, Frank Warne Lee, Karl F. Pelkan and Francis P. Wisner.

These 14 Fellows have done extraordinarily well in the medical profession. Ten of them went into the practice of medicine, surgery, or pediatrics, carrying with them a spirit of independence and critical judgment strengthened by their year at the Hooper Foundation. The pediatrician Karl Pelkan, stating what his student fellowship meant to him, has succinctly answered those who ask what good is training in research to men who are going to be practitioners of medicine:

> The greatest benefit [of his work with George Whipple] was the acquisition of a questioning attitude. "Is this true, and how can I prove it?" This question comes up daily in the practice of medicine and has been of inestimable help to me.

Eight of these ten, Arnold, Belt, Delprat, Hall, Lee, Pelkan, Smyth, and Wisner, settled in California cities, where most of them became prominent in local medical and community affairs. Belt is a leading urologist in Los Angeles, and a bibliophile internationally known for his collection of books pertaining to Leonardo da Vinci. As chairman of the California State Board of Health, he has been influential in the medical affairs of his state. Delprat was president of the San Francisco County Medical Socity in 1945 and Pelkan president of the Santa Clara County Medical Society in the same year. Smyth became professor of pediatrics in the University of California, and later, as we shall see, dean of the San Francisco Medical faculty.

McQuarrie, after long service under George Whipple's deanship in the Rochester (New York) department of pediatrics, became professor of pediatrics at the University of Minnesota, where he trained many young men in his specialty. Foster for many years was chief of the metabolic division of the Henry Ford Hospital, Detroit, Michigan.

Four of the student Fellows went into medical research. Beatrice Carrier Seegal became associate professor of bacteriology at Columbia University, College of Physicians and Surgeons. Nelson C. Davis entered the service of the International Health Board of the Rockefeller Foundation, for which he did important research on yellow fever, malaria and hookworm. At the time of his premature sudden death in 1933 he was Director of the International Health Board's yellow fever laboratory at Bahia, Brazil. Harry Smith went to Rochester in 1924 as George Whipple's senior associate there. In 1930 he was called to the University of Iowa as professor of pathology and in 1945 to the Delafield chair of pathology at Columbia University, College of Physicians and Surgeons. Stafford Warren has continued throughout his career the studies on radiation and its medical effects which he began while a Fellow at the Hooper Foundation. For many years, at Whipple's invitation, Warren directed the department of radiology at Strong Memorial Hospital, Rochester, New York. During the Second World War he held a senior post of great responsibility in the medical section of the Manhattan Project.

Undoubtedly George Whipple's most important contribution through his creation of these student fellowships was to medical education. The preceding paragraphs mention four Fellows—McQuarrie, Harry Smith, Francis Smyth, and Warren, who became full professors of their respective subjects, and one (Belt) who held a clinical professorship. Through the two professors of pediatrics—McQuarrie and Smyth—George Whipple, who in youth gave up pediatrics for pathology, by proxy taught scores of pediatric specialists and teachers. Still more remarkable is the fact that his little group of student fellows provided deans of both of the University of California's medical schools, Smyth at San Francisco from 1942 to 1952, and Warren at Los Angeles 1947-1963. The University's new medical school in the southern metropolis owes much, indeed, to the Hooper Fellows, for one of them, Elmer Belt, through his well-earned personal prestige helped greatly to foster the idea of a medical faculty in the University of California at Los Angeles, and to secure legislative action that made it possible. To Stafford Warren fell the responsibility for organizing the school and directing it as dean during its first two decades. Through these devoted sons of California the benefaction of George and Sophronia Hooper has greatly influenced the teaching and practice of medicine in their state. The Hooper Foundation staff rapidly grew larger. Within two years there were 13 full-time investigators and a dozen volunteer workers representing several departments of the medical school and hospital. Including secretaries, technicians, and caretakers the official family numbered nearly 40 people. By 1920 there were 20 full-time investigators including the student Fellows, 21 volunteers, and eight persons in Karl Meyer's special botulism laboratory. Under George Whipple's leadership these people formed a remarkably close-knit group, enthusiastically sharing each others' interests, and loyal to their director. George Whipple kept a steady administrative hand on everything that went on in the laboratories, as a thrifty New Englander watching the budget down to the last penny. Even his senior colleagues had to get the Director's OK on the details of requisitioned supplies and apparatus, as long as these came from funds for which he was responsible. Yet when the National Canners' Association and other packers' groups put up $30,000 per year for the botulism studies, he gave Karl Meyer a perfectly free hand to spend his fund as he saw fit. His men were but little irked by rigid budgetary control thus tempered by fairness. "He was one of the grandest men to work with I ever knew," said Walter Alvarez, "always kindly, judicious, very fair, and very helpful." Visitors who had known Old-World science in its heyday were charmed by the Hooper Foundation's resemblance to a nineteenth-century European research institute, wth its plain quarters crowded with enthusiastic people working in an atmosphere of free inquiry, under the benign domination of a respected chief.

The entrance of the United States into World War I, in April, 1917, was heavily felt by the universities. War spirit was rampant on the Berkeley campus, where hundreds of undergraduates in training for commissions were put into uniform and housed in temporary barracks, while middle-aged professors, joining a home-defense battalion, drilled on the greensward with wooden rifles. The administration, fearing that valuable teachers and investigators, fired by rash patriotism, might throw their skills away by hasty enlistment, set up a committee to regulate the faculty's assignments to active duty. With George Whipple representing the medical faculty, the President knew there would be no nonsense; older physicians, essential at home, would be kept from rushing off to the army, while physically competent younger men would be released for field service and helped to find their proper kind of duty.

This sort of common sense was operative also in the Hooper Foundation, whose wartime service, conducted without fanfare, was strictly compatible with its resources. There was little change of personnel, for Whipple's older colleagues were obviously more useful to the nation at home than in military service, while most of the younger men were in categories which the armed forces preferred to have continue their medical work, in order to keep up the supply of trained physicians in case of a long war. At the army's request Whipple, Meyer, Walker, and Hurwitz instructed numerous classes of medical officers assigned to the Hooper Foundation for training in pathology and clinical microscopy, and all the senior staff members gave lectures in army camps and hospitals in the Bay region. Whipple, aided by two of the student Fellows, Belt and Smith, did some experimental work on the treatment of wound shock. Otherwise, the Hooper staff attended to its regular business as far as possible under the circumstances.

On the home front Whipple was fighting a battle with enemies of medical investigation that laid upon him a heavy burden of work and of abuse. When he first went to California he knew that sooner or later the Hooper Foundation would have to face an attack by organizations opposed to the use of animals for medical research. Such opposition had been gaining strength in the United States since 1897, when a bill forbidding experiments on animals was introduced in Congress. When this was defeated after a campaign brilliantly led by William H. Welch, the antivivisectionists began attempts to get similar bills adopted by the state legislatures. The Rockefeller Institute of New York came under heavy fire as soon as its leadership in experimental investigation became generally known. Its officers had to fight desperately hard from 1907 to 1911 against legislation that would have prevented much of its work. Well aware of a similar threat to his own enterprise, Whipple at the beginning of laboratory work on Parnassus Heights got in touch with the San Francisco Society for the Prevention of Cruelty to Animals, inviting its agents to visit and inspect the laboratories at any time. To assure the University's support he asked President Wheeler to come over from Berkeley to inspect the new quarters for dogs he had built on the hillside. For defense in time of need, he maintained contact with a national society for the protection of experimental research headed by the eminent Harvard physiologist Walter B. Cannon, and laid in a supply of pamphlets, put out by the American Medical Association, on the need and justification of animal experiments.

These steps were by no means taken too soon. In the spring of 1915 the expected bill against animal experimentation was introduced in the California Legislature. Rallying to the fight against it the leaders of Stanford University Medical School and other prominent physicians and biologists throughout the state, Whipple called also upon influential Eastern physicians, including Simon Flexner, Eugene L. Opie, and J. Whitridge Williams, to write or telegraph to the legislators. He went to Sacramento in person to address the committee to which the bill had been referred, and gave talks at Stanford and other institutions. Meanwhile the antivivisectionists began a publicity campaign of a despicable sort already familiar in the East, the brunt of which fell upon the Hooper Foundation as San Francisco's principal center of animal experimentation. Everyone who advertised a lost dog received an anonymous telephone call advising him to inquire for his pet at the Hooper Foundation. Whipple was accused in the newspapers of knowingly buying stolen dogs, and (in spite of frequent inspections by the SPCA) of cruelly treating dogs and cats in his laboratory. Pressure on the Legislature was sufficient to get the bill passed by both houses, but Governor (later U. S. Senator) Hiram Johnson proved his courage and good sense by vetoing it.

In February, 1916, the Hooper Foundation found itself at the center of a tempest raised by local newspapers, when several people, during a period of some weeks, reported having found lost pets at the laboratory kennels. They got their dogs back unharmed, of course, but the hostile papers made the most of such incidents. Eastern medical schools had long been harassed in the same way. There was nowhere any civic control of the supply of dogs for research, since the humane societies, which almost everywhere held contracts for the collection and destruction of stray animals, were opposed to their use for research. The medical schools were thus forced to buy animals from dealers, who could not always be trusted not to pick up stolen dogs. Laboratories of course protected themselves as much as possible by keeping all dogs for a fortnight or longer before using them, but merely to have someone's pet dog reclaimed now and then was deeply embarrassing. George Whipple, like many other laboratory directors, had to learn the hard way to avoid this difficulty by purchasing no animals locally.

Late in February there was more excitement. The San Francisco *Chronicle* of Sunday the 27th carried on the front page a two-column headline "District Attorney To Probe U. C. Dog Traffic," above pictures of little girls holding in their arms pet dogs supposedly reclaimed from laboratories. There was as yet, however, no personal abuse of medical leaders. The *Chronicle,* affecting fairness, printed Whipple's calm, frank statement explaining the precautions he had always taken against buying animals without confirmation of the seller's ownership. Whipple responded by declaring he would purchase no more dogs in San Francisco. On the 29th the *Chronicle* with lurid exaggeration reported "an almost endless procession of men and women, boys and girls, winding its way up the hill to the laboratory yesterday in search of lost pets."

In spite of the newspapers' incitement to an official investigation the District Attorney kept his head, and in fact the first sensible word from a public source came from one of his assistants who suggested a city ordinance to provide qualified laboratories with stray dogs from the city pound. This idea may have been implanted by Whipple; a state-wide bill of that sort had recently been proposed in Pennsylvania, and though unsuccessful, obviously offered a solution acceptable to all but convinced antivivisectionists and the humane societies that had a vested interest in the collection and destruction of stray animals. Even if the California public was not yet ready for so drastic a reform, the proposal would at least serve as a counteroffensive against the rising demand for repressive legislation. By November, 1916, Whipple was at work on a draft along the lines of the Pennsylvania bill.

On March 1, 1917, with another session of the Legislature approaching, the attack began in a way already familiar to the Rockefeller Institute, Johns Hopkins Medical School and other Eastern institutions. A woman vice-president of the San Francisco Antivivisection Society handed to the newspapers an affidavit of an employee of the Hooper Foundation (who had recently been dismissed for incompetence) alleging cruelty to dogs in the laboratories. Whipple replied to these charges with a dignified statement in the *Daily News* of March 6, in which he outlined the procedures of experimental research and the precautions taken to avoid suffering, including complete anesthesia and thorough after-care of the animals.

About March 12 his counterattack began. Assemblyman N. J. Prendergast introduced the bill Whipple and his legal advisers had prepared, requiring city pounds to supply dogs, under proper restrictions, to recognized research institutions. Up to this point newspaper comment had been more or less decent, but now the lid was off. On March 16 the *Daily News* accused Whipple of favoring the bill merely because it would save money. On the same day it printed a sensational and biased account of a reporter's visit to the Hooper animal quarters. On the 20th another affidavit by a discharged and disgruntled employee appeared in the papers. The next day, March 21, the Assembly's Committee on Medical and Dental Laws, to which the bill had been referred, held a public hearing. For this occasion Whipple and his chief ally, Dean William Ophüls of Stanford University Medical School, had enlisted the powerful support of Ray Lyman Wilbur, president of Stanford University; a prominent Regent of the University of California, Chester A. Rowell; and two well-known clergymen, Father Ramm and Rabbi Meyer. The SPCA representatives, however, got control of the meeting, played up their own speakers, and left only a little time for these supporters of the bill. Nevertheless favorable sentiment was beginning to appear in the Legislature and to meet this the opposing newspapers broke into open abuse. A headline in the *Daily News* on the 24th called Whipple the "College Vivisector," and two days later an editorial in the same paper referred to "Prendergast's bill for cutting up pets alive." In spite of these tactics the Committee on Medical and Dental

Laws on March 28 reported favorably on the bill by a vote of 8 to 1, and on April 1 the Assembly passed it, 47 to 25. What the Senate would have done is impossible to say, for by the time it received the bill great international events were in progress; Congress was debating President Wilson's call of April 2 for a declaration of war against Germany. The State Senators had no heart and little time for local affairs, and at the end of April killed the Prendergast bill by routine referral to a committee of one. Whipple had scarcely hoped for anything more than to put the enemy on the defensive; this the bill had done. Though neither side knew it, the antivivisection movement in California had passed its peak.

Sniping continued, however. In September, 1917, Whipple had to go to police court to defend a man who had shipped him some dogs from Merced, against unfounded charges of improper crating. That fall there was an abortive attempt to get a local ordinance against the use of dogs in San Francisco County. The fight was renewed at Sacramento in 1918 and 1919, but by this time medical scientists had the enormous prestige of the Army and Navy Medical Corps to support them, and the goodwill of a public educated by wartime conditions to respect the achievements of research. The usual antivivisectionist bills were defeated. Losing hope of success at Sacramento, the antivivisectionists in 1920 forced a state-wide popular vote under the California initiative and referendum act. This of course made necessary an extensive campaign of public enlightenment. Whipple found himself once more in the thick of the fight. From early September until Election Day, November 12, he had to spend almost all his time writing and telephoning to people whose help was needed. Karl Meyer, who far more than his chief enjoyed rough and tumble debate, took much of the burden of speechmaking before chambers of commerce, women's clubs, farmers' associations, and similar groups. In a store-room of the Hooper Foundation there are several file boxes crammed with the correspondence of these two men during the 1920 campaign. The vote on the proposed amendment to the State Constitution, prohibiting experiments on animals, was a resounding *No,* by 537,130 to 272,288.

This was George Whipple's last round of the fight in California. Through the whole five years of it his laboratory had been the chief target of misstatements and abuse. It is truly ironical that this scientist whose work was threatened, his time wasted and his energies sapped, was all this time approaching a discovery, achieved solely by humanely conducted experiments on dogs, which was to remove from thousands of human beings the curse of a dread disease, pernicious anemia.

In his *Autobiographical Sketch* George Whipple tells us that his marriage and the assumption of family duties, plus the problems of a new department, were stabilizing factors by which, he says, "My research program was sharpened in focus and my drive was strengthened." This may seem an odd statement from a man whose career had never shown the least sign of instability, nor even of uncertainty or indecision once he had made sure that his career lay in medical research. No doubt he meant to say that the mingled satisfactions and stresses of domestic life and executive work had thoroughly tested his inherent stability and revealed it to himself, giving confidence to face the most uncertain of all his ventures, that of the scientist staking his career upon the precarious hope of achievement in research. To build up a new institution, to make his place in the medical faculty, to fight the enemies of medical progress had called for steady devotion and understanding. So too had married life, for the two young people had undertaken to build a durable marriage upon foundations of extreme diversity in temperament and background, and were spending their first years together under circumstances of strain for him and a good deal of loneliness for her. Many a young doctor's wife can tell a weary tale of family life and social activity giving way to professional duty. The tale may be all the more poignant if the wife has to adjust to life in a new community while the husband is carrying heavy responsibilities for his institution and is at the same time determined to make the fullest use of his own talents in research. A scientist has his work, and if he can carry it on with assured support, among loyal colleagues, he is largely fortified against purely personal stresses. Katharine Whipple, transplanted to San Francisco to take a new role, missed the warmth of friendship and social activity of Charleston and Baltimore and the freedom of college life and of musical studies in New York's metropolitan circles. Yet for these two there were bright hours of companionship in walks on the California hills, and of hospitality from some of San Francisco's finest medical families, notably in the homes of Dean Moffitt and of Wallace A. Terry, professor of surgery. Common interests created strong friendships with some of the rising younger men in the medical school, including especially the surgeons Frank Hinman and Howard Naffziger; John Sperry, a friend of Johns Hopkins days who had settled in practice in San Francisco; and Philip Gilman, George's classmate, now back from Manila. During the Panama-Pacific Exposition of 1915, George and Katharine, alone or with some of these friends, spent a couple of evenings almost every week amid its exciting splendors.

During summer vacations the Whipples went camping in the high mountains, where George could enjoy his favorite sport, fishing. A half-dozen albums filled with his photographs of mountain scenery, of camp life and fellow-campers, and of notable catches of trout and salmon, record these expeditions that meant much to the mountain-born New Englander. In July, 1915, George and Katharine had a "second honeymoon" as he called it, at Lake Tahoe, where George caught some ten-inch trout. In 1916 they visited the Canadian Rockies by way of Banff. The birth of their first child in May 1917 delayed a vacation trip that year until October, when they went to the charming village of Carmel-by-the-Sea, near Monterey. In subsequent summers they were again in the mountains. The Hinmans once accompanied them to Lake Tahoe, where they seem to have had more than the usual tribulations of campers, including a leak of gasoline into the provisions, and a plague of mosquitoes. Yet Frank Hinman retained after 40 and more years a vivid memory of George Whipple down by the Truckee River at sundown, unmindful of the insects buzzing round him, imperturbably fly-casting for rainbow trout, and never failing to bring home fish for supper. In 1919 the summer journey took the Whipples to the Yosemite Valley, and 1921 saw them again in the High Sierras, at Silver Creek.

At home, domestic joys and trials alternated, as in all young families. In September, 1915, George wrote to a friend in Baltimore "We have moved from the millionaire district to a nice neighborhood near the hospital." The house, at 176 Edgewood Avenue, was pleasantly situated on a hillside street, southeast of the medical school buildings and on higher ground, near the edge of Sutro Forest. A year later they bought a lot in Forest Hills, west of Parnassus

Heights, at 2085 Ninth Avenue, where from the designs of an excellent architect they built a handsome house of their own in the French Chateau style. Standing conspicuously at the head of the straight part of Ninth Avenue, the imposing gray stucco house may still be seen a long way off by anyone climbing the gradual slope of the avenue southward. When the house was first built it was alone in the newly developed street, with an unbroken view northward over the Golden Gate and widely also toward the east and west. The Whipples moved into it in February, 1917, and were living there when George Hoyt Whipple, Jr. was born May 4 of that year. Here too was the first home of their daughter Barbara, born June 16, 1921.

Rejoicing over the birth of a son was followed in November, 1917, when he was six months of age, by distress and alarm when the baby boy developed serious symptoms of pylorospasm with acute dilatation of the stomach. The parents had "a horrible week, the worst in my life," as George wrote to his mother, for little Hoyt was near death before and during the operation by Saxton T. Pope, a surgeon called in because of his phenomenal dexterity. Two pediatricians, Vivia Appleton and Charles Fleischner, volunteer workers on George's ever-loyal staff, sat up all night with the tiny emaciated patient after the operation, administering skilled care that helped to save him. This acute surgical phase of the baby's illness was followed by a long stay in the hospital and a difficult convalescence, but at long last the parents had the joy of seeing Hoyt make a complete recovery and grow to sturdy boyhood. For Katharine Whipple, whose health was never robust in San Francisco's climate of frequent fogs and chill winds, the prolonged illness of her first-born child was a severe strain, not quickly relieved.

During these seven busy years in San Francisco George Whipple was himself stricken three times with serious illnesses. In May, 1915, when the Hooper Foundation laboratories were just getting well into action, he had a sharp attack of appendicitis and was immediately operated upon by Wallace Terry. A prompt recovery followed, as would be expected of a sturdy patient 37 years old, in good general condition. When the great 1918 pandemic of influenza swept around the world, he did not escape it. The disease, reaching California rather late in its spread, was very severe there, and because of its tendency to attack young people, raged in the university population with heart-breaking violence. At the Hooper Foundation many people were ill, and one staff member, Marjorie Foster, died. George Whipple's acute attack was followed some months later, in the spring of 1920, by a severe bronchitis and bronchopneumonia that left a badly scarred lung. His convalescence was slow, and as in many cases was accompanied by a trying period of depression. Fortunately he was in the care of able physicians—Moffitt, Kerr, and Alvarez—who had the authority and practical sense to make their strong-willed patient regulate his hours of work and take the exercise he had neglected during long seasons of laboratory and office work. The next summer's camping in the Sierras helped much to clear away the combined effects of infection and fatigue. By September George was fully on his feet and ready for the victorious fight of that year against the antivivisectionist referendum.

Friends of George Whipple's later days, seeing him firm in mind and body and always in complete command of himself, must have been surprised to read, in the *Autobiographical Sketch,* his own intimations of this period of depression. He perhaps wished to warn younger people that even a strong and ordinarily stable man when ill and tired may yield to despondence and anxiety, and yet will recover and again take up the day's work. Whatever scars influenzal pneumonia and its sequelae may have left on his lung, whatever apprehensions lingered in his mind, they made no mark on the record of his scientific achievement. Neither executive duties, nor domestic concerns, nor illness ever stopped the progress of the researches to be narrated in our next chapter, which by 1921 were approaching a climax of discovery.

CHAPTER

5

# SCIENTIST ON PARNASSUS

TO THE NEW LABORATORIES on Parnassus Heights, Whipple brought two lines of research, begun in Baltimore, from which stemmed everything he did in the laboratory thereafter. These investigations, though at first sight quite distinct, were actually related; our account of the work must necessarily weave back and forth between them as did the investigator himself. Each began as a study of the pathological effects of a particular kind of poisoning—or more precisely, chemical intoxication—and each, as it turned out, involved a long, painstaking effort to analyze life processes involving the body's most complex constituents, the proteins. In one case the toxic agent was a simple chemical substance, chloroform, which specifically damages the liver; in the other it was something of unknown nature and extreme toxicity to the whole body, which is formed in the intestinal canal when the intestine is totally obstructed in its upper reaches. The study of chloroform poisoning, as we have seen, had already led Whipple and his associates into a widening series of investigations of jaundice, of the formation of bile, and of the relation of the liver to certain components of the blood, and it was soon to carry them much farther. By noting functions lost through depletion, damage or breakdown of bodily tissues they could ultimately look into the constructive processes of the healthy organism and see how it manages to build, from raw materials in the diet, the essential proteins of the blood and blood-forming organs. To the story of this line of investigation we shall return shortly.

Meanwhile there was urgent unfinished business on hand concerning the other problem, that of intestinal obstruction. In Baltimore, Whipple and his co-workers had found a highly toxic substance in the fluids dammed up in the obstructed intestine. Picking up the work again in San Francisco, the next step was to determine the chemical nature of the toxin. To get enough of it for chemical analysis, Whipple, with F. H. Rodenbaugh, one of his Fellows, and A. R. Kilgore, a volunteer from the department of medicine, prepared a number of dogs with obstructed intestinal loops, from which they collected the crude toxic fluid in sufficient quantity. Several attempts by other workers to identify the toxin had suggested some sort of vague affinity to the proteins or their derivatives. Following up this hint, Whipple and his co-workers found they could precipitate the toxin from the fluid by adding strong alcohol. Purifying the precipitate by standard methods of protein chemistry, they isolated the toxin in the form of a primary proteose; that is, one of a group of substances of complex structure which, when linked together chemically, constitute proteins. Proteoses are made up of peptones, and these in turn of amino acids, the fundamental nitrogen-containing "building stones" of proteins.

If the toxin of intestinal obstruction is indeed a proteose, Whipple reasoned, the experimenter should be able to produce the characteristic toxemia of complete obstruction, in a healthy intact dog, by injecting a proteose solution into his blood stream. This expectation was fulfilled; proteose intoxication thus produced showed symptoms identical with those which Whipple and his colleagues had so often seen in dogs after obstructing the intestine, or after poisoning with the fluid from an obstructed loop: diarrhea and prostration, falling temperature and lowered blood pressure, and finally collapse and death. W. Tileston and C. W. Comfort of Yale Medical School had observed that intestinal obstruction in human patients is accompanied by a high level of noncoagulable nitrogen in the blood, a sign that the proteins of the tissues are breaking down and shedding the resultant chemical debris into the blood. This sign Whipple, Rodenbaugh, J. V. Cooke, and Thornton Stearns found also in dogs poisoned by proteoses. Donald Van Slyke of the Rockefeller Institute, already a great authority on protein derivatives, took a hand in this phase of the study in 1917 when a Traveling Exchange Fellow at the Hooper Foundation. With Irvine McQuarrie, a student Fellow, Whipple found in 1918 that both acute obstruction and proteose injections impair the excretory functions of the kidney; this parallelism was the strongest indication yet obtained that there is an actual toxic substance in the blood during acute intestinal obstruction.

The evidence Whipple and his colleagues assembled during nine years of research in Baltimore and in San Francisco certainly suggested that death in intestinal obstruction results from the formation of a toxic proteose in the lining (mucosa) of the obstructed bowel, and its absorption into the blood stream. Alternative explanations were, however, put forward at the same time and for some years to come. John A. Hartwell of Cornell University Medical College (New York City) claimed that death results from loss of water by vomiting and diarrhea; A. Baird Hastings and his colleagues at the Rockefeller Institute, and others also, believed that the loss of chlorides from the blood is the first step toward death; still others placed the blame upon loss of potassium salts, or upon mere distention of the obstructed bowel. Which of these factors—all of which are present in the patient or obstructed animal—is the primary cause of death is still unknown. As often happens in medical research, however, failure to settle a baffling problem did not mean total loss to either the science or the art of medicine; Whipple and his co-workers learned much about the nature of toxic states caused by infections, x-rays, and other tissue-damaging agents. Later in this chapter we shall come back to their more general studies of tissue damage in intoxications. From all this work in many laboratories, moreover, surgeons have learned that even if the underlying physiology of intestinal obstruction is not understood, they can often relieve the toxemia and get the patient into better condition for operation, by emptying the distended intestine through a duodenal tube.

When Whipple and Charles Hooper resumed in San Francisco their investigation of the formation of the bile pigments, they started from an observation they had published in 1913 (already cited in Chapter 3) that the liver has some sort of constructive role in producing the bile pigments as well as that of merely excreting them. The generally accepted theory was that distintegration of red blood cells in the circulation, as they reach the end of their life span, sets free their hemoglobin, which is brought to the liver and is there changed into bile pigments which are excreted as waste products into the intestine. With this theory Whipple and Hooper took issue, finding it insufficient to explain their observations. They had shown that the liver, though ordinarily the most important place where hemoglobin is converted to bile pigments, is not the only such place; hemoglobin injected into the body cavities (pleural and peritoneal) is readily converted there into bile pigments. On the other hand, they found in their first California experiments that if the blood flowing through the portal system, bringing the products of digestion to the liver, is made to by-pass the liver through an Eck fistula, the excretion of bile pigments is greatly reduced. The normally functioning liver, therefore, must in some way contribute constructively to the formation of these important constituents of the bile. Presumably it prepares, from the products of digestion, something which is chemically antecedent to the bile pigments. Since hemoglobin is obviously such a substance, we can see, looking back, a faint hint here of the most important discovery that was to come from the bile pigment studies, which is that the liver takes part in the building of hemoglobin. In 1916, however, Whipple and Hooper's hypothesis implied only that the liver builds something, not yet specified, which is essential to the formation of bile pigments.

To test this hypothesis, at the Hooper Foundation they prepared dogs by an operation, done under anesthesia, by which an opening (bile fistula) is made from the gallbladder through the abdominal wall to the outside. The common bile duct is tied so as to retain all the bile in the gallbladder, whence it may be collected at intervals through the fistula. Dogs so prepared remain in good condition, contented and lively, if they are properly housed and fed, kept scrupulously clean, and allowed ample exercise. To collect the bile a soft rubber tube is inserted through the fistula and held in place by a binder. A small rubber bag on the outer end of the tube receives the bile. During the daily six-hour period of collection the dogs, tied loosely at their places in the laboratory, stand or sit on their haunches, quietly dozing much of the time. Whipple and Hooper's experiments of this kind were the first on record in which bile pigment excretion was measured with close control of the general condition and weight of the animals, and with constant determination of the bile pigments in blood and urine as well as in the excreted bile. We need not detail here the elaborate, long-continued daily colorimetric estimation of the bile pigments and hemoglobin, the red cell counts, and other necessary technical procedures.

The first of Whipple and Hooper's studies in San Francisco, begun early in 1915 and published in 1916, revealed that the secretion of bile can be influenced at will by modification of the diet, carbohydrates favoring the output of the bile pigments, proteins diminishing it. One in particular of the special diets tried in these experiments opened an unexpected line of thought. When these two investigators first began their study at Johns Hopkins in 1913, they encountered difficulty keeping their bile-fistula dogs in good health, because the loss of all or nearly all the bile from the bodily economy led in a few weeks to emaciation, intestinal disturbances, and death. The bile, in short, is a necessary life factor for dogs (and presumably all mammals) fed on ordinary diets. Whipple and Hooper tried all sorts of rations to keep the dogs in good condition. Naturally they tried feeding bile itself, both fresh and dried, but without significant results. Nor did the addition of blood to the diet suffice, in spite of its content of hemoglobin. Fresh pig's liver, however, brought about marked improvement. Because the dogs would not eat it freely, Whipple tried cooked liver and found it just as good. On cooked pig's or sheep's liver bile-fistula dogs remained in good condition, maintaining their weight from month after month. No other foodstuff tested in his innumerable experiments showed anything like the effect of liver.

Trying to explain this unexpected finding, Whipple and Hooper now explicitly conjectured that something must be formed in the liver which facilitates, or takes part in, the construction of body pigments from which the bile pigments are derived. The body pigments include hemoglobin, certainly a major source of bile pigments though not the only one. Hemoglobin, Whipple reflected, appears first in the red blood cells while they are being formed in the bone marrow, and is presumably made there. "It is possible, however," he wrote in a paper he and Hooper submitted for publication in February, 1916, that "there may be a prehemoglobin substance manufactured somewhere in the body, perhaps in the liver, which may be fixed by the bone marrow cells, and appear as finished hemoglobin. If it can be established that the liver cells form any such substance, a long step will have been made toward the solution of this complex question of hemoglobin metabolism." Thinking over this cautious guess, based upon the study of secondary anemia, Charles Hooper hit upon the idea that a different and more ominous disorder of the blood, pernicious anemia, may result from disturbance of the production of this hypothetical "prehemoglobin substance." He therefore made an alcoholic extract of liver tissue, which with Professor Moffitt's permission he tried on six patients in the wards of the University of California Hospital. Walter Alvarez tried it on two others. The only available contemporary evidence of this experiment is a letter from Whipple to Moffitt, July 25, 1916, stating that the results of the injections, though inconclusive, were hopeful. The treatment in some of the cases had been followed by remission of symptoms and increase of hemoglobin in the red blood cells. Hooper's extract must, in fact, have contained the $B_{12}$ factor which is now known to be potent in pernicious anemia, but nothing came of his effort. He was a sensitive, shy young man, not gifted in winning the cooperation of interns and nurses. The hospital physicians, thinking that he had been deceived by spontaneous remissions, which are common in pernicious anemia, gave him no encouragement and he dropped the tests without preserving any records of his method of preparing the extract. Had he been encouraged to continue, the experiments on secondary anemia in dogs might have led to success with pernicious anemia ten years earlier, within Whipple's group instead of in Boston through men influenced only indirectly by the San Francisco studies.

The trail was getting warm, indeed; but as yet Whipple's thinking about hemoglobin production was not specially focused on a liver factor. It was a sufficiently exciting hypothesis that the production of red blood cells and hemoglobin can be influenced by diet, whatever the effective dietary constituents might be, and he meant to try a wide range of foodstuffs. He and his co-workers adopted a plan of experimentation that was simple in principle but immensely detailed and exacting in operation. They would make dogs anemic by drawing off their blood and would then see what diets and drugs would most effectively cause the depleted blood to regenerate. For such experiments the dogs ought to be more or less uniform in type and size. Whipple had already been breeding dogs in the laboratory and was beginning to develop a useful cross of a bull-dog and Boston terrier with some admixture of the Dalmatian coach hound. These bull mongrels were used in all the experiments on anemia. After carefully determining the blood volume, making a red blood cell count, and measuring the hemoglobin concentration of the blood, the investigators placed the dogs on a diet of white bread and milk (on which, they found, hemoglobin will not regenerate) and on each of two successive days drew one-fourth of the total volume of blood from the jugular vein with a hollow needle and large syringe. This procedure brought the red cell count and hemoglobin percentage down to about half normal. The diet on which the dogs were then placed during the experimental run was calculated to supply a sufficient number of calories to keep up weight and enough nitrogen to maintain a positive nitrogen balance. During the weeks or months of each individual experiment the state of the blood was frequently checked by all the tests and measurements applied in the beginning. The dogs remained well and lively even while their hemoglobin stayed as low as 40 per cent; when the investigators visited them in their outdoor runs the dogs would often come happily bounding toward them, and some of the dogs got so accustomed to the frequent collection of blood samples that they would leap on the table, lie down and stretch out their necks for the needle. The experiments were in fact scarcely harder upon the dogs than upon the investigators and technicians who had to carry on the interminable counts and estimations.

Tested in this way, the effects of various diets on the rate of blood regeneration were strikingly clear. A diet of mixed table scraps would effect complete return to the normal blood picture in four to seven weeks. On lean scrap meat, beef heart, or liver, regeneration was very rapid, reaching completion in two to four weeks. On diets consisting mainly of carbohydrates, or carbohydrates and fats, such as bread and milk or cracker meal, lard, and butter, regeneration was slow, requiring four weeks to five months for completion. Some dogs on high carbohydrate diets could not long maintain the regenerated state, even if they reached it. Contrary to a settled opinion of the medical profession, iron in the form of Blaud's pills, long a favored treatment for secondary anemia, had no effect upon the rate of blood regeneration.

These experiments were reported at a meeting of the American Physiological Society in late December, 1917, and were published in abstract form early in 1918. Whipple was at the time engaged in several other investigations growing out of his earlier work, and published nothing more on blood regeneration in simple secondary anemia until September, 1920, when a series of five papers appeared in the American Journal of Physiology, reporting findings similar to those of 1918, but with considerably greater variety and precision. One of them brought out the fact, of great importance in future applications of this research, though seemingly incidental at the time, that cooked liver may be even more efficient than meat (muscle) in promoting blood regeneration in secondary anemia.

A third name at the head of this report, following those of Whipple and Hooper, signalized the addition of a new investigator to the team. The ever-increasing amount of laboratory work required by Whipple's program caused him to look for a competent aide in the anemia experiments. Among those who applied for the post was Mrs. Frieda S. Robscheit, a young women of alert, self-confident bearing whose blond coloring and a trace of accent told of her German ancestry. Growing up in Chicago in the care of a guardian who was a physician, she thought of studying medicine, but first worked in a commercial pathology laboratory and then, on the advice of the eminent pathologist Gideon Wells, got a job in the University of Chicago's biochemical laboratories doing routine analyses. Diverted from medical studies by marriage, she worked for a couple of years in San Francisco in a physician's private laboratory. George Whipple had not thought of a woman assistant in work which involved, as well as a great deal of biochemical analysis, the handling of a kennel of large, active dogs, plus daily cleaning of the bile-fistula animals and other hard, messy work of a kind ordinarily done by male helpers. When, in the course of his first interview with Mrs. Robscheit, he said that he didn't think much of having a woman in the dog laboratory, she snapped back, "Well, then, Dr. Whipple, here is one woman you don't have to have in your laboratory!" and started for the door. Whipple, amused and impressed by this show of spirit, called her back and gave her an appointment as Fellow in Research Medicine.

Frieda Robscheit proved quite capable of handling the bile fistula dogs, and quickly learned how to leash them to their posts in the laboratory, to dilate the fistulas, and collect the bile samples. As the anemia work progressed, her extensive technical experience, combined with a woman's instinct for housekeeping, added system and precision to the daily experimental work. She took charge of breeding the dogs, trained them to cooperate in the experiments, made up the basal and experimental diets, and supervised the blood chemistry routines. In 1919 her name first appeared in a scientific periodical as author of a paper comparing various methods of hemoglobin determination, printed in the Journal of Biological Chemistry. The next year Whipple nominated her, as a qualified investigator, for membership in the Society of Experimental Biology and Medicine. Her surname, Robscheit, incidently, was Americanized about 1922 to Robbins, but on Whipple's advice, to avoid confusion she called herself, professionally, Robscheit-Robbins throughout her scientific career.

In order to calculate the rate of hemoglobin formation in the anemic dogs, it was necessary to know their blood volume as closely as possible. Whipple and his colleagues therefore compared all the available methods for estimating the blood volume, in order to choose the best for routine use. Besides Whipple, Hooper, and Robscheit-Robbins, five of the student Fellows—Arnold, Belt, Carrier, Lee, and Smith—and also Herbert M. Evans, professor of anatomy at Berkeley, and one of his Fellows, Ava B. Dawson, took part in the experiments. One of the currently used methods employed an anilin dye. Drawing upon Herbert Evans's vast knowledge of these dyes and their biological properties, Robscheit-Robbins tested in consultation with him scores of dyestuffs until she found one, of brilliant red color, which had the necessary qualities of nontoxicity and very slow diffusion from the blood stream. This red dye was employed in all of Whipple and Robscheit-Robbins's anemia experiments in which they needed to estimate the blood volume of the dogs. Later Ava Dawson, testing still other dyes supplied by H. M. Evans, found one (the tolidin derivative T-1824, known as Evans blue), which was better than any other previously used. One of the nine papers published by the group reported the first use, in blood volume studies, of Evans blue, which was soon widely adopted by other laboratories.

Four of the student Fellows—Arnold, Belt, Carrier and Smith, with Mrs. Belt and Smith's brother, Walter K. Smith—added an adventurous episode to the blood volume investigation by forming in 1921 an expedition to study blood volume changes at high altitude. Packing a tent-full of apparatus into the High Sierras, they made camp for four weeks at Long Lake, near Bishop, California, at an altitude of 11,000 feet. In a preliminary period at San Francisco, afterwards in the high camp, and again at sea level, they carried out on their own persons, with innumerable venipunctures and considerable discomfort, even risk, all the tests that were done on dogs in the home laboratory. Their findings showed that the well-known increase in red cell count and hemoglobin values during residence at high altitude is due to an actual gain in cell number and hemoglobin content, not to shrinkage of the fluid portion (plasma) of the blood or some other deceptive factor. In 1922, Whipple, Carrier and Frank Lee added a new tool for work of this kind by devising a method for accurate estimation of the plasma volume and hemoglobin volume, in dogs, simultaneously.

Another phase of Whipple's study of the formation of blood constituents dealt with the regeneration of the proteins of the fluid part (plasma) of the blood. The plasma proteins fall into two groups, albumins and globulins, differing in chemical and physical characteristics. Fibrin, that one of the globulins which has the peculiar property of clotting when the blood is drawn, had already (as we have seen) been studied in Baltimore by Whipple and Hurwitz, who found that it is probably made in the liver. When a tube of clotted blood is allowed to stand, the fibrin-stiffened clot, in which the blood cells are entangled, slowly contracts, leaving above it a clear fluid. This is the blood serum; it differs chemically from the plasma by the absence of fibrin. Those of the plasma proteins which are not removed in the clot, that is to say, all but the fibrin, are usually called serum albumins and serum globulins.

Whipple's interest in the formation and regeneration of the serum proteins began when his colleagues at San Francisco, Karl Meyer and Hurwitz, undertook to discover whether the antibodies which are formed against infectious organisms are identical with or related to the serum proteins. Although they got no positive answer to this question, their work opened up many problems concerning the changes of blood proteins in infectious disease and toxic states. In 1917 Whipple and Kerr joined Hurwitz in experiments in which they depleted the plasma proteins in dogs by withdrawing part of the blood and replacing it with a suspension of red blood cells in salt solution. The animal thus retains a normal red cell count and normal oxygen-carrying capacity, but its plasma proteins are greatly reduced. The rate of regeneration can then be followed during the week or two required to restore the concentration of the plasma proteins. The experiments, published in 1918-1919, showed that the levels of albumin and globulin in the blood are remarkably stable in health and disease, and that these substances are not derived directly from dietary proteins, but are built up through intermediates by slow metabolic processes. A hint was obtained, early in the investigation, that the liver is especially involved in the formation of plasma proteins.

After Meyer, Hurwitz, and Kerr dropped out of this work, Whipple and several of his student Fellows—Belt, Davis, and Smith—carried it on, improving their method of depleting the blood of its proteins. Looking for sites in the body where serum albumin and serum globulin are made, they tried running low-protein solutions through the blood vessels of various organs to see whether they would gain proteins during the passage. Difficulties in getting such solutions to flow slowly for a long time through the organs convinced them that the plasma proteins are essential to blood-flow in the capillary vessels, and that perfusion experiments employing physiological salt solutions and similar protein-free blood substitutes are likely to give fallacious results.

Although Whipple soon put aside the investigation of the plasma proteins (for some years, as it turned out) his group had learned a great deal about the technique of perfusing whole organs. When in 1930 Alexis Carrel and Charles Lindbergh began at the Rockefeller Institute their effort to cultivate whole organs outside the body by use of the Lindbergh perfusion pump, they found that Whipple, Belt, and Smith had published the best-informed statement of the difficulties to be expected. Such success as Carrel and Lindbergh had, unfortunately slight, was influenced by Whipple's insistence upon the necessity of having serum proteins in the perfusion fluid, and of pumping the fluid in pulses closely imitating the normal pulsation of the blood.

With Daniel Foster, Whipple about 1919 resumed the study of fibrin formation. They first worked out an improved method of determining the fibrin content of small samples of blood, giving accurate results with two cubic centimeters, whereas the best previous method required ten. Applying this test in observations on dogs, they found that the fibrin content of the blood, unlike that of the other plasma proteins, is exceedingly labile, varying as much as 25 per cent from day to day, in animals kept under uniform conditions. Diet seemed to be a factor in this fluctuation; the fibrin level was constant in fasting dogs, but rose on diets high in animal protein. Again, cooked liver was found very effective, causing increases up to 100 per cent over the fasting level. After depletion of the plasma proteins, blood fibrin regenerated very rapidly, reaching normal level in 24 hours, whereas the serum proteins required several days to return to normal levels. Trying various ways of altering the composition of the blood—by injection of physiological salt solution, or acacia solution, or by bleeding—Whipple and Foster obtained evidence that there is a constant production of fibrin, or rather of its precursor, fibrinogen. Inflammation and tissue damage of other kinds powerfully stimulate fibrinogen production. The liver is the main source and perhaps the only source of fibrinogen, as the Baltimore experiments of Whipple and Hurwitz had indicated some years earlier. Although Whipple, always cautious about the application of his results, did not discuss the meaning of these findings for the bodily economy, they imply that the body possesses a remarkably well-adjusted mechanism for keeping up the clotting power of the blood as a protection against the effects of wounds and disease.

With Charles Hall and later with Nelson Davis, Whipple returned to the starting point of this wide-ranging program, liver damage in chloroform poisoning, and with increased experience gained from years of experimenting, studied the effects of various diets upon regeneration of the chloroform-injured liver. The general conclusion from a rather complex series of experiments, in which a high carbohydrate diet proved best for promoting the regeneration of liver tissue, was that the body is able to conserve amino acids and other split products of the breakdown of proteins, and (if given the necessary energy supplies) to recast them into the complex liver cells.

By a natural extension of his work on the formation of the bile pigments, Whipple examined also the formation of another important group of constituents of the bile, namely the bile salts. These are compounds of complex organic acids (in man glycocholic and taurocholic acids, in the dog taurocholic and taurocholeic acids) with organic sodium. The bile-fistula dogs which were always available at the Hooper Foundation could be used to study the production of these compounds. When in 1916 Marjorie Foster joined the staff, her first assignment was to develop a suitable method for determining the amount of taurocholic and taurocholeic acid in bile samples. Using her method, Whipple, Foster and Hooper measured the effects of various diets on the production of bile acids, finding that meat proteins increase their output. Taurocholic acid is a compound of cholic acid, derived from the cholesterol of the diet, with taurine, a substance containing nitrogen and sulfur, related to the amino acids. Whipple and his associates proved that taurine is derived from the amino acid cystine, as had been suspected from the chemical relationship of the two substances. They found that taurine and cholic acid, fed separately, are readily combined in the body, presumably in the liver, to form taurocholic acid. The findings of these experiments, and of others in which Francis Smyth took part, on the dietary factors in bile salt production, showed that the amount of cholic acid available apparently determines the level of bile excretion. With another student Fellow, Francis Wisner, Whipple neatly demonstrated, by an experiment based on the foregoing results, that the formation of bile pigments and of bile salts, respectively, depends upon two totally different functions of the liver. Taurocholic acid, like whole bile, is a cholagogue; administered as a drug, it increases the flow of bile. When Whipple and Wisner gave a bile-fistula dog a large dose of taurocholic acid, there followed at once a great increase in the excretion of bile salts, while the rate of bile pigment excretion was unchanged.

Among the multifarious chemical activities of the liver is the detoxication of certain poisonous products of metabolism by combining them with other substances which render them innocuous and promote their elimination in the urine. With the aid of student Fellows, Whipple studied two of these remarkable processes. One of them was the combination of benzoic acid with the amino acid glycocoll, forming hippuric acid. Whether this conjugation takes place in the liver, or in the kidneys, was a much-discussed question. Whipple and G. D. Delprat found that heavy damage to the liver produced by chloroform delayed, though it did not prevent, the synthesis of hippuric acid. They concluded that in this process the liver must be associated with other tissues which can take over the synthesis if the liver's role in it is impaired. With Karl Pelkan, Whipple studied another example of detoxication. Among the breakdown products of organic substances in the body are phenols, members of a group of which carbolic acid is the simplest (and most toxic) member. The phenols are derived from the amino acid tyrosine, occurring in the food proteins, by bacterial decomposition in the intestine. It was known that the body protects itself against the poisonous effects of such substances by conjugating them with sulfuric or glycuronic acid. The conjugation was generally thought to take place in the liver. After Pelkan had worked out a method for estimating phenols in the blood, Whipple and he found that an Eck fistula, diverting the blood from the intestine so that it does not pass through the liver, greatly reduces the rate of conjugation of the phenols. Chloroform poisoning of the liver has the same effect. These observations prove that the liver is the site of the conjugation.

Concluding our review of George Whipple's program of research at the Hooper Foundation, we return to the first theme of this chapter, the study of intoxication resulting from injury to bodily tissues. Impressed by his finding that the toxic state induced in dogs by complete obstruction of the intestine in its upper reaches, results from intoxication by proteoses formed in the lining of the blocked intestine, Whipple asked himself whether similar toxic states seen in many acute infectious diseases (for example septicemia, peritonitis, and pneumonia) may not also result from injury to tissue proteins, producing poisonous split-products. In illness caused by invading microorganisms, it might be difficult to decide whether the effective toxin came from the host's tissues or from the bacteria, some of which are known to contain toxins. Similar general reactions, however, are seen in certain nonbacterial diseases accompanied by tissue breakdown, for instance, acute sterile pancreatitis, and can be produced experimentally in animals by inducing a sterile abscess with chemical irritants. Working with J. V. Cooke of the University of California department of pathology, Whipple studied dogs with sterile abcesses and also with septic infections, finding a rise in the nonprotein nitrogen of the blood and an above-normal output of nitrogenous waste products in the urine. These were sure indications of injury and autolysis of body proteins such as he had earlier observed in proteose intoxication. The obvious conclusion is that in severe septic inflammation also, a great part of the toxic reaction must be truly nonspecific (that is, not caused by toxins from the invading bacteria) and results from primary injury and autolysis of the proteins of the host's tissues.

The next step in this direction shows how the imaginative and widely informed scientist advances knowledge by putting together hitherto unrelated facts. Searching for other instances of nonbacterial tissue damage, Whipple thought of injury from Roentgen radiation. Soon after the x-rays, discovered in 1893, began to be used by physicians, they learned that excessive exposure to the rays caused constitutional reactions, sometimes of severe grade. This fact was first reported in 1897. Ten years later two Boston physicians, David Lynn Edsall and Ralph Pemberton, suggested that these illnesses might be a form of intoxication caused by split-products of proteins decomposed by the radiation. Reading clinical descriptions of x-ray disease, Whipple saw that the symptoms closely resembled those of the proteose intoxications he had produced and studied in his dogs.

Calling upon one of his student Fellows, Charles Hall, to assist him, he exposed dogs to intense x-radiation, and found, as he expected, that they developed symptoms like those of proteose intoxication, and showed changes in blood chemistry indicating extensive breakdown of body proteins. Postmortem examination, however, revealed surprisingly little injury beyond microscopically detectable damage of the lining epithelium of the intestine. Whipple's earlier experiences with intestinal obstruction led him to suppose that this lesion of the intestine might be the key factor in x-ray intoxication. Whipple and Hall's report, published in 1919, gave the medical profession its first warning that the intestinal tract is peculiarly sensitive to x-radiation.

Following up this hint, Whipple and Stafford Warren obtained far stronger evidence for their conjecture. They exposed dogs to massive radiation over the thorax without producing any general reaction, but similar exposure of the abdomen was followed in a day and a half by typical symptoms of intoxication, with serious illness on the third day and death on the fourth. Microscopic study of the intestine revealed extensive destruction of the epithelial cells of the intestinal lining, beginning on the first day after radiation. As a check on the conclusion that the intestine is specially sensitive to x-rays, Whipple had Irvine McQuarrie try the effects of heavy radiation on the kidneys, the rest of the abdominal region being shielded from the x-ray beam. The kidneys proved resistant. The experiments had achieved two important results: they had strengthened Whipple's concept of intoxication produced by protein derivatives of injured tissues, and they had disclosed the danger of excessive radiation of the abdomen. Whipple did not follow this line of investigation any farther, leaving it to his young colleague Stafford Warren, for whom it was the beginning of a professional career in radiology and of a life-time interest in radiation disease which fitted him to serve the nation during the Second World War and afterward, as chief adviser to the Manhattan Project on radiation risks and safety precautions in atomic energy research.

George Whipple, fully occupied all these years with the direction of the Hooper Foundation and with the recurrent struggle against the antivivisectionists, had managed to avoid most of the collateral administrative tasks to which scientists are called. He served for a couple of years as secretary of the recently founded American Association of Experimental Pathology, and during the First World War was a member of the scientific advisory committee of the California State Council of Defense. In 1920 a far heavier burden was laid upon him, the deanship of the University of California Medical

School in succession to Herbert C. Moffitt. To refuse the appointment was out of the question; the Hooper Foundation was becoming more and more closely linked with the school, and moreover, the Foundation and its director were under heavy obligation to the University for the financial support which it had provided against the still unrealized income of the Foundation. The opportunity to build up the school at a time when medical education was advancing all over the country also had its appeal to a devoted pupil and admirer of William Henry Welch.

Whipple found the task interesting but heavy. To maintain contact with the university administration meant frequent trips to Berkeley, requiring three or more hours, often to attend meetings of large committees which seldom accomplished results in proportion to the time consumed. He learned a good deal about the relations of a state university to the legislature, which he had no occasion to use in later life, and much about the administrative and financial problems of universities which was useful when he became a trustee of the Rockefeller Foundation. The most serious problem presented during his brief deanship arose from the divided state of the medical school, with half of it on each side of San Francisco Bay. One of Whipple's first moves as dean was to persuade the new president of the University, David P. Barrows, (elected in 1919 to succeed Benjamin Ide Wheeler) to attend meetings of the advisory board of the medical faculty—a good way to promote mutual understanding between the two divisions, and to show the president the problems his medical faculty was facing. On the difficult, long-postponed question of bringing the school together Whipple took a strong stand which was not popular with either the Berkeley or the San Francisco factions. He proposed to rebuild the school nearer the center of the city, adjacent to the San Francisco General Hospital. Against him on the preclinical side he had the Berkeley professors, including his old friend and quondam co-worker, Herbert Evans, who wanted to unite the school on or near the Berkeley campus—ideally the right solution, but if anything more expensive even than Whipple's plan, for it meant constructing a new hospital at once. On the other side were the conservatives of the clinical faculty, who wanted to stay on Parnassus Heights. If George Whipple's deanship had not been ended in 1921 by unexpected events shortly to be narrated, he would have been engaged in a controversy, lasting for years, that might have ruined his peace of mind. In the end the clinical faculty won out, by forestalling any move until the growth of the hospital on Parnassus Avenue made rebuilding elsewhere unthinkable.

In 1920 George Whipple took it for granted that his career would keep him in California permanently. He had made his place in the University's medical school as dean as well as director of the Hooper Foundation. With a loyal staff in the laboratory, and a steady flow of competent young people through the fellowship program, the Foundation was flourishing and his own investigations were winning an international reputation. He had made many friends in San Francisco and had established his family in a home built to the liking of Katharine and himself. The Pacific Coast, with its mountains, lakes, and rivers, afforded the kind of outdoor recreation he loved. When calls came from eastern universities anxious to have him as professor of pathology, he dismissed them without a second thought. Even the offer of a chair of pathology in New York City, at Columbia University's College of Physicians and Surgeons, failed to tempt him; he felt no regret when, later, his Berkeley colleague Frederick Gay accepted it.

In October, 1920, he received a letter from Rush Rhees, president of the University of Rochester, in up-state New York, telling him briefly about a new medical school to be organized in that city, and asking him to come east at once to look into the project with a view to heading it. This was not altogether a surprise. Rumors of the Rochester undertaking had reached his ears, and he knew that powerful forces were directing a nationwide movement for better medical schools, of which this was a part. But still thinking that his own contribution to the advance of medical education would be made in San Francisco, he was minded to deal with this new proposal as summarily as with the earlier one. Out of courtesy he first replied that he must consult President Barrows before giving a definite answer, and on November 8 he wrote:

I have had opportunity to consult President Barrows concerning your letter of October 21st, and have given the matter very considerable thought. I am sure you must realize that any teacher interested in medical school work and investigation cannot fail to be greatly interested in the problems and great opportunities which confront the University of Rochester. To be consulted in this important period can only carry an implied compliment which gives me great personal pleasure. However, I feel that it would be wrong for an individual in California to make this long journey and incur this considerable expense unless there was a distant possibility that his permanent interest in the medical school at Rochester might be aroused. It may not be fair to make this decision at this time without visiting your city, but I feel that this S.F. school has great opportunities, difficult problems, but a very bright future; and that the time spent already by me in this school makes my services of greater value to it in its period of development than could be the case elsewhere. Also perhaps one who has been through the period of construction in one school approaches a similar period in another school with hesitation, as developing a laboratory of this sort requires much time and effort which does not appear in actual results accomplished in the field of research, which is and always will be the field of greatest interest to me.

This letter, written to avoid an unnecessary trip to Rochester, merely strengthened Dr. Rhees's resolve to win Whipple for the new school. Rhees sent a copy of the letter at once to Abraham Flexner, of the Rockefeller-endowed General Education Board, whose part in the enterprise will appear in the next chapter, remarking that "far from closing the case, it intensifies my impression that he is the man we ought to get." Flexner replied "it reflects the greatest credit on him, and makes me feel more than ever that he has the ideals and ideas which you are seeking." Both Flexner and George Eastman, the Kodak magnate and chief financial supporter of the new school, who also saw Whipple's reply, advised Dr. Rhees to quit writing letters and go to California for a man-to-man talk. Without more ado the president made an appointment to see Whipple in San Francisco in mid-January, 1921. Before leaving Rochester he told the treasurer of the University "I don't know when I shall get back. I am not returning until George Whipple says 'yes'."

In the face of such persistence Whipple could not, after all, consider the matter closed, and had to take stock of the alternatives before him. The president's first letter had stated that the Rochester school would begin without any commitments to the past, and possessed already an adequate endowment. At San Francisco no such favorable conditions existed. The educational difficulties have already been discussed; besides these, the precarious financial situation of the Hooper Foundation presented an immediate problem. The forest lands left as endowment by George Hooper had not yet paid a cent of income, and the university was more and more unhappy about the burden it had assumed under the original declaration of trust. As soon as Karl Meyer's investigation of food processing began to bring in large grants from the packers, the university had begun to cut down its annual appropriations, and early in 1920 warned the Trustees of the Hooper Foundation that it could not much longer provide any support from general funds. Since then Whipple had been urging the university to try to liquidate the forest lands, and at the same time was exploring, without much encouragement, the possibility of help from eastern foundations. A crisis was threatening, of a kind which a scientific investigator should not have to meet. Meyer's work, because of its importance to business interests, would doubtless continue to receive extramural support; Whipple, if he stayed, would continually have to take time and energy from laboratory work to seek outside aid as well.

The Rochester enterprise, Whipple knew, also meant heavy executive work. His college classmate, Edwards A. Park, just appointed professor of pediatrics at Yale, got wind of the Rochester offer and eloquently expressed the fears of Whipple's friends:

I have learned that you have been asked to organize the medical school at Rochester, New York. May I offer my congratulations to you on that score? I cannot but express the hope, however, that you will not accept the undertaking. It will mean that you will stop all work for the next five years except executive work.

It is one thing, Whipple might have replied to Park's plea, to carry on executive duties hampered by inadequate university conditions and by financial worries, quite another to lead a young and hopeful enterprise, unfettered by local interests, and adequately endowed. Aware of his own great power of concentration, Whipple was confident that he could combine the career of dean with that of professor and investigator, if freed of all other duties and problems. When in mid-January 1921, Rush Rhees arrived to keep his appointment, Whipple liked him at once and felt sufficiently at ease in his company to speak frankly. In the course of two long conversations at his office and home, in which Rhees outlined the Rochester project, Whipple told the president that if he went to Rochester, he must keep himself free from the distractions of community service and of outside medical affairs. "I assured him," Whipple recalled years later,

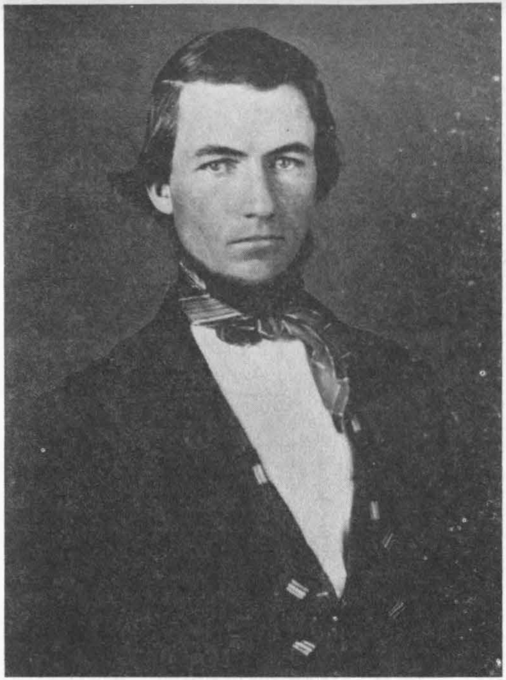
> that I intended to attend one or two scientific meetings a year and one or two administrative meetings, but no more. I hoped that he would permit me to decline local invitations for talks or membership responsibilities on committees when they would interfere with my work, although from the standpoint of the Trustees and interested citizens it might appear that I was selfish and lacking in civic interest. I told him that meeting important people at dinners, club meetings and the like took much time and energy and interfered definitely with my work of the following day.

To this bold stipulation Dr. Rhees agreed, and in parting renewed his assurances that the University of Rochester would expect Whipple only to lead the development of medical teaching and research of the highest type. Others could take care of public relations.

A letter George wrote to his mother on January 29, 1921, shows how the wind was blowing.

> Pres. Rhees of Rochester Unviersity has been out here during the past week and has spent much time with me talking over the plans for the new medical school in Rochester. They now have $10,000,000 available for this project—no strings tied to the gifts, and the desire to develop a school of the type of Hopkins. They wish me to take the position of Prof. of Pathology and Dean. The Trustees expect Pres. Rhees and the Dean to develop the policies of the School and determine the choice of men for the various chairs in the med. school faculty. . . . I shall write to Dr. Welch for advice and hope to come to a decision in this matter before long. Evidently there is a great opportunity there and it has a strong appeal for me. Katharine is much excited.

On the same day Whipple wrote to President Rhees, reviewing their understanding that the medical school was to be physically a part of the University; that it was to have adequate hospital facilities under its own control; and that the buildings and grounds were to be paid for out of income already accumulating from endowment. For himself he stipulated that as dean he would have executive control of the school's affairs, and that facilities for his own research would be provided as soon as possible. These provisions were all acceptable, and as for the hospital facilities, Rhees was able within a few days to tell Whipple that he had another million dollars for that purpose; George Eastman had successfully proposed to the two daughters of his first partner in the Kodak Company, Henry Strong, that they give half a million each to build a university hospital in memory of their parents. On February 25 the president wrote to say that on the basis of Whipple's memorandum the Trustees had unanimously appointed him dean and professor of pathology. Meanwhile, still not sure he had won his man, Rhees asked Simon Flexner at the Rockefeller Institute to give Whipple his own opinion of the Rochester project. A word from the great pathologist, one of Welch's senior pupils, Rhees thought, might influence a younger man with the same scientific background. Flexner wrote to Whipple that the deep interest of Rochester people in the enterprise was a favorable sign; he was confident that a new school there could build upon the advances that time and the growth of medical ideals had brought about in the United States. On March 15 Rhees wrote to Whipple again to say that his memorandum had been made part of the Trustees' minutes. Three weeks later, the agreement with the University now being a matter of official record, George Whipple replied, accepting the appointment as of July 1, 1921.



Solomon Mason Whipple, M.D.

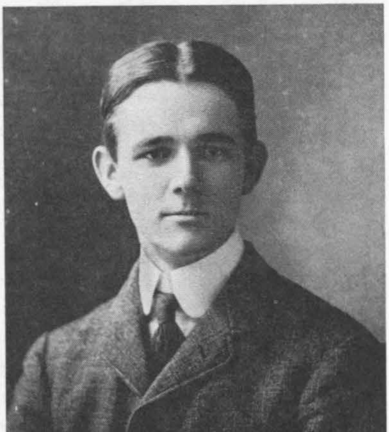
Henrietta Hersey Whipple

Anna Hoyt Whipple

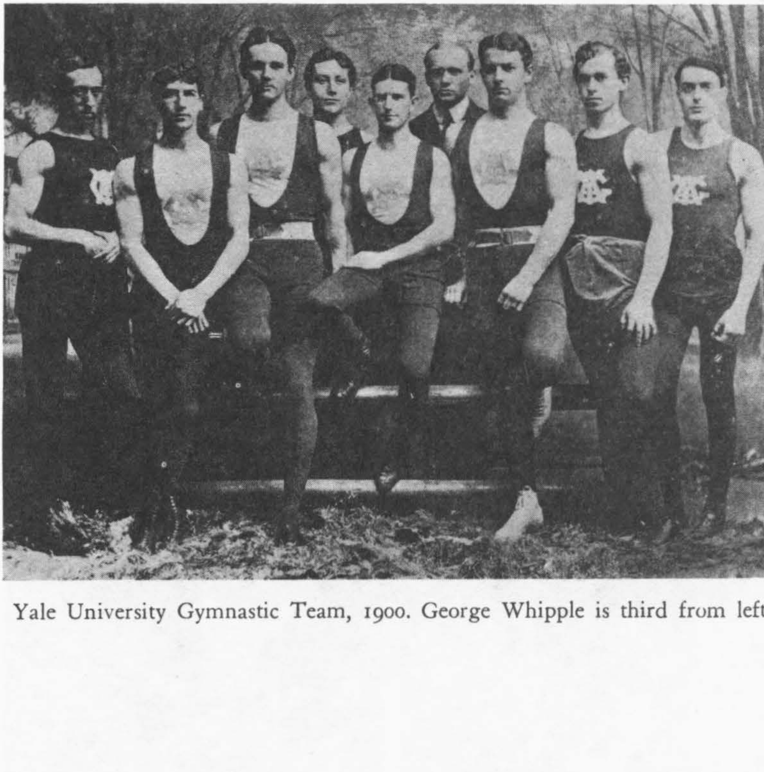
Ashley Cooper Whipple, M.D.

George Hoyt Whipple's birthplace, Ashland, New Hampshire.

George Whipple at 12 years of age.



George Whipple as Yale freshman, age 18. (Pach Bros., N. Y.)



Yale University Gymnastic Team, 1900. George Whipple is third from left.


STATE OF NEW HAMPSHIRE

Inspector's Certificate to Pilots

This is to Certify, That G. H. Whipple has been duly examined by the undersigned, Inspector of Steamboats for said State, as to his qualifications as Pilot of Steam Vessel, Chocorua.
and found to be a competent and reliable person to be intrusted with the powers and duties of Pilot, and he is therefore hereby licensed to act as such until the 31st day of December of the current year, on Asquam Lakes in said State.

Given under my hand this 17th day of June 1902

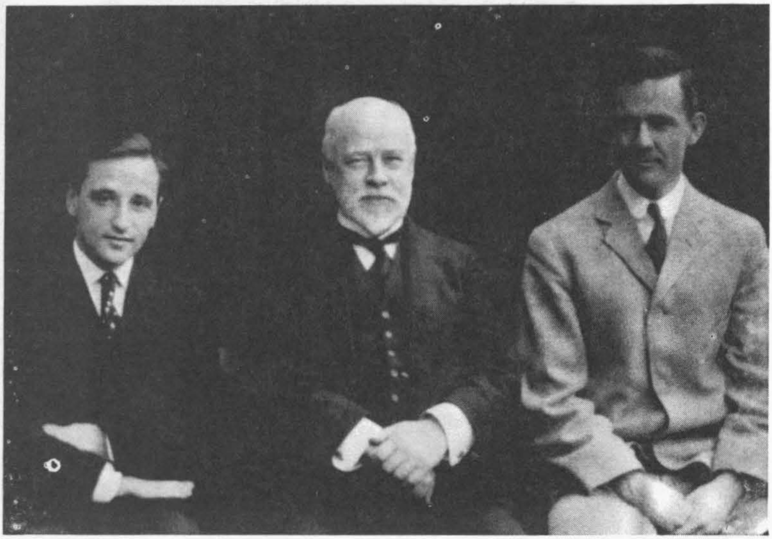
T. H. Worrall
Inspector of Steamboats.

Pilot's certificate issued to George Whipple, 1902.

Steamers *Chocorua* (in mid-stream) and *Ashland*.

George Whipple as fourth-year medical student, 1905.

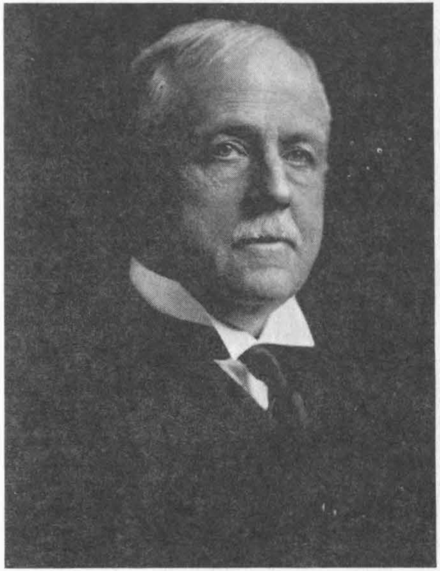
Katharine Waring Whipple before her marriage.



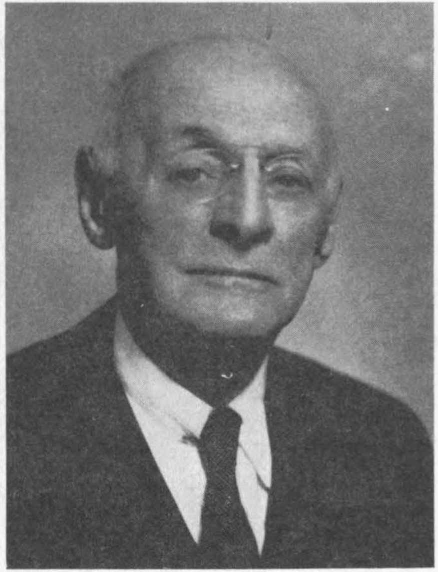
Milton C. Winternitz, William H. Welch, and George H. Whipple, about 1910.

George Whipple as Director of the Hooper Foundation, 1920. Photograph by Dr. Stafford L. Warren.

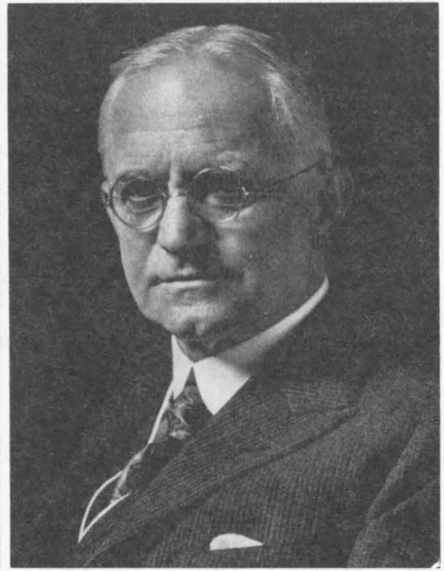
Hooper Foundation Laboratory, San Francisco.



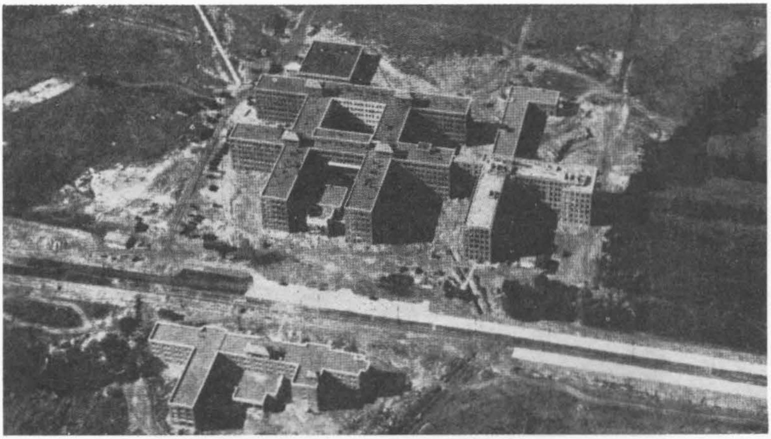
Rush Rhees



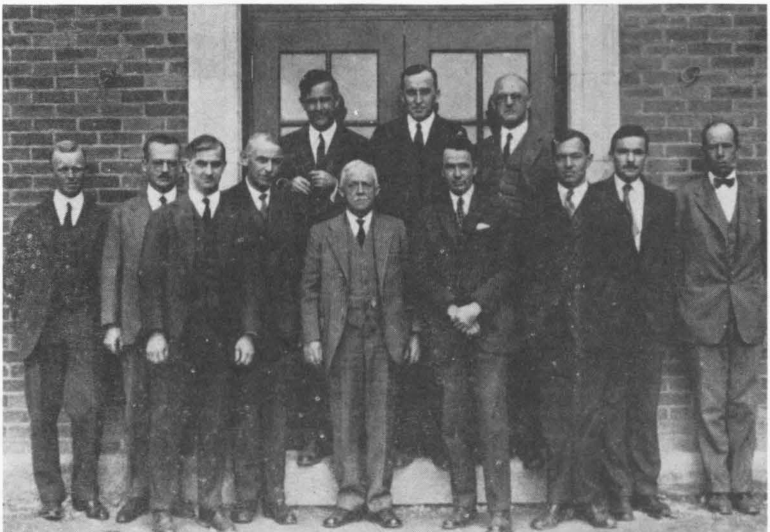
Abraham Flexner
(Conway Studios)



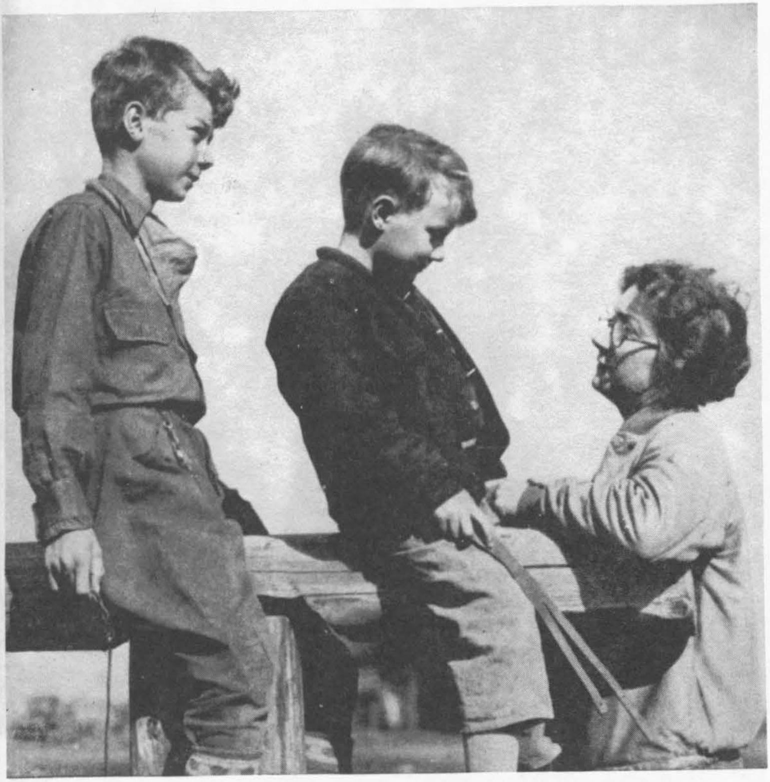
George Eastman



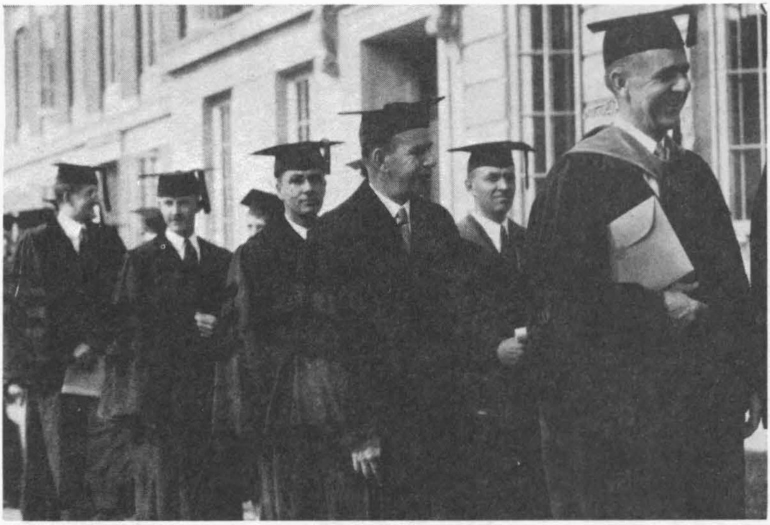
University of Rochester, School of Medicine and Dentistry, Strong Memorial Hospital, and Rochester Municipal Hospital, at end of construction period, 1925.



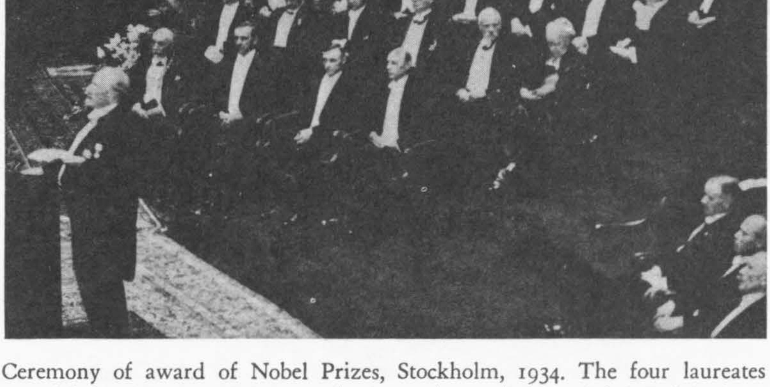
Senior Faculty of the School of Medicine and Dentistry, 1925. (Left to right) Back row, George H. Whipple, Karl M. Wilson, John R. Murlin; Front row, Stanhope Bayne-Jones, Samuel W. Clausen, John J. Morton, Walter R. Bloor, Rush Rhees, William S. McCann, Wallace O. Fenn, George W. Corner, Nathaniel W. Faxon.



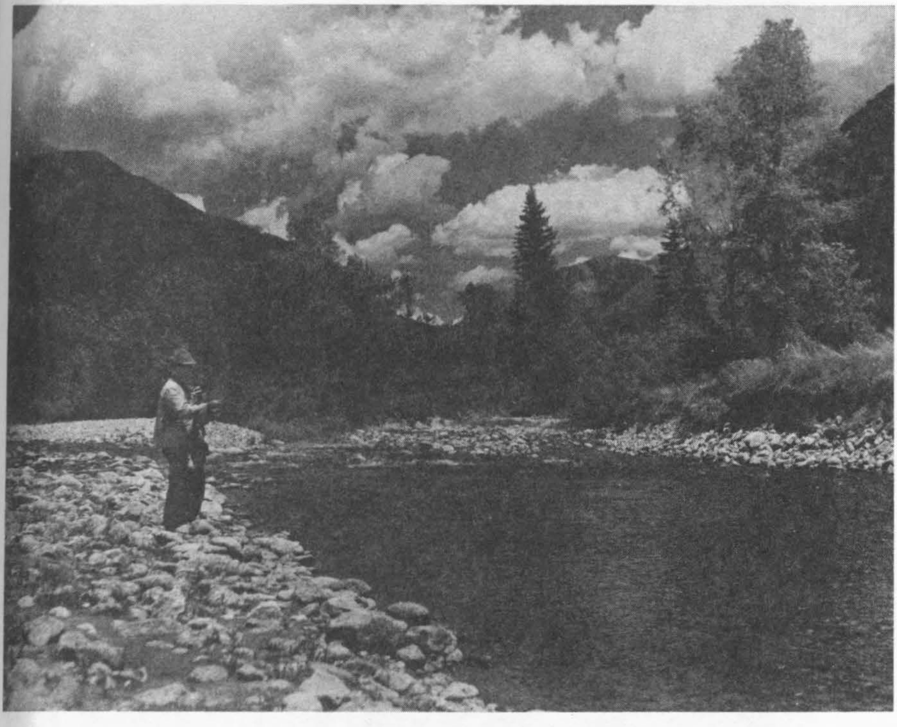
Katharine Whipple, with Hoyt (age 10) and Barbara (age 6).



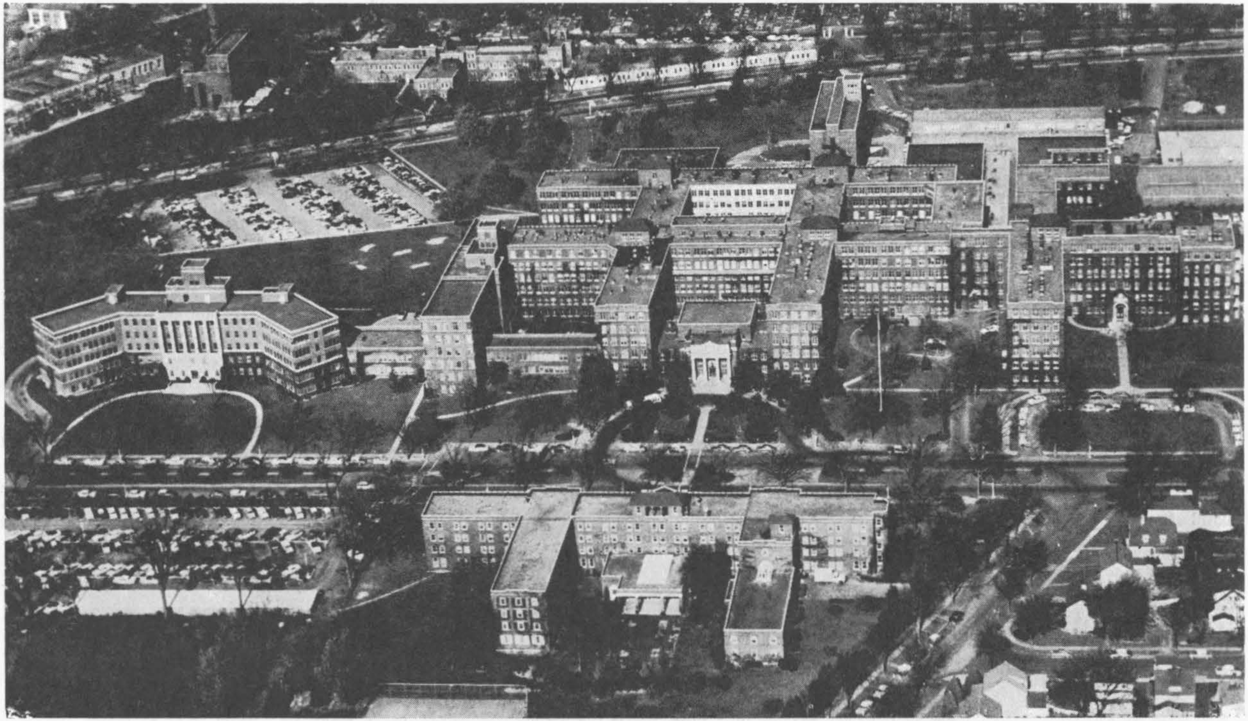
Academic procession at Commencement, 1931. (Right to left) George H. Whipple, Wallace O. Fenn, Nathaniel W. Faxon, William S. McCann, Robert K. Burns, Edward F. Adolph.



Ceremony of award of Nobel Prizes, Stockholm, 1934. The four laureates seated behind Rector Holmgren (at lectern) are (left to right) Luigi Pirandello, George H. Whipple, William P. Murphy, George Minot. (World Wide Photos.)



George Whipple and daughter Barbara fishing in Colorado. Photography planned by Dr. Whipple.



University of Rochester Medical Center, 1950.

Hunting party. (Left to right) Back row, William S. McCann, W. R. J. Wallace, George H. Whipple, John J. Morton; Front row, Stafford L. Warren, Jane Warren, Henry R. Selden.

George Whipple fishing for salmon in the Margaree River, Nova Scotia, 1952. Photograph by Dr. Lawrence A. Kohn.

George Whipple with tarpon rod, Naples, Florida, 1961. (Allan Gould)

CHAPTER

# 6

# ROCHESTER'S OPPORTUNITY

AS RUSH RHEES, talking to George Whipple in January, 1921, outlined Rochester's bold project, Whipple realized that he was being called to the front rank of a new advance in American medical education. Behind their conversations was a long story, familiar to both men, which must be summarized here if we are to understand the task Whipple was undertaking at Rochester. Our system of medical education, begun in Colonial times with high hopes, had undergone serious deterioration. The first two schools, at Philadelphia and New York, were associated with colleges and took as their model the University of Edinburgh. If this pattern had persisted, high standards of medical education might have prevailed throughout the country. Early in the nineteenth century, however, physicians in various cities and towns began to found schools on the pattern of the London teaching hospitals, which were conducted by their faculties without university affiliation. Rapid expansion of our population, creating a need for more and more physicians, led to a proliferation of medical schools lacking the traditions by which their London prototypes were guided, and operated by local doctors often unqualified for intellectual leadership. Nor did the university-affiliated schools succeed in attaining full academic standards. Their medical faculties were practically independent of the university authorities, and their professors, even though they were skilled physicians, found little time for teaching. Up to about 1880 most students of medicine began as apprentices to private practitioners, completing their training by subsequent attendance at medical school. The schools therefore needed to provide only dissecting rooms and lectures on chemistry, physiology, materia medica, medicine, surgery, and midwifery. Some few schools were attached to hospitals where patients could be shown and dressings done in the wards; others had no hospital facilities at all. Even the best of them were little more than trade schools, though here and there a professor of exceptional talent and enthusiasm might rise above the general mediocrity to become an inspiring teacher and even to publish original observations.

The lowest ebb was reached in the 1860's and 1870's. When George Whipple's grandfather made his plea for higher standards before the New Hampshire Medical Society in 1876, the tide had just begun to turn. Heads of universities where the natural sciences were rapidly advancing could not fail to note the difference between their departments of physics, chemistry, and biology and their schools of medicine. Charles W. Eliot began to overhaul the Harvard Medical faculty in 1869 as soon as he became president of the university. The University of Pennsylvania and the University of Michigan soon followed suit, lengthening and grading their lecture courses and setting up laboratories of bacteriology, biochemistry, and physiology, directed by young physicians who had been to Germany for training in these sciences.

A great step forward was the opening in 1893 of the Johns Hopkins University School of Medicine, which set the whole country an example of medical teaching and research as well as of effective association between school and hospital. For some years this was the only one of the country's medical schools of which so much could be said, yet a good deal of progress was being made elsewhere.

By 1900 there were about a dozen schools equipped with good laboratories, in which all the premedical sciences were taught by full-time teachers, many of whom were capable of scientific research. Even these schools, however, lacked one or another essential element. Some did not control an adequate teaching hospital or out-patient service. Some of them were dominated by local practitioners without university qualifications. Abraham Flexner, of whom more will be said shortly, once told President Lowell of Harvard that there was really no such thing as Harvard Medical School, for the institution so designated, he said, was not a part of Harvard University in the same sense in which the faculty of arts and sciences was a part of it. The medical school was running itself; appointments to its faculty, Flexner told the president, were decided at the Tavern Club in Boston by a small group of influential local doctors. At the University of California, whose medical school was affiliated with an outstanding university, George Whipple found, as we have seen, similarly weak control of clinical divisions, an insufficient library, and in the San Francisco division little interest in experimental research and no facilities for it except what he had himself built up.

Aside from these dozen or so relatively good medical schools, the rest ran the gamut through mediocrity to scandalous unfitness for their grave responsibility of training physicians. George Whipple, while a student at Johns Hopkins, could have seen in the same city two unspeakable institutions, one of which Abraham Flexner, inspecting it in 1909, described as follows:

> The school building is wretchedly dirty . . . one neglected and filthy room is set aside for bacteriology, pathology, and histology; a few dirty test-tubes stand around in pans and old cigar-boxes. The chemical laboratory is perhaps equal to the teaching of elementary chemistry. The dissecting-room is foul. This description completely exhausts its teaching facilities. There is no museum or library and no teaching accessories of any sort whatsoever. The college faculty own and conduct a hospital within a few blocks. It is essentially a private institution, of no great value to students.

San Francisco also had such a so-called school, only less picturesquely bad than those of Baltimore, called the College of Physicians and Surgeons. It had no full-time teachers, no resources but students' fees, no laboratories worthy of the name, and no adequate hospital or dispensary facilities.

The American Medical Association, which had worked for a long time to enforce lengthening and grading of the medical course, was sufficiently exercised about these evils to set up in 1907 a Council on Medical Education which grouped the schools in four classes, "A" to "D", according to faculty strength, facilities, and admission requirements, and then began persuading the states not to license graduates of the "D" schools. This effort put some of the worst schools out of business, but to raise the general standard much more was needed than elimination of the bad schools; the good ones must be made better. This was a task of national scope requiring skilled educational leadership to point the way to reform, and large funds to carry it out. The Carnegie Foundation for the Advancement of Teaching undertook in 1909 a direct inspection and description of every medical school in the United States and Canada, by an acute and experienced educator, Abraham Flexner, brother of the celebrated pathologist Simon Flexner, director of the Rockefeller Institute for Medical Research in New York. Mr. Flexner's report, "Medical Education in the United States and Canada," published by the Foundation in 1910, burst with explosive force upon the medical profession, university authorities and a shocked public. It not only finished off the rest of the "D" schools, but forced many in the higher classes to reorganize their teaching and equipment. By killing off all but one or two of the independent schools, the report ultimately brought medical education almost entirely under university control, and simultaneously taught academic authorities to recognize their responsibilities. Numerous universities that had tolerated the affiliation of inferior medical schools were shamed into casting them off or reforming them. The better university schools were impelled to correct the lesser weaknesses that Flexner's report had brought to light.

George Whipple of course knew all this recent history very well. As dean of the University of California's Medical College he was himself taking part in the reorganization under way there. What he could not know until President Rhees gave him some inkling of it as they talked together in San Francisco, was the course of events by which Abraham Flexner's report had led up to the great plans for a medical school in Rochester, in which he was now asked to take a leading part.

Flexner had not stopped with mere exposure of the weaknesses he had found in American medical education. In 1912 he was appointed to the staff of the Rockefeller-supported General Education Board and in 1917 became its Secretary and chief executive. Here he was in a position of power, able to direct millions of dollars into the work of reform. In the 1910 report he had dared to recommend realigning the whole pattern of medical education in major areas of the country, by abolishing certain of the weaker schools, consolidating others, and where necessary creating new ones. As the General Education Board's plans took shape according to Flexner's ideas, they called for supporting five or six new or reorganized institutions in different parts of the country. One of these should be in New York State, ideally, perhaps, in New York City. Flexner felt, however, that as yet none of the universities with medical faculties in the metropolis was ready to administer a school of the type he was calling for. Up-state there were three medical schools, none of true university status; one at Albany, actually independent though nominally a part of Union University at Schenectady thirteen miles away; another at Buffalo, affiliated on paper with a miscellaneous aggregation of professional schools calling itself a university, and a third which was an integral part of Syracuse University. It is scarcely necessary to say that all three of these medical schools are now adequately equipped and staffed; but in 1910 Flexner thought that only Syracuse was in a position to impose university standards on its medical faculty. In his shattering report he had proposed that Syracuse should be given ample support and the other two shut down. As time went on, however, he saw that the Syracuse administration was not ready for the radical reorganization required to put its medical school in the first class; it had no teachers who could take the lead and secure local support to match funds the General Education Board might contribute.

Meantime Flexner's mind turned to Rochester, midway between Buffalo and Syracuse, a prosperous, self-confident city of 250,000 population, with a thoroughly sound college headed by an able and universally respected president. "Dr. Rush Rhees," said Flexner, speaking for the General Education Board, belongs in our judgment to the small group of eminent administrators who have carefully defined their objects and who have by a substantial educational success won the confidence and esteem of all critical students of higher education in America. . . . Because the University of Rochester is sound to the core, because it is in competent hands, because it will take no forward step unless the ground is firm beneath its feet and the necessary means absolutely assured . . . in Rochester there is an opening for the foundation of a medical school of the highest character.

Flexner was not the first man with power to dispose of millions who had perceived the solid worth of the University of Rochester. George Eastman, head of Rochester's largest industry, Eastman Kodak Company, had seen this too, and within the past year or two had given the university large funds to develop a school of music. The university was thus already, by cautious, well-supported expansion, proving its right to call itself something more than a college. If Flexner could win over men like Rush Rhees and George Eastman, the General Education Board might hope to plant a first-class medical school in Rochester.

How Abraham Flexner went about winning these key men is entertainingly told in his autobiography, *I Remember,* and is echoed in Rush Rhees's correspondence. First, meeting Dr. Rhees in New York, Flexner startled him by asking if he would like to have a medical school at his university. When Rhees said yes, if he could have a first-rate one, Flexner got him to arrange an appointment with Eastman. Early in February, 1920, Rhees had a preliminary talk with Eastman, in which, we may well imagine, the shrewd president did not fail to point out the advantages of a university hospital and medical school to the citizens of Rochester and especially to Kodak employees. Telling Flexner that Eastman would see him, Rhees advised him to emphasize the opportunity to create a really superior institution—"That is the feature which has aroused his tentative interest." Flexner, invited a few days later to breakfast with the Kodak magnate at his great house on Rochester's East Avenue, found "a pallid gentleman in his sixties, his white hair covered by a skullcap . . . his soft voice and gentle smile were disarming and reassuring." After breakfasting to the accompaniment of music by an organist from the Eastman School of Music, Flexner spent the whole morning telling Eastman the history of American medical education, already outlined in this chapter. He stayed to lunch and was asked to return for dinner with Eastman and President Rhees. Before he left for New York by the night train he had the promise of two and a half million dollars. By skillful salesmanship at two subsequent meetings in Rochester he got the pledge raised to five millions, enough to justify the General Education Board in matching the gift to make up the amount—ten millions—that Flexner thought necessary for a beginning.

During the course of these friendly negotiations Eastman, promoting a keen interest of his own, introduced the idea of including dentistry in the new school, and of attaching to it the well-equipped dental dispensary which he had presented to the city of Rochester some years before. Thus the institution was designated, from the first, as the School of Medicine and Dentistry. In March Rush Rhees, practically sure of the outcome, asked to meet William H. Welch in Baltimore, and at one of Welch's famous dinners at the Maryland Club received the great man's blessing and Olympian advice on how to go about starting a school of medicine. The General Education Board voted its grant on June 3, and the two gifts were publicly announced, to the great applause of Rochester's people, on commencement day, June 11, 1920.

Two weeks later Rush Rhees was in New York, where he conferred with William Darragh, dean of the College of Physicians and Surgeons, and with L. Emmett Holt, the eminent pediatrician who had been, 20 years earlier, one of John D. Rockefeller, Jr.'s intimate advisers in organizing the Rockefeller Institute. The next day Abraham Flexner gave him a list of men suitable for the chair of pathology and specifically suggested a man to head the school. From New York Rhees went to Baltimore for similar information and advice. After the passage of more than 40 years there can be no harm in revealing, from Rhees's notes, the names of men who seemed to his consultants worthy of the great responsibility of organizing the school. Welch and Simon Flexner nominated Whipple, ". . . the best man," Welch said; "he is reserved, a great character, influential with both colleagues and students . . . is a pathological anatomist, which is essential."

It seems to have been agreed, in fact, by everyone concerned that the post called for a pathologist, who by reason of his scientific interests, intermediate between those of the preclinical and the clinical faculties, could best bring them together in a common undertaking. Abraham Flexner suggested Alonzo E. Taylor, then a leading member of the University of Pennsylvania's medical faculty. Winford H. Smith, Director of Johns Hopkins Hospital, confidently placed Milton C. Winternitz, Whipple's colleague of 1907-1914, at the head of his list. Taylor's competence was evident, and Winternitz was soon to prove his executive abilities as dean of Yale Medical School even though Welch told Rhees that Winternitz was "brilliant but needed restraint." The president, however, impressed from the start by all he heard about George Whipple, made no advances to the others. By November, 1920, as we have seen, he was ready to offer Whipple the deanship.

George Whipple, considering President Rhees's proposal, made careful inquiry about the city to which he was being called. Rochester, he learned, was a relatively young municipality, founded in 1811 by people who settled around the lower falls of the Genesee River. Situated where the line of travel westward from the Mohawk Trail crosses the northward-flowing Genesee, the town acquired a population blended of Southerners, descendants of the people who followed Colonel Nathaniel Rochester over the mountains and down the river from Maryland and Virginia, with New Englanders migrating from the east. Later came many Germans, and in the twentieth century, thousands of Italians. Rochester's first important industry was the milling of flour by water power from the falls; when that business moved westward others succeeded it, mostly of technical nature requiring skilled labor: clothing factories, woodworking, nurseries and seedsmen. In time optics and photography became the chief industries under the lead of the great firm of Bausch and Lomb and of George Eastman, inventor of flexible photographic film and the roll-film camera. These manufactories of cameras, microscopes and x-ray films could be a great asset to a medical school located nearby; and several others of the city's products were as close to the medical field. The Taylor Instrument Company's clinical thermometers and the Castle sterilizers were known to every doctor in the country. A large supplier of laboratory equipment, the Will Corporation, and a nationally known biological supply house, Ward's Natural Science Establishment, were also located in Rochester.

The city stands partly on level ground, once the floor of Lake Ontario, and partly on slightly elevated land rising to low glacial hills on its southern margin. It consisted, in the early 1920's, of a business and industrial area centered around and below the falls of the Genesee and along the tracks of the New York Central Railway, which traverses the city in the east-west direction. Around this business center lies a widely spreading residential zone ringed by leafy suburban areas. There was no architecture of distinction anywhere except a few Greek Revival houses in the old section and a number of nineteenth century mansions along the broad, tree-lined East Avenue. The only really sumptuous house was that of the rich bachelor, George Eastman.

On Prince Street near the business section on a small, well-shaded campus stood the unpretentious buildings of the University of Rochester, founded in 1850. Once a Baptist stronghold, the college had long since been taken out of denominational control by President David Jayne Hill, later U. S. Ambassador to Germany. While still a young and small college it had several very scholarly professors who are reverently remembered. Rush Rhees came to the presidency in 1900 from the Newton Theological Seminary in Massachusetts. Under his administration the university, which had been admitting women students on an informal basis, created a women's college, and in 1920 was organizing its ambitious Eastman School of Music. When George Whipple first looked at its roster he saw the names of two or three scholars of national stature in chairs of English and history, several excellent college teachers, and a few distinguished musicians. Rochester's business and professional circles included more men of strong intellectual interests, perhaps, than other comparable places. The best of them had formed several serious little clubs that met fortnightly at the members' homes to dine elegantly, to hear and to discuss papers by their members on literary, historical, and scientific questions. One Rochester lawyer, Lewis Henry Morgan (1818-1881), won international fame among sociologists and anthropologists by two distinguished books, *The League of the Iroquois* and *Primitive Society*.

The population of the city was relatively homogeneous. There were practically no slums and no paupers. Crime was light. The public schools were excellent, the parks well kept, and good music plentiful. Religious and political tolerance were the rule. The people were exceedingly loyal to community enterprises. Everybody subscribed to the Community Chest in docile compliance with a well-established quota; the Red Cross never lacked volunteers, and when the Rochester Civic Orchestra became a public enterprise, a corps of enthusiastic workers turned out each year to solicit contributions for its maintenance. Civic aspirations were guided by the big business men, led by George Eastman, whose oft-stated aim of making Rochester a city of healthy and happy homes and, as he put it "a good place to live and bring up children," was based on no mere sentimentality but rather on firm business principles. "For a long time," he once wrote, "from the standpoint of making Kodak Company an enduring institution, safe against the assaults of competition for expert services and labor, I have felt that the best thing that could be done was to help make Rochester the best place in the country to live in."

When George Whipple asked about Rochester's municipal government, a matter of great importance to the proposed medical school, Rush Rhees told him, with perhaps some little embarrassment, that things were in good shape in that respect. Like all other American cities, this one had its political boss, George W. Aldridge by name, an astute, fair-speaking man, firmly supported by an overwhelming Republican majority and ruling with a gloved hand. Rather superior in mind and character to most of his kind, he was shrewd enough to keep his hands off the public schools. If he had not done the same with the Health Office he would soon have learned better from the Health Officer, George W. Goler, a sharp-witted, hard-fighting doctor. Big business had made its truce with the boss; his henchmen could have their little jobs and their little rake-offs if he let business go its own way and left the schools and the Health Office alone. As a gentle warning, however, to the Mayor and City Council, George Eastman was paying the expenses of a Municipal Research Bureau that kept a watch on the city government.

Such was the city to which George Whipple was being called—a pleasant, safe, healthy place, efficiently run by high-minded businessmen and unobstrusive politicians; populated by forward-looking people ambitious for the best in culture and education, and more systematically organized to attain it than any other city in the nation. Undoubtedly, George Whipple thought, a good city in which to build an enterprise of great civic value, but also a place where a hard-working scientist had better watch his step. Social life and community service, as he had told Rush Rhees, can waste a lot of valuable time and energy.

President Rhees suggested that Whipple might go to Europe for several months before settling in Rochester, to refresh his mind and observe medical education in Britain and on the Continent. This idea perhaps originated with Abraham Flexner, who strongly favored European travel as a broadening experience for scientists. Whipple did not share this enthusiasm; he felt that American medical education had at this stage little to gain from abroad. He could do more, he thought, to get the Rochester school started if he were on the ground as soon as possible. He and Katharine, moreover, with their two very young children, would find it difficult to manage a European trip, whether he went alone or took the family with him. If he worked in a foreign laboratory, courtesy would require him to put aside his own work to participate in the program of the host professor. He did not want to interrupt his work on anemia when it was going rapidly ahead. Summing up the situation, he thought best to begin at Rochester without delay, and proposed that the University of Rochester should assume the expenses of the anemia work while it was continued temporarily at San Francisco in the care of Frieda Robscheit-Robbins. Karl Meyer, who was to succeed him as director of the Hooper Foundation, had generously agreed to keep the necessary laboratory space available. Whipple asked also for a special appropriation of $2500.00 for the high-altitude expedition of his student Fellows—Arnold, Belt, Carrier, and Smith—already mentioned in Chapter 5. In his anxiety to spell out all these ideas and plans, he wrote President Rhees probably the longest letter he ever composed in his life—six pages, typed on legal-size paper. Rhees assented to the whole program, and in mid-August, 1921, the Whipples left San Francisco for the east. From Washington, D. C., Katharine traveled southwest to Charleston with Hoyt, aged four, and Barbara, four months old, for a month's visit to her family, while George went on to Rochester. A few days' stay as guest of the Rheeses at the President's House adjoining the campus helped much to deepen a friendship between president and dean, already begun and never to be broken. On September 29, Rush Rhees reported to Abraham Flexner Whipple's arrival in Rochester on the 20th and his quick conquest of all with whom he came in contact. "Personally, I am extremely delighted with him," Rhees wrote, "for in addition to his well-known scientific accomplishments and ability, he seems to be possessed of an extraordinary degree of common sense and good judgment."

A few months after Katharine came to join George in mid-October, the Whipples found a comfortable house at 320 Westminster Road, in the East Avenue residential section where many of Rochester's leading business and professional people lived. At the University, George was given a temporary office in the Eastman Building on the campus, where he had scientific men as neighbors, for the college departments of biology and physics were located there. The building housed also a small but highly competent department of nutrition, the Lewis P. Ross Department of Vital Economics, recently established by bequest, whose two senior members, John R. Murlin and Henry A. Mattill, were doing research of considerable relevance to physicians. Next door to the Eastman Building were the administrative offices of the University, where the president was readily accessible for the frequent consultations necessary at the start of the new school.

The first major question was where to build the new Strong Memorial Hospital and the medical school. Everyone concerned agreed that the medical center should be close to the rest of the University. George Whipple had seen too much of separation between faculties at San Francisco, and knew that even Johns Hopkins, his model in most respects when thinking about the new school, had suffered by the distance of its medical faculty from the arts college and graduate school (one mile and a half from the original buildings, four miles from the present campus). Any thought of building on the Prince Street campus was quickly dismissed, because it lacked room for a large addition to the buildings already there. The nearby grounds of the Genesee Valley Club on East Avenue were rejected for the same reason. It was clear, in fact, that a new site must be found for both the college and the medical school, somewhere outside the business and residential sections, with plenty of room for future growth. Some of the Trustees, and others unfamiliar with modern hospital experience, feared placing the medical center on the main campus, though for opposite reasons. Some said that the presence of patients would expose students and faculty to distressing sights and contagious diseases; others predicted that sick people would not travel far from the center of town, particularly to the out-patient dispensary, where the practical teaching of medicine required an ample supply of patients. The first difficulty could be met by placing the college and the medical school on separate but adjacent tracts. As to the other objection, Whipple's verdict was conclusive; he could point to a number of places where public confidence in a well-known hospital was drawing patients from considerable distances. The University of California Hospital stood at the edge of residential San Francisco; several universities were successfully operating teaching hospitals in small cities, attracting patients from distant counties; the Mayo Clinic had actually changed Rochester, Minnesota, from a small town into a growing city whose chief industry was the care of patients and housing their relatives. In this age of automobiles a mere mile or two to the suburbs would not keep patients away.

At the southern edge of the city—as it was then, for Rochester has since spread a mile farther southward—on the east bank of the gently flowing Genesee, where the river makes a great bend toward the center of the city, the Oak Hill Country Club owned an attractive golf course covering 82 acres of rolling land, and to the south of this, separated from the river by a narrow tongue of Genesee Valley Park, lay the Crittenden property, comprising 97 acres of level farm and nursery land. The two tracts are contiguous at one point, or rather would be, did not Elmwood Avenue and a branch of the Lehigh Valley Railroad pass through the point of contact (in a way which can be understood only by looking at a map) thus providing the physical demarcation of the medical installation from the rest of the university, which some people considered desirable. The Trustees determined to purchase all this land, if the golf club would sell (the Crittenden farm being already on the market), to build the medical school and hospital on the farm tract, and as soon as funds could be obtained, to relocate the Men's College on the Oak Hill grounds. Committed at that time, and for many years to come, to the separate collegiate education of women, they would leave the Women's College on the Prince Street campus.

George Whipple thought the site excellent and immediately favored the purchase. Not even the railroad track troubled him; it might present problems to a landscape architect laying out the college campus, but to the practical administrator it meant convenient and cheap delivery of building materials, and of coal for a powerhouse that could be built at the crossing to serve both campuses. The Oak Hill Country Club, with civic loyalty characteristic of Rochester people, agreed to sell. By the spring of 1922, Whipple was assured of a site for the buildings he was already planning.

The Trustees assigned the architectural designing to a leading Rochester firm, Gordon and Kaelber, with McKim, Mead and White of New York as consulting architects—a famous firm that little knew what pressure for economy and practicability it would soon get from two determined men, George Eastman and George Whipple, as its members advised on the esthetic features of the main building. Whipple's first thought was to put up an animal house, for his 40 experimental dogs had to be brought from San Francisco before long. The building would also temporarily house humans, as well as animals, providing office space for the dean and for a few faculty members, as yet unnamed, who would, Whipple hoped, join him within the year. The instructions he gave the architect might well have read, paraphrasing the well-known sign on French freight cars, "40 dogs, 8 men," except that there was to be room for more than 40 dogs and also for frogs and turtles, rats, mice, guinea-pigs, rabbits, and any other creatures research might demand. The building, a plain but neat-looking square brick structure, was put up in record time. Begun in August, 1922, it was finished by the end of November. By that time two members of the new faculty, Nathaniel W. Faxon and Walter R. Bloor, had arrived and were occupying office space on the Prince Street campus. Soon after Thanksgiving Day—favorable omen!—Whipple, Faxon, and Bloor, with two or three secretaries and technicians, moved into the animal house, or rather Research Laboratory, as it was publicly designated. Whipple had a place for his microscope; Bloor set up a temporary biochemical laboratory, and the embryonic School of Medicine and Dentistry began scientific operations under its own roof. In December Frieda Robscheit-Robbins arrived shortly ahead of her 40 dogs—22 adults and 18 puppies of various ages. There had been a good deal of amusement at the Hooper Foundation before her departure. Somebody suggested a circus car with a brass band for this unusual transcontinental journey. Actually the Railway Express Company provided a special baggage car in which the dogs traveled comfortably in individual cages with their own supply of dog food and an attendant to feed and water them. They reached Rochester in excellent condition; Mrs. Robbins was able to resume the experimental program with scarcely a break in its schedule.

Life in the Research Laboratory was conducted with spartan simplicity. The building stood in the middle of a large open field, three long blocks from other habitations. To the south it looked over open country dotted with the noble trees which in summer and winter lend beauty and dignity to western New York's landscape. From Elmwood Avenue on the north, then still a country road, the laboratory was reached by a mere track, generally ankle-deep in mud when not covered by snow. In the depths of winter, the professors carried shovels in their cars, to dig their way in or out if snow blocked the lane. In early spring, in a hollow which is now a pleasant lawn, melting snow made a broad pool humorously dubbed "Lake Faxon" for the genial director of the yet unbuilt hospital. Lunches had to be brought from home until construction of the main building got under way, when a shack was put up for the workmen, operated at first by a male cook of slovenly habits and dubious culinary skill, afterward by another so good that he later became chef of the hospital. The Post Office would not think of delivering mail to so remote a place; letters and magazines were left in a hutch on Mt. Hope Avenue, a half-mile nearer town, to be picked up by one of the staff every morning—a task gleefully handed on to each new professor as he arrived and dutifully carried out until he was no longer the faculty's freshman. But the building was warm and hearts were high through the long, cold Rochester winter, when, as Faxon said, the cloud-cover forms in December and stays till March, and a little snow falls almost every day. In April, 1923, when the trees were leafing out again, Whipple and his companions watched the bulldozers and steam shovels break ground for the main school and hospital building.

Early plans for the school envisioned affiliation with two Rochester institutions, one of which was a projected municipal hospital. The other—the Eastman Dental Dispensary—was already in operation. This notable institution, George Eastman's first benefaction in the field of health, was chartered in 1915 and opened in 1917. Organized after the example of the Forsyth Dental Infirmary in Boston, it provided dental care for needy Rochester children, and at the same time was a training-school for young graduate dentists serving as interns, and for dental hygienists. Often spoken of as a gift to the city of Rochester, it was actually a private foundation, operated by a board of trustees. Eastman's interest in dentistry sprang from his own experience: trouble with his mouth resulting from poor dental care in youth had been relieved by skilled treatment and well-fitted dentures, and he wished to give Rochester children the benefit he had lacked when himself a child. The Dispensary was directed by Harvey J. Burkhart, D.D.S., a man of considerable standing in his profession and the community, 61 years old in 1921. While practising dentistry in Batavia, New York, he was twice mayor of that small city, in 1902-1904 and again in 1915-1916. He served for three years as president of the New York State Dental Association, and for a year as president of the national association. In 1920, the University of Rochester made him an honorary L.L.D. Burkhart had Eastman's full confidence in matters related to his profession and was his chief adviser with regard to the dental clinics he gave to London, Rome, Stockholm, Brussels, and Paris. On several occasions the two men discussed the need for improving dental education, but, as Eastman stated in 1920, neither of them had clearly seen a way of helping to achieve this aim through the Dental Dispensary. When, however, Abraham Flexner approached Eastman with regard to founding a medical school in the city, Eastman at once saw the possibility of combining dental with medical teaching and, as we have seen, made this a condition of his support.

Burkhart at first publicly echoed Eastman's enthusiasm for the affiliation of the Dental Dispensary with the medical school. On June 22, 1920, addressing the Rochester Kiwanis Club, he outlined the plans for giving dental students the same preclinical instruction as the medical students, with whom they would be associated in the same classes, as a preparation for specializing in clinical denistry during the latter two years of the course. "I feel," he said, "that we can establish the best dental school in the world here." Yet in spite of his general assent on this occasion, Burkhart never again committed himself openly to any sort of intimate affiliation, nor did he make any move in that direction. He had been alarmed, no doubt, by the implications of the early conferences between Rhees and Eastman. A letter from Eastman to Rhees, sometime in March, 1920, and one from Rhees to Flexner, March 13, reporting the negotiations, explicitly stated that the Dental Dispensary was to be absorbed, endowment and all, by the medical school. Eastman, of course, had no legal authority to achieve this, having placed his benefaction in the hands of trustees, but a man in his position has other means of getting his own way.

It is probable that Burkhart advised against any such step. At any rate, when Eastman laid his wishes before the trustees of the Dispensary, by letter of June 25, 1920 (only three days after Burkhart's talk to the Kiwanis Club), he did not ask for corporate union of the two institutions, but only full cooperation with the new school in the teaching of dentistry. Even in this modified form, however, the idea of close cooperation disturbed Burkhart, who evidently still feared that the dispensary which he had organized and made a model for America and Europe would lose its independence, and that he himself would be subordinated to a dean almost 20 years his junior. He had heard talk also of emphasizing dental research in the medical school, but thought the dental profession had little to gain by research; it had already solved its technical problems, he said. At any rate, the Dental Dispensary had no place for anything but the services it was already rendering. Skilled politician that he was, Burkhart managed to avoid a show-down without losing Eastman's friendship.

Meanwhile the medical school was discovering that the idea of joint preclinical instruction in medicine and dentistry was ahead of its time, largely because it required that candidates for the dental school must have the same preparation as the medical students. As Basil G. Bibby, Burkhart's successor as director of the Rochester Dental Dispensary, pointed out, high school graduates were unwilling to spend seven or eight years in college and professional school getting a dental degree from what was then an unorganized dental school in a little-known university, when they could be admitted to a well-established university dental school elsewhere and get the dental degree in three or four years. The very few who applied, during the first few years, for admission to Rochester as dental students did not meet the standards of the Admissions Committee. There was therefore no more pressure from the medical school than from the Dental Dispensary to organize a clinical dental faculty. The Dispensary continued to serve the public and the dental profession in its own way, and Eastman's desire that the school of medicine should contribute to the progress of dentistry was eventually fulfilled in a quite different manner.

The Municipal Hospital is another story, in which the principal figure was George W. Goler, Rochester's extraordinary Health Officer. Born in Brooklyn, N. Y., in 1864, Goler took his M.D. degree at the University of Buffalo in 1889, and three years later joined the Rochester Board of Health as medical inspector. While in that position he showed his enterprise and courage by dealing scientifically with epidemic diphtheria only two years after the discovery of the antitoxin. The New York City Board of Health laboratory was then the only place in this country where the antitoxin was being made. Goler went to New York and learned how to make it; returning to Rochester he immunized three Fire Department horses, bled them, prepared their serum and sent it to New York for standardization. His antitoxin was ready for distribution in 1895.

When in 1896 Goler was made chief of the Board of Health staff, he got the organization and name changed to "Health Office" and took the title of Health Officer. Henceforth there was no Board of Health, but only Doctor Goler, who with a devoted secretary and a handful of loyal assistants fought valiantly and without cease for pure milk and pure water, sanitation of schools and restaurants, vaccination against smallpox, and all other relevant public health measures known at the time. In 1897 he established municipal milk depots which attracted the attention of health officials in the United States and Europe. Goler was a stubborn man, afraid of nobody, who would compromise nothing. For years he opposed the pasteurization of milk because he feared that the dairymen, relying on that procedure to make the milk safe, would relax their standards of cleanliness in the milking barns.

In 1904, squeezing funds from a scanty budget, Goler organized a small hospital for infectious diseases, in which he could care for cases of smallpox, scarlet fever, typhoid fever and diphtheria among the city's poor. Under bitter attack for a time from various vested interests, but wangling funds from city officials who respected his aims in spite of his uncompromising belligerency, he kept his hospital going through thick and thin. By 1920 Goler had won public confidence so thoroughly that the municipality was getting ready to build him a large modern hospital on ground he had chosen in an eastern suburb. This for the Health Officer was the goal and the only coveted reward of a career devoted for 28 years to public service; but when he learned that the city was to have a medical school of the highest type, he saw at once how much more could be gained by a union of the two hospitals. Rochester's city patients would benefit by the skill of the medical professors and a better-trained junior staff than an isolated hospital could command; the medical school would double its capacity for teaching medicine at the bedside. Sacrificing his personal ambition to direct the new municipal hospital, he proposed that the city should build it alongside the Strong Memorial and put its medical services in complete charge of the University of Rochester.

According to George Whipple's recollection, the idea of affiliation was Goler's own. A similar thought, however, had also occurred to others. Abraham Flexner's studies of American and European medical institutions had shown him that the American schools being created or reorganized under the reform movement he had himself helped to start, were having to expend a large part of their resources to construct and maintain university hospitals, thus assuming a burden of patient-care which should properly be borne by the community. In Europe, on the contrary, many universities were spared such expense because the municipalities in which they were situated entrusted the medical service of their city hospitals to the university faculties. In October, 1920, he called President Rhees's attention to an agreement the University of Cincinnati had made with that city to conduct the Cincinnati Municipal Hospital;

an arrangement, said Flexner, that might furnish a precedent for similar intelligent action at Rochester and elsewhere. He followed this with other instances of more or less similar cooperation. Dr. Goler's proposal thus won eager acceptance by the university. In September, 1921, Rhees reported to Flexner, in a confidential message, that he was discussing with Mayor Hiram W. Edgerton a plan to affiliate the proposed Rochester Municipal Hospital with the medical school and its Strong Memorial Hospital.

George Whipple, when told what was brewing, hailed it with satisfaction. While dean of the University of California medical school he had proposed, as we have seen, to rebuild the school next to the San Francisco Municipal Hospital, where, however, affiliation close enough to make the scheme work would have been difficult because the hospital was already manned and in operation. At Rochester, where both institutions would be organized simultaneously, there were no commitments to be overcome. In March, 1922, at Rush Rhees's request, Whipple prepared a long, detailed memorandum on the advantages of affiliation, to be used, no doubt, in explaining the plan to the mayor and city council. He was in Rochester in time to take a useful part in working out the precise terms of the agreement. George Eastman also helped with practical advice as well as by putting his powerful influence behind the project. A ten-year contract drawn by a prominent lawyer and trustee of the university was signed April 25, 1922, under which the medical faculty was to conduct the medical services of the Municipal Hospital, and Strong Memorial Hospital would furnish operating rooms, diagnostic laboratories, x-ray service, pharmacy, and other special services. By another generous act Goler secured consent of the city administration and the University to place the laboratory of the Health Office at the medical school, to be staffed and operated by the department of bacteriology. In this way the city obtained the advantage of association with research bacteriologists under the expert guidance of Stanhope Bayne-Jones, and the latter's department benefited by contact with practical public health work.

George Goler expressed his great satisfaction with this outcome by loyal cooperation with the medical school as long as he lived, tempered by vigorous criticism whenever he disapproved of any of its policies. Abraham Flexner wrote to Rush Rhees:

I congratulate you and your associates with all my heart on what is, I am thinking, one of the most helpful steps ever taken in this country in the direction of financing medical education on a high basis and with adequate facilities. If the other municipalities of the United States will imitate the City of Rochester, we can hope to build up clinics equal to those of the great European cities. If on the other hand, our municipalities fail to do what the City of Rochester has done, our medical schools will for the most part be clinically inadequate. The sums needed to support endowed teaching hospitals are so large that I see no prospect of providing them in more than a very few places. For this reason I hold the action of the City of Rochester as most enlightening and far-sighted.

The cooperative arrangement thus formalized has run smoothly for almost four decades, and the contract, promptly renewed each time it has expired, has been widely studied and copied in other cities.

During the 14 months from September, 1921 to November, 1922, when Whipple was cut off from laboratory and autopsy work, he had time, amid all this planning, to make several trips to other medical schools, to study teaching methods and the design and construction of laboratory buildings, as well as to look for promising young men for his faculty. This was a time, moreover, for reflecting upon his research of the past decade and for summarizing it for the medical public. Invited to present a lecture before the Harvey Society of New York, an organization of leading physicians interested in learning about current scientific developments, he spoke on January 7, 1922, on "Pigment Metabolism and Regeneration of Hemoglobin in the Body." In July he published in the journal *Physiological Reviews* a summary statement of his work and that of others on "The Origin and Significance of the Constituents of the Bile." The two publications are a landmark in his career of investigation; the period of exploratory research was giving place to one of critical re-examination and more precise definition of the vitally important processes involved in the metabolism of proteins, bile pigments and body pigments in the liver and the bone marrow.

CHAPTER

# 7

## BUILDING WITH MEN AND BRICKS

GEORGE WHIPPLE chose his men to head the medical school's departments on principles reflecting his own outlook and experience. First of all, he wanted not individual stars, but a team; as he told Rush Rhees, he needed a harmonious group of able people rather than brilliant men each playing a lone hand. He wanted them all to be Americans, or thoroughly familiar with American ways, for they were to lead a new enterprise calling for understanding and moral support from the people of one of the most American of our cities. He wanted young men, who would be more adaptable to new conditions than experienced professors long in harness; in the spirit of his pioneer forefathers he believed that young Americans, when put to the test, can rise to any opportunity. He would choose men of all-round capacity in their respective fields, for he meant to organize his faculty simply, with the smallest practicable number of departments. Of course anatomy, physiology and pathology, distinct disciplines for a century or more, and bacteriology for 40 years, must rank as separate departments. Biochemistry and pharmacology had of late been drawing apart; this Whipple would not allow, at least at the beginning. Internal medicine and surgery were certainly distinct subjects; pediatrics also had won its place as a major specialty. Obstetrics and gynecology must be taught together, not separately as they then were at Johns Hopkins. Newer specialties were to be set up within these major departments: ophthalmology and otology, orthopedics and urology under surgery; radiology under medicine (an unorthodox assignment), even psychiatry a subdivision of internal medicine. Public health and hygiene, Whipple said, do not constitute a pedagogic specialty in a medical school; each department must accept a share of responsibility for teaching them. Thus the school would begin with nine full professors, including the dean, plus the hospital director.

On one major question, the most crucial that medical education was facing at the time, the founders and chief advisers of the new school were at first completely of one mind. The heads of the clinical departments—medicine, surgery, pediatrics, and obstetrics-gynecology—like their preclinical colleagues, were to be out-and-out university professors, on professorial salaries, devoting their full time to their university work, without private practice. Their respective departments, moreover, were to have junior staffs of associate and assistant professors and instructors also on full time. To this strong core of university career men would be added a carefully chosen group of skilled local physicians, who would contribute their invaluable services to students and patients out of professional zeal and for the benefits their connection with the school would give them.

The "full-time" system of clinical teaching was a recent idea in medical education. Since time immemorial clinical medicine has been taught by men in active practice. The Hippocratic oath contains a pledge that the physician will teach his art as well as practice it; and the very title "doctor of medicine" carries the same implication. The great development, however, of the medical sciences in the nineteenth and twentieth centuries, and the resulting advent of full-time teachers and investigators of the preclinical subjects, emphasized the inadequacy of part-time direction of departments by busy practitioners. Such men could not find time to give individual attention to students, nor to direct large staffs and the diagnostic and research laboratories which the clinics were acquiring. Furthermore, in many schools appointments to clinical chairs automatically went to the heads of services in allied hospitals. Professors thus created, however devoted and learned they might be, were primarily involved in local medical affairs, and often did not represent the same academic ideals as the laboratory scientists. Sometimes, indeed, there was an unfortunate lack of sympathy between the two groups, resulting from economic disparity and a different social environment as well as divergent professional aims. Abraham Flexner found this to be the case in so distinguished a school as Harvard, when he studied it in 1909; George Whipple had seen it at the University of California; and even at Johns Hopkins, whose choice of clinical professors had not been hampered by local traditions, there was sufficient dissatisfaction with part-time direction of clinical departments to make the school, in 1913, the first to break with age-old customs and create full-time chairs of medicine, surgery, obstetrics and pediatrics.

Three men who greatly influenced George Whipple while a medical student and junior staff member at Johns Hopkins were on opposite sides of the intense debates that preceded this radical step. Franklin Mall had originally worked out the full-time concept in his own mind following discussions with the far-seeing Carl Ludwig, with whom he was a postgraduate investigator in Leipzig in 1884-1885. Mall often discussed the idea with his intimate associates in the early days of the Johns Hopkins Medical School, one of whom, Lewellys F. Barker, in 1902 put it squarely before medical educators in a much-discussed public address. William Osler, an active teacher in spite of his large consulting practice, opposed the plan from the start, and after 1905 continued to condemn it from his new post at Oxford. Welch, centrally placed in the school as pathologist, was at first undecided, but having to take a stand after Osler's departure for Oxford, became the chief advocate of the full-time plan. With infinite diplomacy and patience he persuaded the Trustees and faculty to accept it, and secured from the General Education Board a large grant to put it into effect.

Abraham Flexner, Secretary of that Board, had in fact pressed the grant on the Johns Hopkins administration and with Mall's connivance maneuvered to get it accepted, for he believed full-time clinical teaching to be essential to the progress of American medical education. With the Board's encouragement and financial support the full-time plan was soon adopted also by Yale and by Washington University, St. Louis, and has since spread with various modifications, to many other schools. Its adoption by the University of Rochester was thus implicit in the university's acceptance of half its endowment from the General Education Board. Whipple's success in enlisting able young men for his professorships, both preclinical and clinical, resulted in part from the assurance he was able to give that the senior faculty would be a band of fellow-workers with equal responsibilities to the school and undivided allegiance to academic principles. In one respect only did the dean, who was a man of ideals but never an impractical idealist, allow the clinical professorships at Rochester to differ from the preclinical; they carried salaries from 25 to 50 per cent higher, because to fill them the university had to compete against the incomes men of the requisite ability could earn in practice.

Strong Memorial Hospital was to constitute a tenth department of the school, and its director would have the status of full professor with an equal voice in the school's councils. This, as it happened, was the first faculty post, after Whipple's, to be filled. To find a man for it, Rhees and Whipple turned to Massachusetts General Hospital, which had a special reputation for sound, yet progressive management. It was known in particular for the excellence of its out-patient department, a phase of hospital administration in which Johns Hopkins, in so many other ways Rochester's model, was at the time by no means up-to-date. The Boston hospital's able director, Frederick A. Washburn, recommended his assistant, Nathaniel W. Faxon, a native of Massachusetts and Harvard medical graduate who had been a family doctor at Stoughton, Massachusetts, from 1906 to 1917, before joining Washburn's administrative staff. Appointed in May, 1922, to be director of Strong Memorial Hospital, Faxon remained at his Boston post until November, meanwhile taking part in several conferences and much correspondence about the building plans of the new hospital.

Whipple's search for his other department heads called for advice from many people, especially William H. Welch, Winford Smith, and Lewis H. Weed, dean of Johns Hopkins medical school, all at Baltimore; from Abraham Flexner of the General Education Board, Simon Flexner at the Rockefeller Institute, and Richard M. Pierce, Director of the Division of Medical Sciences of the Rockefeller Foundation. It also meant many journeys to other cities, where Rush Rhees as well as Whipple could meet and size up the men under consideration. Yet the two men Whipple first recommended to President Rhees he had himself already known well at the University of California. For the chair of anatomy he chose George W. Corner, a Baltimorean, then associate professor at Johns Hopkins, whom Whipple had taught in medical school, and whose work he had observed while Corner was in Berkeley in Herbert Evans's department, 1915-1919. Whipple knew that the young anatomist's ideas about medical teaching fitted him for the new school, because in the first place Corner had begun his professional career with Franklin P. Mall, and in the second place had taken a warm interest, while at Berkeley, in Whipple's novel plan for student fellowships at the Hooper Foundation, and helped to give it a good start by recommending excellent students for the first appointments. Whipple's choice for the chair of biochemistry, Canadian-born Walter R. Bloor, took his Ph.D. at Harvard under Otto Folin, and rose rapidly through successive ranks at Washington University, St. Louis, and at Harvard, becoming professor of biochemistry at the University of California, Berkeley, 1918-1922. Whipple, during his year as dean of the University of California medical school, had learned to know the calm, reliable biochemist and to appreciate his research on the structure of body fats.

Corner accepted appointment to the Rochester faculty in May, 1922, Bloor in June. With three colleagues on his roster by the summer of that year, Whipple had an executive committee which could be assembled on call to discuss further steps with the dean and the wise, always deeply interested President Rhees. To head the department of bacteriology, this group enthusiastically named Stanhope Bayne-Jones, born in New Orleans, an expert microbiologist, associate professor at Johns Hopkins with William G. MacCallum. Bayne-Jones was a student in Whipple's classes at Johns

Hopkins in 1911, and was (though the dean probably did not know it at the time) a nephew by marriage of the great sanitarian, General Gorgas, whom Whipple had so greatly admired in Panama. Bayne-Jones accepted his call in October, 1922; two months later the first man appointed to a clinical chair, William S. McCann, gave his acceptance also. Trained first as a chemical engineer, at Ohio State University, in his native state, McCann studied medicine at Cornell Medical College in New York City. He was a surgical intern and later research fellow with Harvey Cushing at Peter Bent Brigham Hospital in Boston, and then taught for two years at Cornell before going to Johns Hopkins as associate professor of internal medicine under Warfield Longcope. His chemical training prepared him to grasp the new biochemical problems of internal medicine. "When Doctor McCann comes on the ward," said one of his Johns Hopkins students, "we feel that modern medicine has arrived."

Karl M. Wilson was named professor of obstetrics and gynecology in November 1922, and began at once to take part in the selection of other professors, although he did not formally join the University faculty until September, 1923. At the time of his appointment he was associate professor of obstetrics (part-time) with J. Whitridge Williams at Johns Hopkins, and for ten years had been a successful practitioner in Baltimore. Born in Canada, he took his M.D. at McGill University, Montreal. After an internship at Massachusetts General Hospital and three years on the Johns Hopkins obstetrical staff he returned to Montreal for one year as resident gynecologist at the Royal Victoria, before settling in Baltimore. A tall, serious man of commanding presence, he won the confidence of women patients by his sympathetic approach and obvious strength and competence. Happy in the opportunity to return to an academic environment, he spent a year, before going to Rochester, in research in the Baltimore laboratory of the Department of Embryology of the Carnegie Institution.

When this now rapidly expanding group, or Advisory Board, as it came to be called, met to consider the professorship of surgery, for which John J. Morton, a Massachusetts-born Johns Hopkins graduate, had been warmly recommended, Rush Rhees remarked that he had found Morton diffident and retiring, and wondered whether he had a sufficiently forceful personality for a post requiring the utmost strength of character—whereupon George Corner, Morton's classmate in medical school, told of seeing him on a football field, in a match with the powerful Carlisle Indian School team, pitting his 148 pounds by sheer nerve and speed against the redoubtable heavy-weight Jim Thorpe, America's greatest athlete. To this McCann, who had served one summer under Morton on the collecting crew at the Woods Hole Marine Biological Laboratory, added that Morton was always first in the water on every tough or dangerous assignment. With these evidences that the candidate met Whipple's specifications as a leader and team-worker, the president smilingly assented to the choice. Morton's professional training was equally suitable; after graduating from medical school he went to Boston as an intern with Harvey Cushing, then to the Rockefeller Institute Hospital for two years in internal medicine. Later he was resident surgeon at Massachusetts General. He practiced orthopedic surgery in New Haven for two years before joining the Yale faculty as associate professor under Samuel Harvey. Morton accepted his Rochester appointment in May, 1923.

Samuel W. Clausen, professor of pediatrics, a native of western New York, not far from Rochester, studied medicine at Johns Hopkins and served briefly there on the resident hospital staff under John Howland. For seven years he was a member of the full-time staff of Washington University, St. Louis, under another eminent pediatrician, W. McKim Marriott. Clausen, like McCann, was an excellent chemist. His Rochester appointment began in February, 1924.

The last chair to be filled was that of physiology. That branch of medical science had not been advancing as strongly in the United States as in Britain and on the Continent, and there was a dearth of young men suitable for the Rochester post. Abraham Flexner, who was following the organization of the faculty with well-justified interest, felt that this chair at least should be filled from overseas. He urged a candidate of his own—a distinguished European, known to be something of a prima donna—so strongly upon George Eastman that Rush Rhees had to explain to the school's benefactor that George Whipple wanted in physiology, as in the other departments, a man with whom the group could work comfortably. Finally rumors came from England about a young New Englander, Wallace O. Fenn, who was doing brilliant research with A. V. Hill, one of the leading British physiologists, whom he had followed from Manchester to London when Hill took the chair at University College. Fenn had taken his Ph.D. in 1919 at Harvard with W. J. V. Osterhout, nominally in botany, but actually in general physiology. After a four-year instructorship with Walter B. Cannon at Harvard Medical School, he had gone to England on a fellowship created for him by the Rockefeller Institute. Undoubtedly he was slated for the Institute's staff. Simon Flexner, however, generously permitted Whipple to offer the Rochester chair of physiology to Fenn, whose acceptance in May, 1924, completed the roster of ten men heading the teaching departments and hospital. Fenn, 31 years of age when appointed, was the youngest; Bloor, 46 when appointed, was the eldest and the only one older than Whipple. The average age was 37.5 years at appointment, and a little less than 40 when teaching began in 1925.

These facts and figures have been set forth at some length to meet a criticism often leveled at Rush Rhees and George Whipple, that they were simply assembling a junior John Hopkins faculty. As John J. Abel put it to one of the professors-to-be, "you boys are just starting a Hopkins country club up there in Rochester." Actually only five of the ten senior men studied medicine at Johns Hopkins; three were from Harvard (one M.D., two Ph.D.'s), one held his M.D. from Cornell and one from McGill. Four of the five Johns Hopkins M.D.'s had taught in other medical schools as well, and the only one of them whose entire career as student and teacher of medicine had thus far been spent at Johns Hopkins (Bayne-Jones) possessed at least as broad an outlook as the others through his combination of southern birth with Yale collegiate education and through service in World War I, beginning as regimental surgeon with British troops in the trenches, winning the French Croix de Guerre, and ending as sanitary inspector of the U. S. Third Army in Germany. The ten men brought together experience gained in many of the best medical and biological institutions in the United States, Canada, and Britain—the University of California, the Carnegie Institution's Department of Embryology, Cornell, Harvard, Johns Hopkins, Manchester, McGill, the Rockefeller Institute, University College, London, and Washington University, St. Louis. The hospitals in which the eight who were M.D.'s had worked included Barnes Hospital, St. Louis; Peter Bent Brigham Hospital, Boston; Johns Hopkins, Massachusetts General, New York Hospital, the Hospital of the Rockefeller Institute, the Royal Victoria of Montreal, and the University of California Hospital. Three of the professors—Bayne-Jones, McCann, and Morton—had extensive medical and surgical experience overseas in World War I. It would have been difficult to find in the medical world ten young men equipped, as a group, with so broad an acquaintance with the best of American and British medicine and biology, as those whom George Whipple and Rush Rhees had chosen and recommended to the Trustees of the University of Rochester.

George Whipple's ideas about building with bricks and concrete were as definite, and as boldly simple, as those for building a faculty. He had seen quite enough of medical schools split in two by long distances between preclinical and clinical faculties, or by hospital facilities remote from the laboratories. At Rochester he would concentrate the whole establishment in one great building, and put all the school's departments in intimate communication with each other and with the hospital. Taking up his ruler and a sheet of paper he laid out a ground plan of four axes, two running north and south, two east and west, crossing like a tick-tack-toe figure. On this plan he built six floors, each divided between the school and the hospital. Nobody need go out of doors to visit any part of the combined institutions; no department was farther than a hundred feet from a doorway or elevator connecting it with the rest.

At Vanderbilt University, Nashville, Tennessee, another medical dean, G. Canby Robinson, reorganizing his school at the same time, hit upon the identical scheme. Although he and Whipple bantered each other on the question of priority, it was a clear case of simultaneous discovery such as often happens in scientific research, perhaps no less often in architecture. Canby Robinson sheathed the Vanderbilt building in limestone of Gothic design to match the other university buildings; George Whipple resolved to construct his in plain brick. At Baltimore he had begun his career in Welch's old pathology laboratory, the merest brick box; the former veterinary school he had made over in San Francisco for the Hooper Foundation was also of brick, only a little less plain outside than the original

Johns Hopkins laboratories, and still rougher inside. To build in Rochester in much the same way would save money for research without stinting anyone of the real necessities—light, air, and working space. In this determination he had a powerful ally. George Eastman, who had put up at Kodak Park a veritable city of industrial buildings, wanted his money and that which John D. Rockefeller's almoners had given to be spent on a working medical school, not an architectural monument. Many universities, he said, according to Whipple's recollection, had shown how much could be spent on adornment and interior furnishings; he wanted to see how little could be spent while achieving functional efficiency. Eastman thought, moreover, that the university ought to set a good example for the city government, which had been spending, he said, altogether too much on architecture.

When the local architects, Gordon and Kaelber, sent their drawings for the exterior of the school and hospital to their consultants in New York, McKim, Mead, and White, the blueprints came back embellished with handsomely designed classical trim. When the dean and his powerful backer objected, some of the Trustees were appalled by the plain construction Eastman and Whipple wanted. One of them, James C. Cutler of the Cutler mail-chute firm, who afterward gave the university a building (the Cutler Union) and saw to it that it was done in collegiate Gothic, was greatly upset by the medical building. When someone asked him what architectural style it represented, he said "the Early Penitentiary Period." Rush Rhees, facing a divided Board, and himself torn between esthetics and practicality, proposed a middle course, and Eastman thereupon took the business in hand himself. To Rhees he wrote that unless McKim, Mead, and White would abandon the classic style and produce exactly what they were told, he advised cutting them out of the job and getting somebody who would do it. "They have $40,000 to $50,000 in an entirely unnecessary cornice . . . I do not think that from any point of view it is undesirable to have the hospital very plain." To McKim, Mead, and White he wrote

Replying to your letter of the 12th inst., I have seen the new design and think it is a great improvement over the prior one. I still think, however, that you have not reached the highest pinnacle of simplicity. It was fully understood, I think, that this medical building was intended to be a real achievement in the line of simplicity and economy, something that would be outstanding, and I do not think that you have ever tackled the job from exactly this standpoint.

I cannot see that the entrance should have any marked influence on the design of the building. Why not make it a memorial monument and treat it as such against a background consisting of a "factory" building? I think it is very important that we should have the nerve to build a very plain building for its effect in various directions.

In the end Eastman and Whipple had their way. Gordon and Kaelber designed Whipple's tick-tack-toe building with rectangular, unadorned wings and connecting blocks, on a frame of concrete pillars and girders, clad in red brick walls with regular spaced fenestration, and topped by a simple parapet, with no cornices or any other ornamentation. Lawrence White of the consulting firm added a dignified classical portico at the hospital entrance, with four Doric columns surmounted, above the architrave, by lettered commemorative tablets—precisely the "memorial monument against a 'factory' building" that Eastman had demanded.

Time has curiously vindicated the two iconoclasts. What Whipple and Eastman did because they wanted the most good space for their money, our contemporary architects are doing in the name of Art. We are quite accustomed, these days, to rectangular masses with flat, unornamented surfaces, to repetitious fenestration, to roofs without cornices. While no one would rate the original Rochester medical buildings, and those in similar style which have grown up around them, as brilliant examples of modern architecture, they are certainly nearer the taste of the 1960's than anything an unfettered stylist would have built in Gothic, Classical, or Georgian in 1923. Covered by ivy, their outlines softened by trees now grown tall, their entrances and courtyards graced by handsome shrubbery, they sit very comfortably amid the green lawns of Crittenden Boulevard, somehow giving the impression that they house honest people bent on serious tasks.

But we have run ahead of our story, and must go back to the spring of 1923, when the department heads were assembling in Rochester. Pending the provision of facilities there, some of the men spent a sabbatical year in a laboratory at home, or went abroad to extend their research experience or observe clinical practice in

European hospitals. All but Clausen arrived in time to share for a while the simple facilities of the animal house. John Murlin brought there, also, the staff of the Vital Economics (nutrition) department, which was to have laboratories in the medical school though administratively part of the arts college. As the animal house became more and more crowded with human occupants, Whipple saw that the main building must be put up as soon as possible. With the somewhat dazed but effective cooperation of the local architects he took the extraordinarily bold course of beginning construction, with only general blueprints, before the interior was planned in detail, and pushed it so energetically that part of the building was under roof and some of the laboratories occupied while other wings were still naked shells of brick and concrete awaiting completion of the interior plans.

To make this possible, the immense building—which covered one and a half acres, with ten acres of floors and roofing, one and a half miles of corridors, and more than 2,000 windows—was designed in unit blocks, with wings of standardized length and width. As the concrete was poured for the frame of each wing, the wooden molds were moved to the next. Window spacing and ceiling height were standard throughout; pipes for water, gas, and steam and electrical conduits were put in at regular intervals. Each department head had simply to fit the floor plans of his clinic or laboratory into the units of space assigned to him. Under this unheard-of program no general contractor could be employed; the various stages of construction—concrete work, bricklaying, plumbing, heating, and electrical work—were done under separate contracts. George Whipple's office was the center of the innumerable conferences that were necessary to coordinate all this work, and through it all the main responsibility lay upon him for making it succeed. He had been assured that to get the building finished and the school in operation would take five years from the time when he first began to plan it. He did it in four years, and at a cost far below current estimates. The building, with all the laboratories and the 250-bed hospital, cost a little more than $2,500,000; the cost per cubic foot (the figure used for comparison by architects and builders) was $.57, scarcely half that of conventional school and hospital construction at the time.

In designing the interior of the laboratories, Whipple's urge for economy and simplicity had full play. Throughout the building monolithic floors of poured concrete served also as ceilings of the rooms below. In the laboratories no linoleum or tile covered these floors; they were simply filled, oiled and waxed, then left bare. The corridor walls and the partitions between rooms were made of brick laid directly on the concrete, three rows of hard-burned smooth bricks at the base for a mopboard, gray sand-lime bricks above. If such a partition wall had later to be changed, it could easily be taken down, leaving a smooth floor. These walls (in the laboratory wings) were not painted, except that the ceiling of the library, and later the ceilings and upper walls of the dissecting rooms, were painted white to improve the lighting.

All pipes—water, gas, steam, and drain pipes—were left exposed, an arrangement which not only saved money, but permitted additions and repairs without tearing apart the structure. On one feature of the plumbing Whipple saved at least $200,000. Rochester's building code required that all sinks must be installed with traps, which had to be vented individually to the roof. Since there were sinks in almost every room, and in some of the class laboratories (biochemistry for example) as many as 50 sinks in one room, the code would necessitate, as Whipple put it, "a forest of vent pipes interfering with work, to say nothing of being a useless expense." Hearing that Cornell University, in a new chemical laboratory, had done away with separate vents, Whipple took the city plumbing board to Ithaca to inspect the Cornell building, and so impressed its members that they let him do away not only with the vents, but also with the individual traps except on sewage lines and in the hospital.

In the front portion of the building, facing Crittenden Boulevard, which is occupied by the hospital, less austerity prevailed. In quarters occupied by patients, the walls were painted and the floors covered with linoleum. A vigorous effort was made, under the direction of Nathaniel Faxon and his head nurse, Helen Wood, to make the hospital attractive. On the first floor at the main entrance Lawrence White was asked to build a handsome lobby for the reception of patients' relatives and other visitors. After the rejection of his first plans, which called for marble walls and floor and an ornate ceiling, he produced the present comfortable, cheerful and dignified wood-panelled room.

George Eastman of course fully supported Whipple's practical economies and often contributed ideas of his own from experience in the Kodak works. It was he who advised painting white triangular patches in the angles between floor and walls in dark corners on stairways, which still arouse the curiosity of visitors to the laboratories. Only a hardened sinner, he said, would spit in a white corner, a notion wrathfully opposed by George Goler, the Health Officer, who thought the white patches implied permission to spit elsewhere. One feature in which the laboratory wings differed from the "factory" style at first surprised the Kodak magnate; accustomed to the open floors in which his hundreds of operators tended their machines, he once commented on the multiplicity of small rooms in which the medical scientists were to carry on their individual researches. On the important matter of safeguarding against fire, his long experience with highly inflammable substances used in the photographic industry had made him an expert. Certain improvements he suggested in the design of vents and flues, in the x-ray department and chemical store-rooms, were so much ahead of current laboratory and hospital practice that when fire underwriters inspected the nation's hospitals in 1929 after the Cleveland catastrophe caused by fumes from burning x-ray films, Strong Memorial Hospital was the only place, it is said, where they found nothing important to criticize.

Whipple had a local contractor make and install the built-in laboratory furniture, such as work-tables and wall-benches; chemical tables supplied with water, gas, air and electricity; and chemical hoods. This contractor had on hand a large amount of unusually sound, well-seasoned western pine lumber, from which he built the furniture in consultation with the department heads who were to use it, and installed it under their inspection. Although this equipment had something of a home-made look, it was strong and practical, and most of it is still in use after almost 40 years. To equip laboratories in this way takes much more planning and care than ordering from a catalog, but standard fixtures made by firms specializing in laboratory furniture would have cost twice as much.

In February, 1924, when the main building was well under way, the nurses' residence on Crittenden Boulevard, opposite the front of the hospital, was begun, and in September the hospital staff residence was started behind the main building. The staff house contained rooms not only for the interns and residents, but also for the unmarried junior members of the preclinical departments, an unusual feature intended to promote Whipple's aim of bringing all elements of the school into one group with mutual interests. Another feature of the school's design on which he insisted had the same purpose—a common dining room for all members of the clinical and preclinical faculty, in which those who lived outside the hospital lunched together with the resident staff, at tables seating eight people, where an intern or a young instructor found himself welcome to sit beside the dean or any of the professors, and all joined in general conversation without regard to rank or age.

One of the marvels of this creation of a first-class medical school out of nothing in four years was the assembling of a library of 20,000 volumes of books and periodicals, adequate for all branches of medical teaching and research, all shelved, catalogued and ready for use before the first students arrived. The dean was of course fully conscious of the importance of a library in a center of medical research, and when he first drew his ground plan of the main building, he placed the library at the very heart of the structure, on the main floor along the center court. However, since he had no experience in library organization, nor acquaintance with the technical lore essential to the gathering of books, he left this task to others. The university librarian, Donald B. Gilchrist, an excellent administrator, took special interest in the medical library, and on his advice President Rhees and the dean quite early in the planning period secured an expert consultant, James F. Ballard of the Boston Medical Library, who directed the purchase, largely in Europe, of complete sets of periodicals and standard reference works. As the new professors were appointed they began at once to prepare lists of books in their special fields, which Gilchrist secured as rapidly as possible. In comparison with older medical libraries, the collection thus skillfully assembled was useful out of all proportion to its size, because it contained nothing irrelevant or obsolete. Whipple placed the library in the charge of a small committee of the more bookish professors, gave them an adequate budget, and left them free to develop the further growth and use of the collection.

Much might be said about other service divisions of the school and hospital—the purchasing office and supply rooms, machine shop, pharmacy, laundry, and kitchen. The dean had to familiarize himself with all of these installations, and to make decisions about them, even when his colleagues worked out the plans. In spite of this mass of detail perpetually on his mind, he found time in 1923-1925 to organize and equip his own department of pathology and to direct his research program, which never ceased from the time when the dogs arrived from San Francisco.

Long before the school could be opened, news of the new enterprise got about widely among the colleges and the medical profession by word of mouth and by occasional newspaper items and comments in scientific journals. Naturally every premedical undergraduate at the University of Rochester hoped for admission, but Whipple and his colleagues wanted a student body of national scope, gathered from many colleges. In April, 1925, a small pamphlet of the *University of Rochester Bulletin* series formally announced that the first class would be admitted in September of that year. The requirements for admission were much the same as those of other good American medical schools, but stated in a notably liberal way, with a minimum of fixed course requirements. Unlike Johns Hopkins, which alone demanded a B.A. or B.S. degree, Rochester required only three years of college training, but actually most of its students completed college before entering. In accord with the trend of the times, the fixed requirement in chemistry was high—three years of college work—whereas only one year of college biology was considered essential, instead of two, as formerly in most schools. A year of college English and a reading knowledge of French or German were requisite; Latin, to the extent of two years of a high school course, was rated as highly desirable but not essential. The announcement stated, however, that candidates with more extensive training in sciences and languages would be given preference, and broadmindedly added that the committee on admissions would be "favorably influenced by evidence of unusual attainment in any branch of learning which a candidate may appear to possess in addition to the prescribed subjects." The dean and the three of his colleagues who constituted the committee were busy that spring and summer interviewing dozens of candidates, from whom they chose

20 men and 2 women, representing 11 colleges in the United States, one in Canada, and a Swedish gymnasium.

Arrival of the first class of students almost doubled the personnel of the laboratories—in the fall of 1925 there were 28 faculty members working in the building—and added to the feeling of expectancy and hope that already reigned in the barely-finished classrooms and corridors. While the building was being erected, the men who helped to plan it could in imagination picture the place in full action, no "factory" but a modern intellectual work-place inhabited by busy investigators, physicians, and students, well equipped with apparatus and books, buzzing with activity. Yet there is no denying that until this dream came true and occupancy gave personality to the building, it did look uncompromisingly bare. In the spring of 1925, before the students came, when only a few workers were scattered through the endless rooms, George Goler brought a well-known Austrian zoologist to see the school. They chanced to meet three or four of the most youthful-looking professors, at work in rooms as yet sparsely furnished, with doors not yet hung. On leaving the building the visitor exclaimed "Vat kind of a place iss it? The building iss a barn, the professors are all boys!" Time has corrected both these faults. The original professors have all retired from teaching, the youngest of them in 1960. Some of them, and as time went on, their successors, saw fit to soften the bareness of their offices with rugs on the floor and hangings at the windows; others tolerated, even rejoiced in the simplicity of their surroundings. George Whipple, dean emeritus, still working in 1963 in one of the rooms with bare concrete floor and exposed pipes, which he built in 1923-25, has decorated his walls with something that means more to him than plaster and paint—a collection of photographs and other mementoes of his early faculty and their successors, who for almost two-score years have been advancing medical science in that same building.

CHAPTER

# 8

# THE DEAN'S THREE-LEGGED STOOL

AT AN INTIMATE DINNER of the University of Rochester medical faculty in 1934 when George Whipple won the Nobel Prize, Wallace Fenn, professor of physiology, revealed an unsuspected gift for light verse by reading a parody of *The House That Jack Built,* telling of the school that George built and all its inhabitants from the dean to his dogs. Brought out again, by request, from time to time, this amusing piece grew by accretion; for the occasion of Whipple's retirement in 1955 Fenn added a new stanza beginning

> With wisdom born in New Hampshire's hills
> And a high disdain for useless frills,
> He sat him down on a three-legged stool,
> And man by man there grew a school . . .

And indeed, to those who worked in the house that George built, the best-remembered sight of their dean is that of a tall figure in a white coat, seated on a high laboratory stool, before a microscope, with a tray of slides beside him, from which he would turn with a smile to welcome the colleague coming in to consult him. Newcomers to his laboratory were sometimes a little daunted by an oddly quizzical look largely produced by a peculiar pair of eyeglasses, crescent-shaped at the bottom for reading, with the tops cut out because he had excellent vision for distant objects. This old-fashioned equipment—"preacher's glasses" as they used to be called—so amused the medical students that once at a party they hilariously presented the dean with the missing tops. Peering over his crescentic lenses George Whipple looked more like the firm but kindly teacher that he was at heart, than the chief executive of a heavily endowed enterprise. Nor did the surroundings lessen this impression. A work bench along the walls held microscope lamps for use by the pathology staff when they met to review autopsy slides with their chief The blacktopped center table was generally piled high with application papers from hundreds of college students wanting to enter the school. There were indeed no useless frills in this combined laboratory and office, no easy chairs, no rugs on the concrete floor; the quartered oak desk held but one telephone.

Whipple had, it is true, the luxury of two offices instead of one. In an early talk with President Rhees he had insisted that his workplace as professor of pathology should be separate from the Dean's Office. The latter was just around the corner of the corridor from the pathology department's quarters, far enough away for the desired separation of functions, near enough for the dean to reach it in a minute or two. His administrative suite consisted of two small rooms, one of them for his own use, where he read the official mail, dictated letters, and received callers on the school's business. The adjacent office, as plainly furnished as the others, was that of his executive secretary. During Whipple's entire term as dean, 1921 to 1953, this post was held successively by two loyal and efficient women—Laura Olmstead Dunson until her sudden death in an automobile accident in 1929, Hilda de Brine thereafter.

On the principle (not always honored by educational institutions) that "where people are organized for thought, the simpler arrangements are kept, the better," Whipple set up the Dean's Office in the simplest possible fashion. Staffed only by the executive secretary and, after the first year or two, one typist, the office had charge of application papers and all the correspondence concerning admissions, student records, preparation and publication of the annual bulletin (catalog) of the school, preparation of material for the president's report, and alumni records. Only two large segments of the dean's routine—preliminary screening of applications and student loans—were handled elsewhere by Walter Bloor, associate dean, in his own office in the department of biochemistry. All this work ran from year to year without hitch or confusion, and yet with so small an array of typewriters and filing cabinets that a casual visitor would scarcely have noticed the Dean's Office, inconspicuously tucked away in a side corridor. The faculty regarded it as a great joke when, in the 1930's, a survey committee from the Association of American Medical Colleges, scrutinizing the virtues and shortcomings of the school, could find nothing for unfavorable comment more serious than the allegedly insufficient space, office equipment, and personnel of the Dean's Office.

Along the way from one of George Whipple's offices to the other were the rooms occupied by his immediate colleagues of the department of pathology—a large laboratory equipped for chemical work, in which Frieda Robbins had her desk, and individual rooms for the junior pathologists. For his first associate professor, Whipple chose Harry P. Smith, one of the Hooper Foundation Fellows who had gone to Johns Hopkins and to Columbia University for further training. Another of the Hooper Fellows, Stafford L. Warren, came also to Rochester in 1926 to head the x-ray department as associate professor of medicine under William S. McCann; a third, Irvine McQuarrie, joined Clausen's pediatrics staff the same year.

Dean Whipple would set no special hours for consultation with his professors, who were always welcome to see him at any time without an appointment, and generally found him in his laboratory. Here, indeed, many man-to-man discussions of policy were held, and even though on such occasions the dean might quit his perch at the microscope to sit for a while in his desk chair, the three-legged stool remained a symbol of the significant fact that the school was organized and led by a working scientist. American medical schools have been administered in various and diverse ways, ranging from one-man control by a dean to a council of the whole faculty. In the long run neither dictatorship nor all-out democracy can succeed in so complex a business. Whipple and his colleagues agreed that the Johns Hopkins medical school had evolved an excellent system of control, in which the school's affairs are directed by an advisory board—so called because its decisions are subject to review by the trustees of the university—made up of the department heads with the university president as chairman. From the standpoint of the department heads, this is a democracy; from that of the faculty at large it is an oligarchy, in which each professor is a potential dictator over his own departmental staff. The system works well, however, as long as the juniors trust their respective chiefs to represent their interests fairly.

In an old-established school with experienced senior professors the dean may become merely the executive officer of the board, but in a young school he must definitely take the lead, and this he can do most effectively if he is himself an outstanding investigator and teacher. At Rochester Whipple was clearly the head of the enterprise. His decisions prevailed, but he made them as does the captain of a team, not as a dictator. One does not contend with a leader who possesses more experience than one's self, makes up his mind firmly after thorough reflection, knows exactly what he wants, and talks only when he means business. George Whipple had occasion to exert his authority particularly in matters involving expenditure. Not sure, at first, how deeply the young professors would share his own sense of responsibility for the funds entrusted to him, he kept his hands tightly on the purse-strings until the laboratories were equipped and the departments safely running on their individual budgets. With infinite care he reviewed every requisition for apparatus and supplies, assenting to each item he thought necessary but not yielding a cent for frills. William L. Bradford, now professor of pediatrics, relates that when he entered Bayne-Jones's laboratory for a year before the pediatric clinic opened, he was told to make out a requisition for equipping his workroom. Looking about the school, he noticed that some of the men had $35 swivel chairs (this was in 1926!), and requisitioned one for himself. He badly wanted an electric centrifuge, but that was $150, and he did not list it. Bayne-Jones took the list to the dean; when it came back the swivel chair had been stricken off and a plain one ordered instead, but at the bottom of the list Whipple had written in a centrifuge.

If, now and then, a staff member thought one of these decisions arbitrary, the dean's patient, reasonable, slightly pained explanation closed the matter. Once, however, in the early days the Advisory Board disagreed *en bloc*. It was a question of rugs for the bedrooms in the staff house. In Rochester, bare concrete floors get very cold on a winter morning. The dean said that in his youth he had survived some very cold weather in New England, and when he lived in the Johns Hopkins Hospital he had no rugs on the floor of his bedroom. The money could be put to better use. Faxon, the hospital director, and the clinical professors argued for a little comfort under foot for their residents and interns. When President Rhees, quietly amused by the debate, put the question, the dean found himself in a minority of one—and took his defeat with good grace.

Once his Yankee caution had given place, after thorough observation of his professors, to confidence in their judgment, Whipple relaxed his direct control of fiscal details. On matters with which one or another of them had more experience than he, or was obviously ready to take over, the dean's confidence was freely and promptly given. Control, for example, of the library budget, of relations with the city's health office laboratories, of student financial problems, of the procurement of cadavers for dissection, were fully entrusted to individual professors or small committees. Curricular questions—what and how to teach one's own subject, when to give examinations and what kind to give, how to grade students—were left to the professors with great liberality. The same respect for individual responsibility that made the dean insist on his own authority in administrative business impelled him to trust his colleagues in their own fields. Professors were free to try any sort of pedagogic experiment. With his blessing one of the preclinical departments once gave a final examination made up entirely of questions set by the clinical professors, and another year held no final examination at all. When the first course of instruction ever given in the school, in microscopic anatomy, was being planned, the professor in charge of it thought he had better explain his somewhat unorthodox ideas to the dean, for whose subsequent teaching of pathology a knowledge of histology was requisite. Whipple listened with attention to his colleague's proposal to disregard the specifically human peculiarities of cells and tissues, and teach the general principles of histology instead. In place of the usual sections of preserved human organs from the autopsy room, or of animal organs chosen primarily for their similarity to human tissues, he would use fresh animal tissues best adapted to illustrate fundamental structural features and physiological activities. Some professors of pathology, he knew, would resent this neglect of practical details. "Not I," said Whipple—and the reply was typical of his attitude in such matters—"you teach the principles; we'll take care of their application to human pathology."

The dean's three-legged stool had its role not only in the building of the faculty, but also in his thorough-going effort to secure outstanding students, for he conducted that vital business not from the dean's office, but from his laboratory room. The task of the committee on admissions was to choose the best men and women from a crowd numbering, year after year, 10 to 20 times the available places. After the executive secretary had assembled the applicant's filled-out questionnaires, their college records, and supporting letters from their college teachers and other professional people, Whipple and the associate dean, Walter Bloor, chose the more promising collegians, as indicated by these papers, and summoned them to Rochester. There they were shown the school and then sent the rounds of the admissions committee—Whipple, Bloor, one other preclinical and one clinical professor—for a series of interviews, each lasting sometimes a half-hour or more. Only those candidates who lived at a great distance, on the Pacific Coast or in the deep South, were sent for interviewing to local physicians known to the school.

After one of these interviews with Whipple, the applicants often remembered not only the kindly manner with which he received them and the searching questions that followed, but also how neatly he managed to end the visit promptly. "The interview was a brief one," said one of the earliest students. "The medical school building had not been completed, and the dean's office was still in the dog laboratory. When I, after answering Dr. Whipple's questions, unable to think of anything brighter to say, observed that the dogs were certainly noisy, he replied that they had nothing else to do. I suspected that this was my cue to go."

All fall these interviews were in progress as candidates kept coming. Once a week the committeemen gathered in the dean's laboratory, and seated on stools around his center table, with piles of application papers before them, proceeded to choose the candidates they liked best. Four men, representing diverse fields of medical science and practice, were bound, in their very human task, to apply different interests and tastes. The dean, their chairman, was motivated by the practical need to fill each class with men and women who would waste no part of the great opportunity they were given. He focussed the committee's attention on the essentials—high college grades in the sciences, especially biology and chemistry, with good but not necessarily outstanding records in other subjects; good health, mental and emotional stability, agreeable personality, and monetary resources or borrowing power sufficient to avert financial disaster during the school years. As for special accomplishments, which the catalog promised would be given favorable attention, members of the committee might variously favor students who added to good work in science unusual proficiency in the classics, or history, or one of the arts. Such personal tastes of the committeemen were respected; perhaps the wise dean perceived that each of them, himself no less than the others, was more or less unconsciously looking for students made in his own image. George Whipple certainly had excellent reasons for his own criteria. A doctor's son himself, he argued that doctor's sons make especially good medical students, because they know, better than others, what kind of a career they are entering, and are prepared for its rigors, in school and in later life. Having been a hunter and fisherman since boyhood, and a "Y" athlete at Yale, he favored out-of-doors men and athletes because they are healthy and strong, and above all captains of college teams, who are natural leaders. It would be slanderous to suggest that a keen young fly-fisherman might also have been at a special advantage, but he would at least have had a delightful interview with the dean.

A whisper got around that Whipple's seven years in San Francisco had made him something of a Californian, and that applicants from the West Coast were in high favor, on which, if true, he might have commented that young Californians, after all, are a sturdy, affable lot, likely to make good doctors. A number of them were, in fact, admitted, and like most of the athletes, justified the dean's hopes.

These same early classes included men whose special qualifications included the ability to write superior English prose, read Latin or speak a modern foreign language; one or two musicians, a scattering of M.A.'s, M.S.'s, and Ph.D.'s in various sciences; a bachelor of divinity, and a very good student who had worked his way through college by tending bar at a country club. The committee sometimes took long chances. To an applicant admitted because his general qualifications seemed to outweigh very poor college grades, Whipple felt impelled to write when notifying him of his admission, "but if your scholastic record here resembles in the least your scholastic record in your undergraduate course, do not expect to be with us more than six months." This gamble paid off; the young man took his medical degree in the middle third of his class, and is a successful physician.

Applicants from foreign countries, Whipple thought, were in general unacceptable, however well prepared, because this was an American enterprise, planned to train physicians for work in our own country, not abroad under very different conditions; every foreigner admitted would keep out an American. The dean dismissed as impractical the idea that Rochester could afford to train a few men to lead medical education in less advanced countries. Other members of the admissions committee sometimes tried to defend an idealistic and necessarily unprovable policy in such matters against Whipple's hard-headed realism. One of them, for example, spoke up (quixotically, the dean said with some justice) on behalf of a well-recommended Chinese youth, son of a high official in exile after the Japanese overran their homeland, who hoped to return when the invaders had been driven out, and to help resume the westernization of Chinese medicine. The dean's irrefutable certainty that not in the young man's lifetime would any such dream come true, ended that day's discussion.

When at the beginning of each school year the entering class assembled in the amphitheater to get its first instructions, Dean Whipple was always present to welcome them in a brief talk. After that most of them saw little of him until his course in pathology started in the fall of the second year. To the general run of medical students he seemed at first rather formidable. "His personality," one of them said, seemed to be reflected by the austerity of the unpainted walls. We knew, of course, of his ceaseless industry in his continuing study of the metabolism of body pigments. It came as something of a surprise to us in our second year to find that this able administrator and famed investigator was also an exceptional teacher. In the classroom he was clear and concise. He seemed to have inherited an economy of words from his New Hampshire forebears. Most of us will remember him best as we sat in those uncomfortable stands about the autopsy table. We will remember him with his apron, his half-moon glasses, giving his keen exposition of the evidences of disease that lay before him and his lucid reconstruction of the course of events as he saw it.

Whipple did not teach pathology by formal lectures, but rather at the autopsy table and by demonstration of pathological organs and tissues, study of microscopic preparations, and quizzes which were really conferences between the teacher and his pupils. His method of presentation was quite unlike that of the teachers he had most admired when a medical student, for with all his knowledge of pathological anatomy and physiology, he neither possessed nor tried to imitate Osler's ebullience and allusiveness, Mall's subtlety, or Welch's rich store of historical information. Aiming only at a concise, orderly, unadorned statement of the facts, he carefully defined the limits of current knowledge, presenting conflicting interpretations without going into unnecessary hypotheses. Thus he explained the most complex patterns of disease in the simplest possible way and in the plainest language. His enthusiasm for his subject— an indispensable attribute of all good teaching— revealed itself indirectly in the thoroughness with which he himself studied his material and the pains he took to expound it clearly.

Whipple's skill as a teacher lay, however, not only in clear exposition but also in his ability to build up the students' confidence in their own power of thought. "He treated the student," one of them wrote,

as an adult who was to be shown new facts and guided into the habit of careful and critical thought, not as an apprentice to be bullied into learning. . . . Whether in the weekly oral quiz, the demonstrations of pathological specimens in the autopsy room, or in the study of slides under the microscope, we always had the feeling of Dr. Whipple's willingness to discuss a problem as between two people with a common goal. . . . He provided an advanced course on how to think.

Two characteristics most often mentioned by former students may surprise readers only casually acquainted with George Whipple, who have seen in the foregoing pages of this book so many evidences of his firmness and reserve. These are kindness—as one alumnus has put it, "gentleness in the handling of both human tissues and human beings"—and humility, of a kind that rests on the assurance of his own inner strength. "I have heard him openly apologize to a student," another former pupil wrote, "for embarrassment caused by the student's misinterpretation of a question Dr. Whipple asked in one of his quizzes. His patience and tolerance made pretense and bombast completely out of place."

As professor of pathology and dean, Whipple was intolerant only of superficiality and lack of purpose. For a student to do poor work was a reprehensible waste of laboratory space and of the faculty's time. Just as Whipple had striven, while planning the buildings, to get as much good space as the available money would buy, so in conducting it he aimed to use the school's endowment and facilities to make only good doctors and scientists. When dealing with a serious deficiency in studies, or a grave disciplinary problem—rare in a student body of Rochester's quality—Whipple weighed the probability that the student in question could be salvaged, and if the chance looked small, his recommendation to the Advisory Board was to get rid of the man and give the place to someone who would profit by the opportunity. Some of the younger faculty members were puzzled when they found that their dean at first also classed mental illness with moral delinquency and infirmity of purpose as a bar to the continued study of medicine. Physical illness George Whipple understood and allowed for; several young men who came down with pulmonary tuberculosis, for example, were generously helped to take the cure and return to work; but men trained, as Whipple was, at Johns Hopkins before Adolf Meyer introduced modern psychiatry there, were pessimistic about mental illness and regarded a breakdown as a sign of unsuitability for a career as exacting as that of medicine. When, on one occasion, a preclinical professor and one of the hospital's psychiatrists laid before the dean the case of a badly disturbed student whose illness they felt resulted from comprehensible stresses and was being cured, he yielded with reluctance to their plea that the young man be readmitted, predicting that time would prove their hopes to be in vain. Yet less than 20 years later, under Whipple's leadership, psychiatry was raised to departmental status in the school, a large new wing was built to accommodate its expanding clinic, and an outstanding psychiatrist, John Romano, was appointed full professor and given a place on the Advisory Board.

Whipple's deep-seated confidence that sound young Americans can rise to great opportunities led to his boldest innovation at Rochester, the creation of a student fellowship system which extended to all the preclinical departments the program he had successfully begun at the Hooper Foundation in San Francisco. The departments of anatomy, biochemistry, physiology, and bacteriology, as well as pathology, each had the privilege of selecting annually, from the class completing its scheduled course, a student who had shown exceptional ability, to be offered a fellowship for the following year. Students who accepted the opportunity became for the time being junior members of the faculty, and lived, if they chose, in the staff house. They took part in the research of the departments to which they were attached, and helped to teach the laboratory courses which they had themselves taken the previous year. Students offered such a fellowship rarely declined it, even though it meant adding a year to the time required to complete the medical course. Practically without exception they measured up to their opportunities and as a group became a valuable element in the school. Their demonstration that by a year's hard work in the regular courses one can learn enough of an intricate science to begin teaching it was a profound example to the students of the succeeding class, who readily accepted the student Fellows as teachers and later as classmates when at the end of the fellowship year they returned to regular studies. Bridging the gap between student body and faculty, the student Fellows showed that in professional study based on research, there are no masters and pupils but only older and younger students.

Since anatomy was the first subject of the curriculum, that department had the honor of appointing the first Rochester student Fellow. Willard M. Allen, who courageously staked his second year of professional studies upon a scheme so novel, is now professor of obstetrics and gynecology at Washington University, St. Louis. Edward J. Manwell, the first student Fellow in pathology, is a much-appreciated physician in Northampton, Massachusetts; Donald S. Martin, first student Fellow in physiology, became dean of the Medical School of the University of Puerto Rico. Their successors include many men with careers of similar usefulness and distinction. Some of those who held the fellowship in pathology have recorded their appreciation of the opportunity to work in close association with George Whipple. "The year I spent as a student Fellow in pathology," one writes,

I look back on as the most stimulating and profitable time in all of my medical training. Then I learned much about careful, detailed observation, about objectivity in arriving at conclusions, and the importance of always trying to visualize what is going on in the tissues when making a clinical diagnosis. From the man himself I learned the wisdom of patience, objectivity, and the placing of the long view above the short one without losing sight of individual human values.

"My fellowship in pathology," says another,

came at a time when I was floundering a bit. At the end of my second year I wanted very much to spend some time digesting and reflecting on what I had learned. The opportunity to spend it in the pathology department was just what I was looking for. The work gave me a chance to use knowledge of anatomy, physiology, biochemistry, and bacteriology. I had the opportunity to get a first-hand conception of what research consists of and to learn pathology by teaching it. I think that the main values derived from my fellowship were a prolonged association with men of high caliber, familiarity with some of the inner workings of a medical center, and a better understanding of the integration of the preclinical and clinical departments in the functioning of the school.

A third points out one of Whipple's characteristics that meant much to his Fellows:

In spite of Dr. Whipple's outward conservatism, he has a strong sense of nonconformity . . . a constant appreciation of a spark of difference in people. . . . His secret is the sincere feeling that a man's development and education are the product of the individual, rather than the system.

George Whipple himself, when asked after his retirement what he considered his most significant contributions to medical education, placed first his introduction of student fellowships. Almost 40 years after he began the program at Rochester, he has the satisfaction of seeing it in full operation, a permanent feature of the school's educational system.

Under the pact he had made with President Rhees to protect his time for research, teaching, and administration, George Whipple took no part whatever in official Rochester civic and professional activities. He sought acquaintance, of course, with leading physicians especially interested in the school, consulting them on matters of general policy such as the appointment of physicians and surgeons to the part-time staff; but he rarely attended meetings of the local medical societies, and only when the speaker or the topic especially interested him. The city's medical men at first hardly knew what to make of such reserve and seeming indifference to professional ties, but finally got it through their heads that the dean was simply a man exceptionally bent on minding his own business. Those who had good reasons for taking up his time found him quite approachable and the rest left him alone. There were a few influential physicians who were hostile to the school, but the effect of their opposition was small in comparison to the similar reaction in Baltimore when the Johns Hopkins Medical School was started. Any danger that the dean's aloofness might harm the school by failing to win the goodwill of the city doctors was averted, first, by the understanding and helpfulness of some of the leaders of the local profession, notably George W. Goler, the Health Officer, the prominent surgeon Edward W. Mulligan, and the pediatrician Albert D. Kaiser, and second, by the willingness and ability of some of the senior faculty to associate with the city's physicians and to represent the school in their organizations. Especially useful in this respect were Stanhope Bayne-Jones, always warmly generous with his time and great experience in public health problems, the enthusiastic, well-informed professor of internal medicine, William S. McCann, and the friendly master surgeon, John Morton.

Whipple held closely also to his resolve to attend only one or two scientific meetings each year. It is characteristic that the two professional societies in which he was most interested both represented, in the 1920's and 1930's, new movements involving rising young medical men and scientists. One of these was the Association of American

Physicians, which he especially enjoyed because it kept him in touch with the broad field of clinical medicine, and annually renewed his associations with many old friends and former colleagues. The other was the American Association of Experimental Pathology, organized by men who were breaking away from conventional pathological anatomy into physiological and biochemical pathology. He had been its secretary for a year or two soon after its organization, while he was in San Francisco, and was elected its president in 1925. With growing fame and maturity he was finally drawn also into the official ranks of the older, more orthodox society in his own field, the American Association of Pathologists and Bacteriologists, which made him its president in 1930.

Dr. Rhees once in a while brought up in conversation with Whipple some civic or national activity in which, he hinted, the dean's participation might be justified, but Whipple steadfastly declined to take these hints. Only once did the president speak out; when in 1927 Whipple was asked to become a trustee of the Rockefeller Foundation, Dr. Rhees frankly pointed out how deeply obligated the University of Rochester was to the Rockefeller family and their eminent advisers, who had made possible the establishment of the medical school, and plainly indicated his wish that Whipple should accept the appointment. To this presidential command Whipple gracefully yielded and served on the Foundation's board for sixteen years, 1927-1943, with such satisfaction to those who directed the affairs of the Rockefeller philanthropies that he was appointed also to the General Education Board (member and trustee 1936-1943) and the Rockefeller Institute for Medical Research (now called simply the Rockefeller Institute), serving on the latter's Board of Scientific Directors from 1936 until in 1943 it was merged with the Board of Trustees, of which he was also a member from 1939 until he retired as Emeritus Trustee in 1960.

In 1929 Whipple was elected to the National Academy of Sciences. Membership in the Academy not only constitutes a highly prized recognition of eminence in research but also, in accord with the purpose for which President Abraham Lincoln called the Academy into being in 1862, opens broad opportunities for participation and leadership in national scientific affairs. Whipple expressed his appreciation of the honor by occasional attendance at the Academy's annual meetings in Washington, but he never cared for a role in its administration, and managed to avoid entanglement in the extensive and often burdensome committee work of the Academy and its associated National Research Council. Such chores, he felt, by taking time from his crowded Rochester schedule as investigator, professor, and dean, would distract him from the kind of service to science for which he was best adapted and which, in fact, had earned him membership in the Academy.

The incessant work and anxieties involved in organizing the school and directing it during its first decade took their toll of the dean's health and strength, though fortunately not through major illnesses, but in a good deal of fatigue and frequent respiratory infections. Especially in April and May of each year he suffered from congestion in the ethmoid sinuses, most inaccessible of those cavities of the facial and cranial bones which have caused so much human misery. Much of this congestion he attributed to allergic response to pollens from trees and plants burgeoning in Rochester's short but intense springtime. At that period of the year he kept on his desk an atomizer filled with a decongestive solution with which he frequently sprayed his nose and throat, even, without the least embarrassment, during an interview or a committee meeting. After a few seasons in Rochester he acquired a face-mask resembling the gas-masks of the First World War, equipped with an air-filtering membrane. This object, hanging by a strap around his neck, accompanied him wherever he went. Legend says that in the worst part of the pollen season he wore it even in the hospital dining room, pushing it aside only long enough to take in nourishment. When in 1943 the Rochester Museum of Arts and Sciences at a formal evening meeting awarded him its Civic Medal, Whipple carried his mask with him in case the air in the hall should irritate his nose and throat. Quite regardless of appearances he took his place in the front row on the platform with the unusual appurtenance slung over the bosom of his full-dress shirt. A member of the college faculty, seated near the back of the hall, avers that an old lady sitting near him whispered to her companion "What is that object he's wearing around his neck?" to which the other replied "That must be the Nobel Prize." The mask, however, could not conveniently be used during a running conversation or in conferences, and until the advent of air-conditioning enabled Whipple to ventilate his laboratory office with filtered air, he excluded pollens as much as possible by simply keeping the door and windows shut. A meeting of the pathology staff or the admissions committee on a warm spring day under those conditions could be a highly soporific occasion.

As to his minor ailments, George Whipple's philosophy, once expressed in conversation with his friend Ned Park, is that "the people who live longest are those who are often ill and therefore have to take good care of themselves." When attacked by a cold or the grippe he went directly home to bed, surrounded himself with appropriate remedies, and remained incommunicado until he felt like going back to work. "When I am sick," he once wrote to William H. Welch when the latter was ill, "I do not like to see people and I recognize the same feeling in others." In spite of all the research that has been done on common colds, George Whipple's way of getting over them is the best one yet known to the medical profession and in his case provided much-needed periods of rest and solitude for a man often weary in body and mind.

Rochesterians of the leading business and professional set are very sociable folk, who readily take eligible newcomers into their circle and are always eager to make the acquaintance of people who come to the city, as did the Whipples and their colleagues of the medical faculty, to share in its important enterprises. During the first years of their residence in Rochester George and Katharine had enough dinner invitations to have kept them out, in mid-season, almost every evening. For George this was an intolerable drain upon his daily store of energy; a late evening could spoil the next morning's work and a string of them was far more fatiguing to him than to people who naturally enjoy society for its own sake. Never keen for the casual give-and-take of light conversation, he was simply bored by parties where he had to meet strangers and people in whom he was not interested.

His reticence and taciturnity on such occasions became something of a legend in Rochester, and like other legendary lore was often exaggerated. There is the story, for example, of a socially prominent lady who found him an uncommunicative dinner companion and when at last they rose from the table sweetly said "Well, Dr.

Whipple, I hope you haven't said anything this evening that you'll regret later." This was an intelligent woman who might better have used her wit to get him talking on something that interested him; but sometimes he had still worse to face—the scatterbrained kind of society woman, unequal to sensible conversation with an eminent man, who meets the situation with trivial chatter and embarrassing personalities. The type has been amusingly sketched by Sinclair Lewis in a dinner party scene in *Arrowsmith,* his novel about medical scientists, written during these same years. George Whipple could not stand such a companion any better than Martin Arrowsmith; after such an ordeal he simply would not meet the lady again. More than once when he learned that someone of that type was to be at a party to which the Whipples were invited, Katharine had to make last-minute excuses for their absence.

Only two kinds of Rochester people, however, supposed that George Whipple was fundamentally inarticulate or uncommunicative—those who bored or irked him by triviality or affectation, and those who did not know him well enough to break through his reserve. Close acquaintances were well aware that this was the defensive mask of a man too serious for light chatter or petty sociability, and lonely under the weight of his heavy responsibilities, who longed for the solid friendship and relaxing company of men sharing his tastes and interests. Congenial people always found him ready for a talk about matters of mutual concern—medical science and education, university affairs, national politics; about hunting and fishing, with fellow sportsmen able to appreciate his out-of-doors wisdom and match his anecdotes; or about experiences and friendships shared in earlier days. In the daily work at the medical school he never lacked words for clear and often humorous teaching; and those few people who, once in a long while, by stupidity or arrogance overtaxed his patience, called forth an outburst of sulfurous profanity, ample in its variety and of more than adequate length; and yet—such is Yankee self-control—seldom directed at the offender in person, but reserved for the recounting of the incident to a sympathetic friend or to Katharine.

Two of the characteristically Rochesterian dinner clubs, to which reference has already been made, elected Whipple to membership soon after he settled in the city. The elder of these, The Club, or

"Pundits," included in its membership President Rhees, Dr. Mulligan, and several trustees of the University of Rochester, as well as other cultivated professional men. To the annual duty of preparing a paper for presentation at one of the fortnightly meetings, a further burden was added by The Club's rule, at that time, that every member must discuss the evening's discourse impromptu, and at some length, no matter what the subject. Both requirements were irksome to men not in the habit of either writing or talking unless directly interested in the topic under consideration. Such a man was George Eastman, whose membership in The Club lasted only two years; in 1910 he read a paper on "The Growth of Photography from a Commercial Point of View" and in 1911, one on "Fixed Prices," a subject of critical concern to his company and the U. S. Government. George Whipple's connection with The Club ran an oddly similar course. He too presented a couple of papers, one in 1923 on "Medical Education," and the other in 1924 on "Problems of Research Medicine," after which he followed Eastman's example by resigning, on the ground that the meetings and his annual paper took up too much time and energy. He held his membership in the Fortnightly Club for some years longer but finally relinquished it for the same reasons. It is a pity that we have no record of the talks in which he gave his well-informed and influential fellow members the benefit of his thinking on the current state of medical research and teaching.

George Eastman made his great house on East Avenue a social center where he frequently entertained the leading business and professional men and city officials, not for sociability alone but also to bring them together for the benefit of the city's cultural development. At his small intimate dinners George Whipple was sure to meet men of affairs well worth knowing. Every Sunday, moreover, in the fall, winter, and spring the Kodak magnate invited 150 to 200 guests for a late afternoon and evening musicale which began with an hour of chamber music by the Kilbourn Quartet, named for Eastman's mother and made up of professors from the Eastman School of Music, playing the violin, viola, and 'cello. Their programs usually included music by one of the classical, romantic, or modern composers from Haydn to Ravel. This was followed by an informal supper, after which Harold Gleason, Eastman's private organist and professor at the Eastman School, continued the musical program for another hour with classical selections on the Eastman House pipe-organ.

Members of the medical faculty and their wives were regularly invited to those musicales, the professors two or three times each season, the dean much more often. No one who liked music and good society could fail to enjoy these evenings. For George Whipple they satisfied a fondness for music which few of his acquaintances knew he possessed, for in the first place he never spoke of it, and in the second place did not care to indulge it through long hours in a crowded concert hall. While at Yale, at dusk on a Saturday evening in winter, he had often climbed to the gallery of the college chapel, a solitary listener to the organist practicing for the morrow's services. The organ and the string quartet at Eastman House appealed to the same quiet liking for music, now heard in surroundings of great elegance and comfort. In later years the radio has happily enabled George Whipple to enjoy a favorite symphony or band concert without stirring from his own easy chair.

George Eastman, who like many old bachelors liked the society of congenial women but cautiously sought safety in numbers, regularly entertained at Saturday luncheons a few ladies, usually wives of senior Kodak or university men. Katharine Whipple, soon after moving to Rochester, became one of a group, including also Nannie Bayne-Jones, wife of the professor of bacteriology, Mary Folsom, wife of the Kodak Company's treasurer, Marion B. Folsom, and Marion Gleason, wife of Harold Gleason the organist, all of them agreeable and talkative companions for the lonely millionaire. Thus the mutual respect and friendship that grew up between George Eastman and George Whipple was strengthened by Eastman's pleasure in Katharine's vivacious company. In 1924, the Whipples and Mrs. Alice Peck Curtis of Rochester were asked to join a cruise to British Columbia on a boat chartered by Eastman. On the way west the party of four stopped at Kamloops, where Eastman had engaged a guide and transportation to Kanouff Lake. They caught some very fine Kamloops trout and smoked some of them for future use. The next stop was Vancouver, then Seattle, where the boat "Westward" was being outfitted. Near Seattle the travellers visited Mrs. Henry Strong, widow of Eastman's first partner, whose name is perpetuated in Rochester's Strong Memorial Hospital, and added her and a friend to their party for an ascent of Mt. Rainier before they departed for British Columbia. While in Canadian waters the sportsmen enjoyed excellent fishing for king and silver salmon and steelhead trout.

In several subsequent years the Whipples visited Eastman at his North Carolina place, Oak Lodge, a comfortable house for six or eight persons on the magnate's farm and hunting preserve of several thousand acres. Here the principal sports, to George Whipple's delight, were quail shooting and horseback riding. In 1928 George visited Eastman for quail shooting at Rotherwood plantation near the Kodak Company's plant at Kingsport, Tennessee, placed by its friendly owner at Eastman's disposal. On all these trips George Whipple took his Kodak as well as his shotgun, and over the years assembled a large collection of photographs of Eastman and his out-of-door friends in camp, in the hunting field and at the picnic table. The best of these pictures have been reproduced in a booklet, *George Eastman, a Picture Story of an Out-of-doors Man—Camping, Fishing, Hunting,* compiled by George Whipple and privately published by Eastman Kodak Company in 1957. Leafing through this handsome record of the great inventor and industrialist's holidays with his friends, one looks in vain for Whipple himself, except in a few group photographs, for generally he was behind the camera; but the loving depiction of mountain and lake scenery, great catches of fish, bird-dogs in action, life in camp, open-air cookery, and relaxation by the camp fire, reflects as in a mirror George Whipple's affection for outdoor life, country sports and the friendship of good companions.

By 1927 the two Whipple children—Hoyt, then ten years of age, and Barbara, six—were old enough for long vacations in camp. Every summer from that year until 1936, the whole family spent a couple of months in ranch camps in Colorado or Wyoming, to enjoy horseback riding, and fishing, most often on Pine River in southwest Colorado, in mountain country amid 13,000-foot peaks. They travelled by car with George at the wheel all the long way from Rochester to the West, and took the opportunity on various trips to explore the Grand Canyon, the cliff dwellers' sites, Yellowstone Park, Jackson's Hole, and Glacier National Park. On these long drives the going was often rugged, and accomodations by the wayside frequently crude, adding a sense of adventure to George's driving and to the family's enjoyment of their wide-ranging tours.

But even after the dean's return, in the fall, to his three-legged stool, his outdoor recreations continued. Rochester is situated just north of the lovely Finger Lakes region of western New York, where more than a half century ago the ring-necked Mongolian pheasant was introduced and now thrives among the wooded lakeside hills and open fields. No game bird is more attractive to the sportsman than this one, with its brilliant plumage, its graceful body, its whirring rise and arrow-swift flight when flushed by the dogs. In winter, temporarily safe from the hunter, Monroe County pheasants actually paraded themselves under George Whipple's very eyes. A good-sized colony of them inhabiting surburban fields near the medical school came daily to scratch for food on a patch of open ground in full view from the dean's laboratory windows. Thither also came almost every day a flock of seagulls from icy Lake Ontario, seven miles away, intending to feast on the same provender. Many a pitched battle did George Whipple watch, itching for his shotgun, but well pleased to see the strong, swift, beautiful pheasants fling themselves upon the gulls and put them to screaming flight.

Whipple was introduced to pheasant shooting by Dr. William R. J. Wallace, a dental surgeon native to the region who knew the country well. With this warm-hearted, high-spirited man, Whipple formed a group from the medical school, including in the earlier years Bayne-Jones, McCann, Morton, and Stafford Warren, together with a few of the top executives of Eastman Kodak Company, Frank O. Lovejoy, Thomas J. Hargrave, Albert K. Chapman, and a lawyer, Willoughby Middleton. William L. Bradford, pediatrician and experienced quail hunter from Missouri, joined the group in 1932; he, Wallace, and Warren were George's most regular shooting companions. Their principal hunting ground was a large preserve operated by LeRoy Garnsey on the west side of Cayuga Lake, ten miles from the village of Seneca Falls. The group usually shot on Saturdays or Sundays in the open season, often meeting before dawn at the Whipple or Wallace home for a breakfast which all helped to cook. After driving to the lake, an hour and a half away, they had a two-hour hunt, then lunch, and another two hours in the fields.

George Whipple took command of these hunts, dividing the party into pairs or threes each following one dog. He himself always owned an excellent dog or two, keeping them at the lake the year round. His companions especially remember a graceful well-mannered pointer called "Lady," and "Chum," a large black Gordon setter, one of the best trailers and retrievers ever seen in the Finger Lakes country. He demanded complete obedience from his dogs, which he had trained himself, enforcing it by use of a shrill whistle and—to quote William Bradford—"words of praise properly balanced with other words not in the same category." When the dog pointed, George waited for his colleagues to get into shooting position, by this delay permitting any and all members of the party to make one or more misses. Warren and Whipple regularly had the largest bag. George Whipple, his pheasant-shooting friends say, is just about the best sportsman with whom any of them has ever hunted. "I don't know," one of them writes, "which he enjoyed more on our hunts—the out-of-doors, the exercise in the crisp autumn air, the performance of the dogs, or the companionship of his friends. Doctor Whipple has often remarked that one learns a lot about a man while hunting with him. What I have learned about the dean is, that great as he is as scientist, teacher, administrator and counselor, he is equally great as a sportsman."

CHAPTER

9

# LIVER, BLOOD, AND IRON

WHEN GEORGE WHIPPLE departed in 1921 from San Francisco, he left behind him a large back-log of research in various stages of completion, to be carried on by his assistants and Fellows, and by his immediate co-worker, Frieda Robscheit-Robbins. Somehow he found time at Rochester during the years of transition, 1922-1923, although intensely occupied with new tasks, to correspond with his former associates and, as each project was completed, to write or at least edit the reports for publication. The record of his published work shows no break in the number or clarity of the papers; looking over the list of contributions of which he was author or co-author at this time, one would never guess that they came from an investigator who during these same years had been organizing and building a school of medicine.

Whipple's research papers are put together in a more or less uniform way which he learned, he says, during undergraduate days at

Yale, from his admired teacher, Lafayette B. Mendel. Almost every article, after beginning as usual with a brief *apologia* or statement of the problem to be investigated, proceeds at once to state, in a few lines or a short paragraph, the general conclusions he had drawn from the work about to be described. To give the reader in this way an immediate forecast of the outcome does away, of course, with the suspense with which some scientific investigators, like writers of short stories, try to hold attention. On the other hand it focuses the reader's mind upon the aim of the research, helps him see why the investigator chose the particular procedures and technical methods next described in the paper, and points clearly to the analysis and discussion with which, according to general custom, it closes.

This expository technique is obviously better adapted to the reporting of well-defined individual experimental investigations than to comprehensive reviews, for which a different method is needed. It is especially effective, however, in the oral delivery of communications at scientific meetings. Reading an article, one can always turn to the end to see how the work came out; hearing it from the platform, one has to wait and may lose the thread of the discourse. Whipple's hearers, given their clue at the start, found his technical presentations extraordinarily clear and easy to follow. In 1932, for example, Harvey Cushing, Whipple's former teacher at Johns Hopkins, at the time professor of surgery at Harvard, and himself a vigorous, graceful speaker, heard Whipple address a small audience made up mostly of medical students. Not only did Cushing at the end of the talk warmly express his admiration in a discussion from the floor, but a few days later he wrote

> I simply must take a moment to send you a brief word about your talk before that group of boys the other night. What I was impelled to say when I got up to Hippocratize the group came from my heart. My old friend Graves, the gynecologist, who was sitting by me, when you had concluded said "That, in matter and delivery, is the best medical address on any subject I have ever listened to, and it gives a new idea of the technique of presenting a subject. But I shall never aspire to doing anything myself so well." And to this I said a hearty *amen.*

Whipple's investigations during his first decade at Rochester, presented to the scientific public in 62 reports and four reviews published between 1924 and 1933 inclusive, followed a course already familiar to readers of early chapters of this book. In every stage of his career as an investigator, we find Whipple persistently concentrating upon a central theme of greatest interest to him at the time, or a couple of interrelated themes. He turned aside now and then only to clear up a subsidiary problem that must be solved in order to get on with the main task, or to look into some unexpected findings of possible importance. Sometimes the accessory problem became a major one—we shall see this happening in a later decade when Whipple began to study intensively the regeneration of plasma proteins—sometimes it was dropped, or turned over to an able associate, as for example, the question of x-ray intoxication was left to Stafford Warren.

In the period 1914-1923 the two major themes, as we have seen, were the formation of bile salts and bile acids, and the regeneration of hemoglobin in anemia produced by bleeding. By the time Whipple resumed active research at Rochester the latter investigation, which had already disclosed the existence of dietary factors in the liver and elsewhere, effective in building hemoglobin, became overwhelmingly important, and the work on bile constituents was dropped, not to be resumed until 1928-1930, and then in a limited way only.

In a paper sent early in 1925 to the American Journal of Physiology, Whipple and Robscheit-Robbins laid down a new plan of research. Their experiments at the Hooper Foundation had convinced them, they said, that the rate of hemoglobin regeneration in the body can be modified at will by dietary factors. Although these experiments had been largely qualitative, they gave promise that an extended series of more precise experiments would yield far more valuable information about the construction of hemoglobin in the healthy body and in disease. Up to this time Whipple and Robscheit-Robbins had been working with simple anemia in dogs, produced by two or three large hemorrhages at the beginning of the anemia period. The dogs were recovering from the hemorrhage while the diets were being tested. The rate of hemoglobin production in such experiments doubtless represented a combination of spontaneous recovery from the initial hemorrhage with the extra production stimulated by the test diet. From now on Whipple and Robscheit-Robbins would eliminate the confusing effect of spontaneous recovery by keeping the dogs in a constantly maintained state of severe secondary anemia. Holding the amount of hemoglobin in the blood at a uniformly low level by repeated bleedings, they would insure a steady and maximal demand for the restoration of hemoglobin and red blood cells. From the amount of blood that had to be drawn at frequent intervals, to hold down the hemoglobin level, the number of grams of hemoglobin formed on a given test diet could be calculated.

Carefully reviewing the advantages and disadvantages of various animals that might be used for this study, Whipple decided to continue the use of dogs, which will eat with alacrity any sort of food mixture, can be kept in health for long periods even if severely anemic, and are large enough to permit adequate and frequent sampling of the blood.

The dogs used by Whipple and his colleagues at Rochester belonged to a strain begun at his San Francisco laboratory by crossing bull terriers with Dalmatian coach hounds. The cross-bred but physically rather uniform strain combined the vigor and stamina of the terrier with the gentleness of the Dalmatian. These dogs possessed valuable anatomical features—white color, short hair, long bellies well adapted to gall bladder and Eck fistula surgery, and large, resistant jugular veins, easy to tap with a needle with very little discomfort to the dogs. They became quite well known to experimental pathologists and physiologists throughout the country, and Mrs. Robscheit-Robbins, who had charge of their care and breeding, was often called upon to demonstrate them and to discuss their useful qualities at scientific meetings.

Using the newest and best methods of measuring blood volume and red cell volume, together with well-tried methods of counting blood cells and estimating hemoglobin, Whipple and Robscheit-Robbins proceeded to work out a standard basal ration, in the form of specially cooked bread, supplying complete dietary requirements for the adult dog, even in severe anemia, yet devoid of all ingredients that would favor regeneration of hemoglobin and red blood cells. As finally adopted, the ration (known as "salmon bread") contained wheat flour, starch, bran, sugar, cod liver oil, canned tomatoes, canned salmon, yeast, and a salt mixture. Dogs fed exclusively with this mixture over long periods (ultimately four years and more) remained well and lively month after month while producing only about two grams of hemoglobin per week. To this basic diet the investigators added foodstuffs and other substances to be tested for their power to speed up hemoglobin formation. On such a simple plan, put in effect by endless, unremitting laboratory routines of measuring hemoglobin and counting red blood cells, weighing out diets, and caring for the scores of sturdy, voracious dogs, the investigation proceeded to notable success.

Naturally the first dietary factor to be tested was liver, which in the San Francisco experiments had already rivalled, perhaps excelled, other meat foods in hemoglobin production. By May 1925, two and a half years after the dog colony was transferred to Rochester, Whipple and Robscheit-Robbins were able to report a highly significant result. "Liver feeding," they wrote,

remains the most potent factor for the sustained production of hemoglobin and red cells. This favorable and remarkable reaction is invariable in our dog experiments no matter how long continued the anemia level, no matter how unfavorable the preceding diet periods may be, and regardless of the substances given with the liver feeding.

Beef heart, which had been found in the San Francisco experiments to favor hemoglobin production, ran a poor second to liver in the more stringent and more precise Rochester tests, and ordinary beef muscle (lean meat) was still less potent. This report, with its unequivocal emphasis on liver feeding, published in the American Journal of Physiology, volume 72, pages 408 to 418, is the most important single paper, as regards George Whipple's world reputation as a scientist, in the whole of his immense lifetime list of more than 300 scientific communications.

For a very long time physicians treating cases of anemia had been using iron salts, given as a tincture or the well-known Blaud's pills containing ferrous carbonate, with apparently good effects. In the San Francisco experiments, immediately after observing the high hemoglobin-forming potency of lean meat, heart muscle, and liver, Whipple and Robscheit-Robbins asked themselves whether this potency could be due to iron in the effective foods, but found no evidence that treatment with iron itself was of any value. Now, in 1924-25, they tried Blaud's pills again in the long-standing, severe anemia, and this time they obtained positive results. Under the conditions of a serious shortage of iron in the body, Blaud's pills proved to be of considerable value, producing 20 or more grams of hemoglobin per two-week period, as compared with 80 to 100 grams on a liver diet. In the paper in which this finding was frankly contrasted with the earlier negative result, Whipple still emphasized the superior potency of liver, and with due caution made the significant prediction that in human beings food factors will be found more efficient in the control of simple anemia than iron or other drugs, and should be given serious consideration even in complex anemias such as pernicious anemia.

Now followed a long period of patient, thorough testing of all sorts of diets to discover how the hemoglobin-forming potency is distributed in the whole range of foodstuffs, and—it was to be hoped—to get clues to the precise chemical nature of the substance or substances possessing this beneficent property. The National Live Stock and Meat Board began to be interested in this new scientific evaluation of meat products, and through the National Research Council contributed research funds for its continuance. Paper after paper flowed from Whipple's laboratory until the series on "Blood Regeneration in Severe Anemia" reached by 1930 its 21st installment. Green vegetables proved mostly inert or of low potency; even spinach, which in the short-term experiments at San Francisco showed some value, did not in severe anemia justify its popular repute. Dairy products turned out to be useless. Whole milk, excellent as it is for most dietary requirements, is conspicuously inadequate in hemoglobin-producing ingredients—a startling piece of news for physicians who had often prescribed a milk diet for anemic infants and young children. Fresh and dried fruits were found better, especially apricots, which yielded 40 to 45 grams of hemoglobin per fortnight in the standardized anemic dogs—roughly half as much as liver.

Among animal foods, brain and pancreas (sweetbread) had some potency, but spleen tissue and (suprisingly) bone-marrow, the very tissue in which the red blood cells are formed, were not very effective. Through all these wide-ranging trials, liver maintained its supremacy. Chicken livers proved as good as beef; fish livers, however, seemed devoid of potency. The kidneys of both pig and beef gave an unexpectedly good result, standing next to liver among all meat products tested. Reporting this finding Robscheit-Robbins and Whipple could only conjecture that the kidney feeding is effective, not by a direct stimulatory action upon hemoglobin production like that ascribed to the liver, but because the kidney retains and stores hemoglobin-building materials to conserve them from loss by excretion in the urine, and thus amasses a supply of them which, as a dietary ingredient, it furnishes to the anemic dogs.

While carrying on this thorough exploration of foodstuffs of many kinds, Whipple of course gave much thought to the chemical basis of the dietary effects he and Robscheit-Robbins had discovered. In 1927 they reported a preliminary attempt to extract a specific hemoglobin-producing substance from liver. Following the usual procedure of biochemists looking for an active substance of unknown nature, they extracted large quantities of fresh ground beef liver with acidulated water and with alcohol, thus obtaining three "fractions," that is to say the watery and the alcoholic solutions and the insoluble residue. Tested on anemic dogs all these fractions possessed hemoglobin-building potency, and the sum of their individual effects roughly equalled that of whole liver. This result suggested that no single substance is responsible for the remarkable properties of the liver diet.

At this time investigators in several other laboratories were studying various types of experimental anemia, among them the team of E. B. Hart, H. Steenbock, C. A. Elvejem, and J. Weddell, experienced nutrition chemists at the University of Wisconsin. These men, studying anemia of rats caused by insufficient diets, were led by Whipple's reports to try feeding various liver fractions, and discovered that beef liver burned to an ash had a favorable action. To test and follow up this unexpected finding on their dogs, Whipple and Robscheit-Robbins called to their aid Warren M. Sperry, a young biochemist from their colleague Walter Bloor's laboratory, and C. Arthur Elden, a chemically trained physician. The four investigators soon confirmed the Wisconsin results, discovering that not only ashed liver, but also the ash of kidney tissue and of apricots, was definitely effective in stimulating hemoglobin production, with about half the respective potencies of those foodstuffs given whole, either fresh or cooked. How the inorganic residue of ashed tissue, consisting entirely of inorganic oxides and salts, can so actively stimulate the formation of an extremely complex organic compound such as hemoglobin, remains a puzzle. Whipple was forced to conjecture that there is a "salt effect" by which the inorganic compounds somehow catalyze organic reactions involved in building the hemoglobin molecule.

That various organic substances, no doubt including the amino acid "building stones" of proteins, are equally necessary became more and more certain as the investigation went on. The team of Whipple, Robscheit-Robbins, Sperry, and Elden proceeded to try a wider and more sophisticated range of extraction methods than those used earlier by Whipple and Robscheit-Robbins, using several different extractives and varying the pH (acid-alkali balance) of the extraction fluids. Practically all fractions and residues of beef liver obtained by this searching analysis proved to contain materials which the anemic dog could utilize to form new hemoglobin and red blood cells. "In spite of every endeavor," their joint report declares, "the amount of potent material found in the various residues is consistently large. All this evidence makes it more certain that a large number of factors (organic and inorganic) are concerned in the liver effect as studied in simple anemia due to bleeding." This conclusion of Sperry, Elden, Robscheit-Robbins and Whipple, set forth in 1929, still stands after more than three decades. To keep it in mind will help make clear a remarkable train of events begun in 1926 when George Minot and William P. Murphy of Boston applied Whipple's discoveries concerning the dietary control of simple anemia to the quite different problem of pernicious anemia.

Against this intractable disorder of the blood, until 1926 physicians could do no more than palliate the patient's symptoms, while watching his condition slowly deteriorate, with occasional periods of temporary improvement, until death ensued two to five years after the onset of illness. There was no clue to the fundamental nature of the disease, although it was relatively easy to diagnose by its combination of pallor and weakness with disorders of the stomach, and by microscopic examination of the blood, in which the red cells are reduced in number and irregular in form, with a variable content of hemoglobin. Because there was no obvious cause of these severe alterations of the blood, the disease was classed as a "primary" kind of anemia in contrast to the secondary varieties occasioned by hemorrhage, infections, and certain poisons and dietary insufficiencies.

When the medical world finally realized the importance of the discovery by Whipple, Hooper, and Robscheit-Robbins that liver feeding is beneficial in experimental secondary anemia, physicians naturally thought of trying liver in pernicious anemia also. This idea had occurred, in fact, to Whipple himself and his associates; we have seen that as early as 1916 Charles W. Hooper made a few experiments, unfortunately inconclusive, at the University of California Hospital, in which he administered liver extracts of his own devising. In 1923 a biochemist, R. B. Gibson, and a physician, C. P. Howard, at the University of Iowa Hospital, impressed by the early papers of Whipple, Hooper, and Robscheit-Robbins, put some of Howard's pernicious anemia patients on a diet rich in meat and liver and observed improvement sufficient to make them urge physicians to adopt this treatment. Their suggestion, however, did not attract wide attention, probably because they attributed the improvement to iron present in the meat and liver diet, whereas physicians generally were convinced after long experience that iron has little power over the disease, and indeed Whipple and his co-workers had found inorganic iron ineffective in their short-term experiments on secondary anemia. Not until the new, more thorough and precise experiments at Rochester put liver well in the forefront of hemoglobin-producing dietary factors did the full implications of the discovery take hold upon the mind of a young internist who was in a strategic position to make a thorough trial of the liver diet in pernicious anemia.

George Richards Minot (1885-1950), member of a famous Massachusetts family, and a graduate of Harvard Medical School, served on the resident staff of Massachusetts General Hospital and at the Johns Hopkins Hospital in Baltimore, and in 1926 returned to Harvard as an assistant professor of medicine. Especially interested in diseases of the blood, he took a leading part in the study and treatment of pernicious anemia as attending physician to the Massachusetts General, Huntington Memorial, and Peter Bent Brigham Hospitals. Well aware that physicians had found that pernicious anemia is often associated with a faulty diet, and that the patients often do better when placed on a well balanced, high-calorie diet containing an excess of nitrogen, he was struck by the possibilities suggested by the work of Whipple's group. "The most important recent work concerning the effect of food on blood regeneration," he wrote, "has been done by Whipple and Robscheit-Robbins and their associates. This carefully controlled work on dogs has demonstrated clearly the value of certain foods, especially liver, in accelerating blood regeneration following acute hemorrhage."

In testing the liver diet on his pernicious anemia patients, Minot had the help of William P. Murphy, associate in medicine on the staff of Peter Bent Brigham Hospital. To Murphy fell the hard work of persuading the patients to swallow a half-pound or more of liver every day, and to direct the routine of daily observation with frequent blood counts and painstaking microscopic examination of blood smears stained with dyes for special observation of the red blood cells. Minot foresaw that he could not rely on the usual diagnostic methods to keep check on the value of the treatment, because the course of the disease is often marked by deceptive temporary remissions. Therefore he paid special attention to the microscopic blood picture, and soon noticed that within a week after the liver diet was begun some of the red blood cells showed delicate networks of a substance stained blue by the standard dye mixture. These reticulocytes, as they are called, are young red blood cells, newly shed from the bone marrow into the circulating blood, and their presence showed that the liver diet was already doing its beneficent work. This simple but fundamental technical step provided a reliable basis for estimating the individual patient's day-by-day progress in spite of symptomatic fluctuations, thus guiding the physicians and encouraging both them and the patient to persist in the long, tedious course of study and treatment.

Minot and Murphy's first report on the liver diet in pernicious anemia, published in the Journal of the American Medical Association in August, 1926, won world-wide attention. It is a remarkable fact that George Minot, who thus had a leading part in one of the great achievements of twentieth-century medicine, was himself a living testimonial to an earlier medical discovery of equal note. A victim of severe diabetes, he had been saved from death by the advent of insulin, discovered in 1922 by Frederick G. Banting and Charles H. Best, and thus preserved, lived to make his own contribution to human welfare.

As usual when an organ or tissue is found to possess specific physiological potency, the investigators next set out to extract from fresh liver whatever it contained that gave such striking relief in pernicious anemia. With the cooperation of an experienced tissue chemist, Edwin B. Cohn, Minot's group within two years succeeded in obtaining an extract of high potency. As soon as a sufficient quantity could be spared, the Harvard Committee on Pernicious Anemia, which had it in charge, with Minot's cordial consent made it available to Whipple and Robscheit-Robbins for testing on their anemic dogs. Large-scale production of the purified material was then carried on by the pharmaceutical manufacturer, Eli Lilly and Company of Indianapolis, whose research director, George H. A. Clowes, had acquired considerable experience with liver extracts through investigations for other purposes.

Whipple was not surprised when the tests showed that Cohn's preparations and those of Eli Lilly and Company, which were fully potent against pernicious anemia, were relatively inert, as compared with whole liver feeding, in severe experimental anemia in dogs. The difference between primary and secondary anemia, thus revealed, strengthened an inspired guess which Whipple had made in 1927, that pernicious anemia is a "deficiency disease"; that is to say, it results from the body's lack of a specific substance normally available in the diet. In pernicious anemia liver feeding, or a suitable extract of liver tissue, evidently furnishes this specific substance; in the secondary anemia of Whipple's experiments, what the liver furnishes, as he and his co-workers had already shown, is an array of protein derivatives, presumably amino acids, and minerals including iron. The clue Minot had gotten from Whipple's work was therefore an indirect one.

To satisfy the curiosity of readers not familiar with these exciting scientific events, and to keep clearly in mind the nature of Whipple's contribution, we must add that the substance found in the liver which is curative in pernicious anemia, has turned out (in line with Whipple's early conjecture) to be a vitamin, namely $B_{12}$. In recent years skilled management of the disease and great improvement of the vitamin preparations have made it possible for the physician to control the symptoms of pernicious anemia in many cases by a single injection at intervals of several days or even weeks, properly supplemented by iron and a well-planned diet.

The sudden and surprising course of events by which Whipple's investigations had stimulated other investigators to work out a successful treatment for pernicious anemia did not distract him from the study of secondary anemia. He and Robscheit-Robbins continued testing various dietary factors on the anemic dogs. An array of minerals present in the body and in foodstuffs—manganese, zinc, aluminum, antimony—proved to be inert as regards hemoglobin production. Eggs were ineffective, gelatin slightly active, spinach and cabbage relatively poor, onions, orange juice and chlorophyll inert. In summary, after all these exhaustive experiments liver and iron remained the only food factors of real importance in treating secondary anemia.

The success of Eli Lilly and Company's biochemists in concentrating the pernicious anemia factor suggested to Whipple that they might be able also to concentrate the hemoglobin-building substances of liver that are potent against secondary anemia, even though Whipple's own team had proved that no single substance but a whole group of protein or amino acid materials was concerned in this activity. In 1926 he joined forces with George B. Walden, a colleague of G. H. A. Clowes at Eli Lilly and Company's laboratories, in testing various concentrates that had been prepared in the work on the pernicious anemia factor. One of these, known as Number 55 because it was insoluble in 55 per cent alcohol (and consequently was quite distinct from the pernicious anemia factor) proved to contain in highly concentrated form about three-fourths as much potency against secondary anemia as the whole liver from which it was made.

After this finding was announced in 1930 by Whipple, Walden, and Robscheit-Robbins, Fraction No. 55 was placed on the market for use in treating secondary anemias. Put up in capsules which also included iron, it was widely used for several years and brought the manufacturer a good deal of revenue. Before long, however, medical men in general practice, finding it difficult to distinguish pernicious anemia in its earlier stages from secondary anemia, preferred a drug useful in both conditions. Eli Lilly and Company therefore gradually gave up the sale of No. 55 as a separate drug and instead added it, together with iron and certain vitamins, to the pernicious anemia factor ($B_{12}$). The combined product, known by the trade name of Lextron, remains on the market at the present time.

To insure the potency of Fraction No. 55, first as a separate product, later as an ingredient in Lextron, Eli Lilly and Company arranged with Whipple to have it tested regularly on his anemic dogs. The tests placed no great burden on the Rochester research program, because they were made part of the routine process of standardizing the hemoglobin output of the dogs which was continually going on under the direction of Robscheit-Robbins.

For this help in testing their products, Eli Lilly and Company recompensed the University of Rochester, at first under a general contract, later paying separately for each batch tested. At this time, when the progress of medical discovery was bringing many new therapeutic materials to the market, the whole question of financial returns from useful medical researches was being warmly debated. Most American physicians were opposed to the restrictions imposed by patenting; others, and also many university administrators, argued that patenting such materials permitted scientific control of their purity and potency, and incidentally brought in revenue legitimately earned by the research laboratories. Certain products and methods, notably insulin and the irradiation of foodstuffs to enhance their vitamin content, were in fact patented by universities and their use granted to manufacturers under license.

Whipple did not take out patents on the preparations he and his co-workers had helped to develop. He preferred to entrust them directly to a pharmaceutical manufacturer whom he knew to be fully ethical and highly respected by the medical profession. Responding to this confidence, the executives and chief scientists of Eli Lilly and Company were deeply impressed by his practical judgment and the insight into business problems which he evinced without lowering his scientific standards. During the period, 1926-1953, in which Whipple's laboratory conducted tests for the company, the fees not only augmented the annual research budget of his Rochester department, but also built up year by year a reserve fund which in 1955, when Whipple discontinued his work in the laboratory on retirement from the professorship of pathology, amounted to more than $700,000. His final disposition of the Lilly Fund for the benefit of research and teaching at Rochester will be described in a later chapter.

During the work on anemia Whipple pursued several collateral lines of research. One of these had to do with the hemoglobin which exists in muscle tissue, to which it imparts the red color of raw meat. In muscle, as in the blood, hemoglobin is a carrier of oxygen, facilitating the rapid oxidative reactions on which the contraction of muscles depends. It was known that the hemoglobin of muscle is not constantly in balance with that of the blood as are salts, for example; it remains, so to speak, in its own compartment, and some biochemists thought that the two substances may not be chemically identical. Other investigators had claimed that there is at least a fluctuation of muscle hemoglobin in response to changing amounts in the circulating blood, as if the one could replace the other. Such uncertainties made it necessary for Whipple, early in his study of severe anemia, to make sure whether or not muscle hemoglobin was confusing his results by substituting for blood hemoglobin when the hemoglobin level of the blood is low. His first step, taken in collaboration with a member of his departmental staff, Robert S. Kennedy, was to compare muscle and blood hemoglobin with the spectrophotometer, a very sensitive instrument for characterizing colored substances. The two curves of light absorption proved so nearly alike that Whipple and Kennedy at first considered them identical. A physiological similarity also revealed itself when the investigators injected muscle hemoglobin into the body cavities, or into the muscles or veins, of bile-fistula dogs. Like hemoglobin from the blood, it was promptly broken down and converted into bile pigment.

Other experiments, however, brought out definite physiological differences. Whipple found, for example, that during growth from puppyhood to adult stature, and under various conditions of exercise and inactivity respectively, the amount of muscle pigment varies widely while blood hemoglobin holds to a fairly constant level. Exercise builds up muscle hemoglobin, whereas a muscle paralyzed by loss of its nerve supply loses it rapidly. Prolonged anemia, on the other hand, has little effect on muscle hemoglobin, reducing it but slightly. "The demands of anemia," Whipple wrote, "cannot rob the striated muscle of its hemoglobin. The body ranks the necessity for muscle hemoglobin on a par with the need for blood hemoglobin." From the standpoint of the individual's ability to move and work, he dryly added, this is a fortunate circumstance; and recalling his experiences in the hunting field, pointed out another advantage of the body's protection of the energy supply of its muscles: "We know that during long periods of hard physical exercise, as in training, a hunting dog will store a maximum amount of muscle hemoglobin which is a most important reserve against the explosive liberation of energy, which the striated muscles may exhibit." With Robscheit-Robbins and A. H. Groth, Whipple found that young dogs, fed on liver, build muscle hemoglobin somewhat faster than on the control diet, just as they build blood hemoglobin, but at a much lower rate. Still another difference between the two pigments was found by Whipple and one of his student Fellows, Edward J. Manwell, when they injected each of the two substances into the blood stream of experimental animals and found that the kidneys excrete muscle hemoglobin far more freely than blood hemoglobin, which they hold back and thus conserve it for re-use in the blood. It appears that muscle hemoglobin does not get into the blood stream and the kidneys have not evolved a means of conserving it. Because of this low threshold, when it is given to anemic dogs they do not retain enough of it to use in building new red blood cells.

Puzzled by these physiological differences between the two substances, which as yet they could not tell apart by spectrophotometry, Whipple and Robscheit-Robbins next tried the most sensitive of all methods for distinguishing substances of protein nature, that of specific immunological reactions. Sending purified specimens of the two kinds of hemoglobin to Ludwig Hektoen, celebrated immunologist of the John McCormick Institute for Infectious Diseases, in Chicago, they asked him to compare the power of the two samples to elicit specific precipitins when injected into rabbits. By this test a clear difference was revealed. Going back to the spectrophotometer, Whipple and Kennedy again compared muscle and blood hemoglobin, this time taking their samples from fowl as well as dogs, and found in both species the same slight differences which they had seen, but not considered significant, in their first observations on dogs. With W. W. Woodruff he made similar studies on human muscle. This painstaking series of investigations, begun in 1926, finally assured Whipple that his assays of dietary factors in anemia were not being vitiated by errors resulting from the utilization of muscle hemoglobin, under the stress of anemia, in place of blood hemoglobin. Consequently after 1929 he dropped this line of inquiry.

The problems posed by the participation of iron in the formation of red blood cells and hemoglobin continued to interest Whipple and he returned to them several times. In 1930, in a paper on the optimum amount of iron in the diet, he wrote

> If some patient reviewer should attempt to read all the published literature dealing with iron effects in anemia, both experimental and clinical, he would be busied for weeks and even months. The casual reader may inquire how all this work could be done and yet the internal body metabolism of a simple material like iron remain in dispute. But iron is an elusive sprite which mocks the investigator and will probably furnish many interesting new puzzles in the years to come.

One of these puzzles had to do with the body's mechanism for conserving iron compounds set free in the blood stream by disintegrating red blood cells, at the end of their relatively brief life span of about four months from the time they enter the circulation from the bone marrow. This iron is not lost through the kidneys, because (as already mentioned) those organs do not readily excrete either blood hemoglobin or the somewhat simpler material formed in its first disintegration. These substances can be assembled and stored in the liver and spleen, available for use either by the bone marrow to build new red cells, or by the liver and other tissues to form bile pigments. In 1931 and 1932 Whipple, aided by several young physicians and medical students, including Robert P. Bogniard, William H. Havill, John M. Lichty, William V. Newman, Luther W. F. Oehlbeck, and Gordon B. Taylor, investigated many details of the iron-conserving mechanism. Their findings were useful in a renewed attack on the problem some years later, when radioactive "tagging" of biologically important substances provided a new and better means of tracing iron throughout its complicated course in the animal body.

Throughout their work on liver feeding in anemia, Whipple and Robscheit-Robbins gave consideration as far as possible to the hemoglobin-producing factors in the human liver in various diseases of the blood-forming organs. The general conclusion, published in 1933 and 1934, was that disease of the liver, even of severe nature such as cirrhosis and cancer, does not greatly lower its potency to stimulate hemoglobin production, nor does anemia of either the simple or the pernicious type. To check this result in secondary anemia, Whipple and Robscheit-Robbins went to the heroic length of experimenting with a horse, which they kept severely anemic for several weeks. At autopsy they found its liver still highly potent in stimulating hemoglobin formation.

Whipple wanted very much to study the life cycle of the red blood cell. This could best be done if he could by some experimental means clear the bone-marrow of most of its blood cells, and then watch the new cells as they arose. For this purpose, the kind of anemia he could readily produce by repeated bleeding was completely unsuitable, for it resulted in a plethora of marrow cells too densely crowded for the study of individual cell-lines. With Samuel S. Shouse and Stafford L. Warren he made repeated attempts, in 1930, to produce the desired aplastic anemia in dogs by x-radiation and injections of colloidal silver, but secured only complicated and confusing results. In another investigation collateral to his main line of research, Whipple with J. P. Hanner studied the effect of liver disease on the well known phenolsulphonphthalein test for kidney function, showing that when this red dye is given to a normal animal 10 or 15 per cent of it is excreted not by the kidneys, but by the liver. A damaged liver cannot handle the dye, and thus forces the kidneys to excrete more of it. An unusually high elimination of phenolsulphonphthalein in the urine of a patient under study therefore suggests the presence of liver disease.

In 1928-1930 Whipple and his associate professor, Harry P. Smith, reopened the investigation of bile salt metabolism. Between the lines of their report of December, 1928, on this subject, one reads an amusing hint of one of those controversies which sometimes enliven a scientific meeting, and often, when the smoke has blown away, result in clearer understanding of the matter under dispute. Whipple's earlier work on bile salt metabolism, carried out at San Francisco with Marjorie Foster, Charles Hooper, Francis Wisner, and Francis Smythe, was done with the usual type of bile fistula as mentioned above in Chapter 5. Such fistulas, which open on the animal's flank, become infected with various microorganisms which, however, do not impair the dog's health if it is well cared for. About 1923-1924 George Whipple's Johns Hopkins classmate, Peyton Rous, and his colleague Philip D. McMaster, at the Rockefeller Institute, devised another way of making and using a bile fistula whereby the bile is kept sterile anl may be collected continuously. Using this method, they obtained certain measurements of bile formation, under specific dietary conditions, which contradicted those of Whipple's group. Peyton Rous recalls a meeting of the Association of American Physicians in 1924 or 1925 at which this discrepancy was discussed, and according to Rous's recollection he and Whipple sharply disagreed about it. "We had an almost disgraceful fracas," said he long afterward; "George knew more about the liver, but I thought I knew more about the bile." Their discussion, if it had only been recorded, would have illuminated these pages with a lively picture of the contrasting temperaments of two masters of American medical science, whose mutual respect and admiration, however ruffled that day, was to grow ever stronger through the rest of their lives. George Whipple now remembers nothing of his friend's onslaught, but he still had it in mind in 1928 when he resumed the investigation, this time using the Rous-McMaster method. These new and highly technical experiments showed, in brief, that among dietary factors it is the proteins which stimulate the liver to produce bile acids and bile salts. Lipids and in particular cholesterol, generally thought potent in this respect, proved relatively inert.

Open and sometimes bitter controversy used to be standard procedure among scientists, but in our time it has gone out of fashion. George Whipple was even less often involved in such contentions than some of his fellow-scientists. His care in performing experiments and caution in drawing conclusions protected him against hasty attack, and his way of meeting criticism with deliberate reasonableness generally disarmed those of opposing views. At about the same time as the Rous-Whipple "fracas," however, another of Whipple's findings was vigorously questioned by an able and persistent critic, Arnold R. Rich of Johns Hopkins Medical School. Whipple and Hooper, as mentioned above in Chapter 4, had reported that when the dog's liver is excluded from the general blood circulation by an Eck fistula, combined with ligation of the hepatic arteries, bile pigments are still formed in good quantity, a finding which suggests that the body can make bile pigments elsewhere than in the liver. Rich criticized these experiments on the ground that Whipple's operation did not completely exclude the liver from the circulation; when he prepared dogs in the same way, test injections of ink in the blood vessels found their way into the liver. Rich himself devised an operation by which the liver was totally removed, and found that during the few hours in which the animal survived, hemoglobin introduced into the circulation was not transformed into bile pigments.

This issue was hotly debated at several scientific meetings and in a number of papers, but was finally resolved in an unexpected way by F. C. Mann and two colleagues at the Mayo Clinic, who introduced still another way of excluding the liver, by total removal, but with much less disturbance of the circulation in the rest of the body, including the muscles, than under Rich's procedure, which excluded most of the trunk and the limbs. In Mann's dogs bile pigment was formed and appeared in the blood stream, in the absence of the liver. Whipple's group, in short, had obtained the correct result with an imperfect experimental method; Rich's more rigorous attempt had given misleading results through complications which he did not foresee. In 1925 Rich, having repeated and confirmed Mann's work, handsomely assented to the possibility of extrahepatic origin of bile pigments.

In 1932 Whipple and two members of his department, William B. Hawkins and Frank B. Queen, reported experiments which provided a new clue to the function of that most puzzling organ, the spleen. The three investigators had occasion to remove the spleens of a number of dogs in each of which they also made a bile fistula at the same time or earlier. Neither of these procedures alone seriously disturbs the animal's health; a dog can live for years without a spleen, and one with a bile fistula opening to the outside or into the pelvis of the kidney (as in this experiment), also lives for years in good health. The combination, however, to Whipple's surprise proved fatal. After a few weeks or months a strange reaction sets in; the dog begins to excrete excessive quantities of bile pigment, reaching eight or ten times the usual daily amount. Severe anemia develops, with damage to the blood capillaries, and death follows from bleeding into the lungs, digestive tract, or body cavities. This discovery that the spleen is essential to life in a bile-fistula dog implies that it contributes in some fundamental way to internal bodily metabolism. The immense quantities of bile pigments formed under the peculiar stress set up by this experiment posed another riddle; the bile pigments had been thought to be derived solely from hemoglobin, but the body's store of that substance is by no means large enough to provide for the excessive output. Whipple and his colleagues Hawkins, Robscheit-Robbins, and Khun Sribishaj (a Rockefeller Foundation Fellow), were forced to elaborate a hypothesis, too technical for further explanation here, that the animal body is able to synthesize the pyrrole aggregate which is an essential component of the pigments involved in blood and bile formation, and to turn it directly into bile pigment without first building it into hemoglobin.

In connection with these studies of liver function, Whipple in 1933 undertook with Hawkins and Angus Wright, assistant resident pathologist of Strong Memorial Hospital, to reexamine the question of cholesterol elimination in the bile. This was long before physicians began to be curious about the relation between cholesterol and arteriosclerosis, but that peculiar substance already greatly interested physiologists and biochemists. One of the three papers reporting the investigation begins with a paragraph very characteristic of Whipple's way of justifying his scientific curiosity:

The blood and body fluids are so crowded with "chemical messengers" and vitamines that to some readers it appears a miracle that these substances ever reach their destination. Cholesterol has been looked upon as an innocent bystander, inert and going along with the crowd. Some of the recent work with hormones and vitamines would seem to focus attention on cholesterol as a close relative of other sterols and perhaps of ergosterol and the group of fat-soluble vitamines. Further work with hormones (estrin and the male hormone) indicates a chemical constitution relating these "messengers" to the sterols. . . . Therefore instead of an innocent bystander cholesterol may prove to be a messenger of importance and authority related to many vital processes. (*Journal of Experimental Medicine,* volume 59, page 411, 1934).

Angus Wright began the investigation by checking the accuracy of a colorimetric method for estimating cholesterol in bile, already in use by other investigators. Finding it unsatisfactory, he developed a method of his own, based on previous work by Walter R. Bloor, Rochester's professor of biochemistry, for determining the esters of cholesterol, i.e. compounds in which it is linked with an acid to form a kind of organic salt. Whether cholesterol in the bile is chemically free or esterified was a debated question at the time. Wright's finding, which still stands unchallenged, that there are no cholesterol esters in bile made the problem less complicated for Whipple's group. With this beginning they carried out a thorough study of the normal excretion of cholesterol and its fluctuations under experimental conditions and in disease. The results, too technical for presentation here, threw considerable light on certain clinical tests of liver function and on the diagnosis of biliary disease. Without fanfare they became part of general professional knowledge.

We must not forget that during all these years of intensive research in experimental physiology, George Whipple remained an expert pathologist. In the autopsy room and at the microscope he kept on studying and teaching the fundamentals of pathological anatomy. Physicians in Rochester and neighboring cities, as well as his own staff and students, recognized his encyclopedic knowledge of the changes wrought by disease in human tissues and constantly sought his advice in difficult cases requiring microscopic diagnosis. In 1931 his professional duty gave him an opportunity, as it had long years before at Johns Hopkins, to make a thorough study of a rare and little known disease. The first case was that of a five-year-old girl of Italian parentage, who had been under observation at the Clifton Springs Sanitarium with symptoms of a peculiar type of anemia, and who died in Strong Memorial Hospital soon after admission in a moribund state. Whipple's careful autopsy and subsequent study of sections of the organs revealed that the lesions were those of so-celled Cooley's anemia, first clearly described by T. B. Cooley of Detroit, Michigan, in 1927-28. A younger brother of this girl died of the same disease a few months later. About the same time one of the University of Rochester pediatricians, William L. Bradford, had under his care a Rochester child of Italian descent presenting the same symptoms, in whose case it seemed best to remove the spleen as the probable seat of blood destruction. Sections of that organ and of a specimen bit of liver tissue removed at operation to aid the pathological study, confirmed the diagnosis of Cooley's anemia. Later a pair of twins, again of Italian descent, were referred by a physician in a neighboring city who suspected the same disease. One of them died and was autopsied by Whipple, adding another case to the pathetic roster. He and Bradford, pooling their experience as pathologist and pediatrician, published in 1932 an article in which they gave by far the most complete description of the pathology of this disease presented up to that time. In 1936 they reported three more cases with complete autopsy findings, adding also descriptions of tissues from two cases sent them by Dr. Cooley. These reports have become classics in their field. Cooley had called the disease "erythroblastic anemia," but Whipple's analysis of the lesions showed that this name was not truly relevant. Other designations of the disease antedating Cooley's recognition of its uniqueness were even less apt. Seeking a better name for it, based on the fact that the disease (which is probably hereditary) occurs chiefly in Italians, Greeks, and Syrians, peoples of the Mediterranean region, Whipple proposed to associate it with the Mediterranean Sea. Ransacking his memory of schoolboy readings in the *Anabasis,* he came up with the word Θαλασσα, from which he coined the term *thalassic anemia,* for the benefit of physicians if not of philologists condensing it to *thalassemia*. The doctors, however, with their incorrigible fondness for eponymic titles, continue to speak of "Cooley's anemia," just as they cling to "Whipple's disease" for the condition Whipple himself wanted to call *lipodystrophia intestinalis*.

After this thorough-going demonstration of his old-time skill in pathological anatomy, George Whipple returned with unabated energy to experimental physiology.

CHAPTER

# 10

# RESPECT AND ADMIRATION

AT THE CRISIS of his youthful career, in 1907, facing the decision to devote his life to research and teaching rather than the practice of medicine, George Whipple wrote to his mother that "the great thing in life is to know the great men in medicine, become acquainted and form friendships with them, and gradually win their respect, perhaps praise and admiration." Anna Whipple did not have long to wait before she saw this hope realized by the growing reputation of her son's work, and his call to San Francisco and later to Rochester. Appointment in 1927 to the distinguished board of trustees of the Rockefeller Foundation, and election in 1929 to the National Academy of Sciences gave further evidence of wide recognition. In 1929 also *Popular Science Magazine* divided between George Whipple and George Minot its $10,000 award for scientific achievement, in acknowledgement of their contributions to the relief of pernicious anemia.

Yale University at its 1927 Commencement conferred on Whipple the degree of Master of Arts, a token that his collegiate Alma Mater recognized a rising star among her alumni. The same year Colgate University awarded him an honorary doctorate of science. By this time he should have been accustomed to the receipt of new honors, yet that same year when the mail brought a diploma from Austria, he could not believe it genuine. A member of the Rochester medical faculty, summoned to the dean's office by telephone to help decipher a foreign communication, found Whipple scrutinizing an imposing document. "This looks to me," he said, "like something from one of those damned European diploma mills, but have a look at it before I put it in the waste basket." It was, in fact, a certificate of corresponding membership in the Medical Society of Vienna, one of the world's capitals of medical research, signed by no less eminent physicians than Anton von Eiselsberg and Julius Wagner-Jauregg. In 1931 a similar tribute from the Royal Medical Society of Budapest was accepted without any such preliminary questioning.

If George Whipple needed still stronger evidence to convince him of his standing in the world of medical science, he got it on the afternoon of October 25, 1934, when the Rochester *Times-Union* called his home to say that a cablegram just received from Sweden reported that the Nobel Prize for Medicine would be awarded to him jointly with George Minot and William P. Murphy. Astonished and shaken by the news, when the reporter asked for a statement, George said that he was flabbergasted, and this comment was duly transmitted to the nation through the United Press. George would have left it at that, but under urging for something more, according to the reporter he "allowed hardly a moment to elapse before diverting the limelight" to Mrs. Frieda S. Robscheit-Robbins as a principal collaborator in his work, together with several others of his technical staff. He was unable at the moment, he said, to make any further comment.

When this message came George was alone at home and thus had time to pull himself together before Katharine returned from an afternoon tea-party and the children from school and play. Breaking the news to the family, he pledged them to secrecy. More than once, he told them, false rumors had got about concerning the Nobel Prize awards, to the chagrin of those affected. For himself, he would not believe the newspaper until official notification came from Stockholm. Anyway, if the report happened to be correct, how could he face the embarrassment of being talked about, congratulated, and lionized? For the present, the Whipples had better dodge the reporters and their friends as well.

The news of course was in the afternoon papers and the city was soon buzzing with it. The senior faculty members of the medical school—the nine department heads who had been Whipple's daily associates for the past decade—delighted by this great honor to their chief, thought themselves entitled to be the first to celebrate it. Hastily exchanging telephone calls, they arranged to meet after dinner at Karl Wilson's house, a block or two from Whipple's, to go to the dean's home in a body, taking with them enough rye and bourbon for a proper party. Arriving at the Whipple residence they found it dark, and there was no response to the doorbell. George, afraid of an onslaught by reporters and by his friends, had taken the family downtown to dinner. The baffled celebrants had to trudge back to Wilson's and hold their party without the guest of honor.

Next day the Whipples' telephone rang without ceasing, reporters called at all hours, telegrams and letters arrived in a flood of excitement and goodwill. Photographers came to take pictures for the daily press and the national weeklies. There must have been some banter with the *Time* man about Whipple's youthful appearance as compared with Minot's bald dignity, for that magazine described Whipple as "a lean, alert man who takes pride in his full head of hair, and would like to take to the woods until the fuss is over." George and Katharine would have to leave for Stockholm in less than a month; there was barely time for him to prepare his official lecture, and for Katharine to get together a wardrobe for the royal and academic gatherings associated with the award. Only to his immediate colleagues could George grant an evening for the party he had escaped on October 25—this time a quiet happy stag dinner with the senior medical faculty, unembarrassed by publicity. Wallace Fenn began the after-dinner festivities by reading the original version of his poem *The House that George Built,* a gay narrative of the dean's achievements which has become a perennial classic of the medical school. The men presented Whipple with a handsome traveling bag, and by way of jest at his elevation to the Nobel-ity, gave him a coat-of-arms newly drawn up, bearing on its shield a liver, a syringe and a blood-counting pipette, crossed by a bend bilious with erythrocytes glissant, acquiring hemoglobin; the crest a microscope surrounded by the victor's laurels; the supporters a dog anemic and a calf rampant; the motto: *In hepate salus.*

George and Katharine left Rochester on November 21. Two press photographers were at their house until 11:00 P.M. on the night before, and two more pursued them to the train-side. They sailed next day on the Hamburg-America Line ship *Albert Ballin* for Bremerhaven, where after a fine leisurely voyage they arrived December 3. Reaching Stockholm by rail on December 4, they had time to look about that handsome city and a day or two later visited Upsala. While George called upon The Svedberg, the famous biochemist, himself a Nobel laureate, one of the faculty wives took Katharine on a tour of the historic university town. Back at Stockholm in the afternoon the Whipples joined the other two prizewinners and their wives at the home of Laurence A. Steinhardt, United States Minister to Sweden, to receive instructions as to ceremonial practices and dress during the forthcoming ceremonies. A fellow-countryman, Harold C. Urey, who had been awarded the Nobel Prize for Chemistry, could not go to Stockholm because his wife was expecting a baby just at this time. For the Minots the journey to Stockholm involved deep concern. George Minot depended for his life upon regular injections of insulin, and although his wife was able to administer them, he brought from Boston with him, in case of need, a medical friend, Richard P. Stetson. It is an extraordinary fact that Minot, whose life had been saved by a previous medical discovery rewarded by the Nobel Prize, received the news of his own award, brought by a hospital attendant, while he was standing at the bedside of a man suffering with pernicious anemia, who in one week had been brought by liver extract from the verge of death to hopeful convalescence.

While the three men were conferring with the Minister the ladies had tea with Mrs. Steinhardt. It was Katharine Whipple's first meeting with the Minots and the Murphys. George Whipple and George Minot had been friends for some years and Whipple's relations with William Murphy were equally friendly though not so close. The three men were content with the unprecedented triple division of the Nobel Prize award, for reasons clearly set forth in the official citation by Professor Gunnar Holmgren:

Your Majesty, Ladies and Gentlemen,

The Caroline Institute has awarded this year's prize for Physiology and Medicine to three American investigators, . . . in recognition of their discoveries respecting liver therapy in anaemias. . . .

Of the three prize-winners it was Whipple who first occupied himself with the investigations for which the prize has now been awarded. He began in 1920 to study the influence of food on blood-regeneration, the re-building-up of the blood, in cases of anaemia consequent upon loss of blood. . . . The method Whipple adopted in his experiments was to bleed dogs, that is to say to withdraw from them a certain quantity of their blood, supplying them afterwards with food of various kinds. By that method he discovered that certain kinds of food were considerably superior to others, inasmuch as they gave stimulus to a more vigorous reformation of blood, that is to say stimulated the bone marrow—in which the blood-corpuscles are produced—to a more vigorous manufacture of red blood-corpuscles. It was first and foremost liver, then kidney, then meat and next after that certain vegetable articles of food too, e.g. apricots, that proved in an especial degree to have a strongly stimulating effect. Whipple's experiments were planned exceedingly well and carried out very accurately, and consequently their results can lay claim to absolute reliability. These investigations and results of Whipple's gave Minot and Murphy the idea, that an experiment could be made to see whether favourable results might not also be obtained in the case of pernicious anaemia, an anaemia of quite a different type, by making use of foods of the kind that Whipple had found to yield favourable results in his experiments regarding anaemia from loss of blood.

It was the excessive loyalty of some of Whipple's and Minot's friends that gave rise to rumors of jealousy and unfriendliness between these two men. We can forgive with a smile the maternal pride that led Anna Whipple at Ashland, New Hampshire, to cancel her subscription to the Boston Transcript because that eminent newspaper, she thought, gave all the credit to Minot; we can understand as well as regret the journalistic inaccuracy, in Rochester and elsewhere, which too often credited Whipple rather than Minot and Murphy with discovering a cure for pernicious anemia. Whipple's biographer, however, owes it to all three men to repeat that

Minot and Murphy in their first paper on liver treatment adequately acknowledged the clue they had received from Whipple's work and to deny the rumor, which is still afloat almost three decades later, though completely false, that in a public address Minot disclaimed any such influence.

Overzealous friends in fact had begun unnecessarily to take sides long before the Nobel award. When in 1929 George Whipple was nominated for membership in the National Academy of Sciences, Simon Flexner, in a speech advocating his election so ardently emphasized his accomplishments that Lawrence Henderson of Harvard accused Flexner of unfairness to Minot. Henderson protested to William H. Welch with such vigor that Welch felt it advisable to inform Flexner of the protest. George Whipple would have been greatly concerned had he known at the time of this flurry among his distinguished friends, now at long last revealed by letters found in a certain dusty archive. Three years later Harvey Cushing, in a letter to Whipple, by implication accused unamed Boston clinicians of ungenerous neglect of Whipple's part in the research on anemia. To all such contentions the calm acceptance of a joint Nobel award by the three laureates, and their friendly association at Stockholm, gave pause, but rumor, like Cerberus, is never slain until the last of its hundred heads is lopped off.

The round of academic hospitality to the American laureates and their wives began December 8 with a dinner for 25 at the apartment of Hans Christian Jacobaeus, professor of internal medicine, and Mrs. Jacobaeus, where the Whipples had their first experience of the elaborate Swedish social customs, with their traditional formality of toasting the ladies across the table, and a solemn round of handshaking after dinner. On the 9th there was tea with Professor and Mrs. Hilding Berglund, and a formal dinner given by Gunnar Holmgren, Rector of the Caroline Institute, the great Stockholm medical center.

On the afternoon of December 10 the Minots, Murphys and Whipples, arrayed in full dress, were met in the lobby of their hotel by Count Tolstoy, a courtier detailed to escort them to the Concert Hall for the ceremony of award. Arriving at the hall, the men were taken backstage while their wives were seated at the front of the auditorium, with only the royal party between them and the stage. King Gustavus sat at the very front, on a throne-like chair facing low steps from the stage, down which the laureates would come to receive their diplomas.

Katharine's written recollections of the occasion include a lively picture of the huge hall crowded with distinguished-looking people in full evening dress, many of the men in court costume with decorations; the stage banked with flowers and greenery and set with carved chairs for the Nobel Prize Committee and the laureates of the present and former years. The ceremony proceeded with utmost dignity. A fanfare announced the entry of the laureates. Luigi Pirandello, the laureate for literature, came first, then George Whipple, Minot and Murphy, and all four were seated in the front row of the stage. Formal addresses followed, in Swedish. Minister Steinhardt accepted on behalf of Harold C. Urey the first award given, that for chemistry. Rector Holmgren spoke at length about the three medical men and their work, and finally, changing to perfect English, called them forward one by one to receive their diplomas from the King. First among them, amid a blast of trumpets, George Whipple, whose youthful hope had been some day to win the good opinion of medical scientists, rose and stood before a glittering audience of courtiers and savants, and took from a King's hand the emblazoned testimonial of a whole world's respect and admiration; and in the brick house on the hill in Ashland, New Hampshire, Anna Whipple marked the day as she had marked another, 29 years before, when her son became a doctor of medicine.

Last to receive his diploma was Pirandello, grave, white-haired, bearded, his slight frame hung with the great gold chain of some European academic distinction. Katharine observed with amusement that the old playwright knew perfectly how to walk away backwards from the royal presence according to protocol, whereas George Minot gave up the attempt half way to his chair, and George Whipple and William Murphy did not even try.

After the ceremonies, during a prolonged round of handshaking on the part of the Nobel Prize Committee and the laureates, Minot and his physician, Stetson, withdrew for a few minutes so that Minot might have his injection of insulin, and then solicitous Count Tolstoy rounded up the Americans to get them to Stockholm's magnificent Town Hall for dinner, at which the King's grandson, Prince Gustavus Adolphus, was to preside. After formal greetings by the royal party, the Prince offered Katharine Whipple his arm and the two led the march into the great Gold Room, the Prince in military full dress, Katharine in black satin with white jacket and black satin shoes. As they entered the hall, velvet curtains were drawn back, two uniformed pages blew a fanfare on golden trumpets hung with blue national banners, and all the men and women rose and bowed and curtsied to their Prince and the American lady on his arm.

At table Katharine had Prince Gustavus Adolphus at her left and his uncle, Prince William, the King's second son, at her right. The two princes were excellent conversationalists and responded quickly to her Southern sociability. At one time both of them were talking to her at once and all three laughing together over someone's *bon mot*. After dinner Count Bernadotte joined the Whipples for a while, seizing the opportunity to discuss his gastric ulcer with George. The evening ended with a dance at which Katharine received compliments on her dancing from her last partner, a gallant Swedish medical professor.

The week went on with rare festivities—a banquet for 101 people at the Royal Palace, and on the 12th George's scientific discourse at the Caroline Institute. The United States Minister entertained at dinner at his residence for the American laureates, and the Italian Ambassador for Pirandello, but by this time George was coming down with a bad cold, and Katharine missed the opportunity to meet Pirandello personally.

The Whipples left Stockholm by night train on December 13. They had an uncomfortable trip to Bremen, where they arranged to stay overnight at the same hotel as Minot's party, in case George should require medical attention. The voyage on the North German Lloyd liner "Europa" was extremely rough. George, still groggy with his cold, kept to his cabin all the way across. Delayed two days by heavy seas, the ship reached New York on December 23. The Whipples went at once to Rochester. A couple of newspaper men were waiting for them at the railway station, and next day George had to receive another lot of reporters in his bedroom.

He went back to his laboratory as soon as he had shaken off his cold and the fatigue of the journey. He was not however allowed to escape further official recognition of his new fame. The doctors of Rochester must have their chance to rejoice with him. In their Academy of Medicine were many of his friends, as well as some who had thought him neglectful of local professional interests, in his concentration on research and teaching, and some who had opposed the University's affiliation with the Municipal Hospital. All this was forgotten amid the wave of civic and professional pride, and the Rochester Academy of Medicine organized a grand dinner on January 15, 1935 at the Oak Hill Country Club on East Avenue. The 550 diners included, according to the Rochester papers, representative scientists, physicians, educators, administrators, and leaders of business and industry. Rush Rhees, president of the University of Rochester, sat at the head table with Katharine Whipple beside him. The mayor of Rochester was there; the governor of New York was represented by Dr. Thomas J. Parran, State commissioner of health. President Franklin D. Roosevelt sent a special message from the White House. Messages were read also from the president of the American Medical Association, the president of the University of California, and the director of the Rockefeller Institute. George Whipple's old colleague of Johns Hopkins days, Milton C. Winternitz, came from Yale by special invitation to make the principal address. Other old friends and associates attended regardless of distance—Walter Alvarez from Rochester, Minnesota, Irvine McQuarrie from Minneapolis, Harry Smith from Iowa City. Stanhope Bayne-Jones, that very day named dean of Yale Medical School as successor to Winternitz, came from New Haven. Eli Lilly of Indianapolis, whose firm had made liver extracts for both Whipple and Minot, was there to honor the investigator whose work he had helped to make medically effective.

In this assembly, so largely made up of old friends, nobody wanted to make George uncomfortable by adulation and the affair became a big family party. Winternitz's talk was full of comical memories, "very funny," said a reporter, "but more or less apochryphal." Others talked more seriously about George's contributions to medical science and education; one of his own faculty, expressing the affection of his immediate colleagues, spoke of the steady head and staunch heart with which he had guided the medical school. In reply, masking his embarrassment with humor, George said he could never live up to the excellence attributed to him, nor ever live down this occasion. "I expect that when we leave here tonight, stretcher bearers will carry out all the mangled, maimed, and bleeding adjectives, treat and restore them, and finally put them back in circulation."

Then he spoke of his debt to his associates in research, calling upon Mrs. Robscheit-Robbins to stand and receive the applause of all present for her outstanding part in the anemia work. "Research is a joint endeavor," he continued, "and so is the whole effort to place medical science at the service of the people." To solve the problems of illness in the community, the medical profession and the hospitals of Rochester must cooperate in every possible way with the educational, scientific, social and governmental agencies of the region, each contributing its own talents and ability. To some members of the Rochester medical profession these brief words were an acknowledgment of generous collaboration; to others they must have conveyed a reminder of past differences and a gentle admonition for the future; to all they plainly said that the School of Medicine and Dentistry would continue to do its share through intensive research and teaching.

At another dinner on April 19 at the Waldorf-Astoria in New York, tendered to the four American Nobel laureates of the year, by an organization called World Peaceways, he would not speak at length, merely introducing himself by name—"the middle initial stands for hemoglobin," he said. Commencement season brought a spate of academic honors demanding journeys to far corners of the nation. The University of California called him back to Berkeley for an honorary LL.D. on May 18, Tulane University of New Orleans also made him LL.D. on June 12, and Wesleyan University awarded him the degree of D.Sc. on June 16. The Imperial German Academy of Science sent him its diploma of honorary membership. Trinity College, Hartford, conferred the D.Sc. in 1936, and the University of Athens an honorary doctorate in 1937.

If George Whipple had possessed the least tendency to vainglory, however, a fortuitous concurrence of Nobel Prize speakers in New York on December 12, 1935, would have taught him the fickleness of popular acclaim. On that evening, when he gave the first of two William H. Welch Lectures at Mount Sinai Hospital, Alexis Carrel of the Rockefeller Institute made one of his rare public appearances with an address at the New York Academy of Medicine. His sensational title, "The Mystery of Death," drew excited attention from a public that recalled his work with the so-called "immortal" chicken heart culture and half expected the famous surgeon-scientist to reveal some new step achieved in his laboratory toward physical immortality. A crowd of 5000 people stormed the hall and had to be restrained by the police. Without actually claiming any new discovery, Carrel, as always half scientist, half mystic, deliberately whetted the hope that science could win if not immortality, at least a longer span of human life. Next day the *Herald Tribune* reported the address and all the attendant excitement in news articles occupying eight column feet of space. The *New York Times* used six column feet. "All this mightily annoyed many an orthodox scientist," said *Time* magazine on December 23, quoting the redoubtable Anton J. ("Ajax") Carlson, physiologist at the University of Chicago, where Carrel years before did some of his best surgical research: "This is neither science nor modern medicine. I cannot believe that Dr. Carrel is willing to befuddle and mislead the public and injure science and medicine for the shallow fame of personal publicity!" *Time* then reported Whipple's discourse, implicitly emphasizing his soundness as compared with Carrel, but with journalistic inexactness about his achievement:

> Altogether different was the simultaneous appearance four blocks away of Dean George Hoyt Whipple of the University of Rochester School of Medicine and Dentistry, winner of a Nobel Prize for discovering the value of liver diet in overcoming pernicious anemia. Important doctors completely filled Mount Sinai's auditorium, listened decorously while Dr. Whipple, his throat raw with a cold, described how blood is formed and regenerated within the body.
>
> Only newspaper to report on Dr. Whipple's points was the *Herald Tribune,* in nine column inches.

More honors to George Whipple followed in subsequent years. The University of Toronto gave him in 1938 its Charles Mickle Fellowship, actually an honorary award, as "the member of the medical profession who has done the most during the preceding ten years to advance sound knowledge of a practical kind in medical art and science." In 1939 he received the George M. Kober Medal of Georgetown University, highly prized in medical circles because of the wisdom with which its recipients have been chosen by the Association of American Physicians. On that occasion a Rochester newspaper, correctly judging his reaction to another formal honor—for Rochesterians had at last begun to understand him—remarked in an editorial "No doubt Dr. Whipple, appreciatively but modestly, will carefully put away this newest medal, struck by the United States Mint itself, and then quickly return to his laboratory, intent on some new discovery." In 1938 also he was elected member of the American Philosophical Society of Philadelphia, the nation's oldest learned academy, whose friendly semiannual meetings he and Katharine enjoyed more and more when in later years he had time to attend them.

Even Whipple's dogs ultimately shared his honors. In the 1940's an organization called Friends of Medical Research, sponsored by the New York Academy of Medicine and the Medical Society of the State of New York for the defense of experimentation upon animals, set up an annual award to animals that had served the cause of research. In 1946 two of the Rochester Dalmatians, Josie, four years old and Trixie, one year old, received the award "on behalf of their ancestors who twenty years before had contributed to the fundamental research which led to the discovery of the liver treatment for pernicious anemia." At the ceremony of award, held at the American Museum of Natural History in New York City, no less a personage than the Surgeon-General of the United States Army, Norman T. Kirk, spoke in defense of animal experimentation, whose benefits he said had been notably evident during the Second World War. Mrs. Robscheit-Robbins, representing the University of Rochester, was photographed for the newspapers as she presented Josie and Trixie to General Kirk to receive their medals, and speaking on behalf of her canine charges declared that "these dogs have served as blood donors just as human donors have served during the war."

As a member of the board of trustees of the Rockefeller Foundation George Whipple found himself in high company, concerned with world-wide scientific and philanthropic affairs. Among his fellow trustees, as one of the wisest of them, Raymond B. Fosdick, recalls,

. . . were such highly articulate and colorful figures as Charles Evans Hughes, President James R. Angell of Yale, President Ernest M. Hopkins of Dartmouth, and President Ray Lyman Wilbur of Stanford. When Whipple became a trustee George Vincent was head of the Foundation —one of the great public speakers of his generation, urbane and radiantly witty. In a sense it was an age of giants, and our board meetings reflected the brilliance and sparkle of clashing minds. . . . Whipple was a quiet and unobtrusive figure at our meetings. At the beginning, I suspect, he may have felt a bit overwhelmed in such an atmosphere, for he was always a supremely modest man who spoke in gentle, persuasive tones. . . . So deep was the respect in which he was held by his fellow trustees that a word from him, spoken in his quiet tones, went a long way.

At the time of his appointment the Rockefeller Foundation was deeply engaged in the support of medical education around the world, and in the development of research in special fields such as endocrinology and human heredity. In 1933 it launched a broad program in psychiatry. In the consideration of these medical undertakings Whipple was a useful and influential member of the board. The officers of the Foundation often traveled to Rochester to consult him, and upon these men, particularly the enthusiastic, sometimes rather pontifical Alan Gregg, director of the Division of Medical Sciences after 1930, Whipple had a steadying and stimulating influence. After observing for seven years his contribution to the Foundation's affairs, in 1936 John D. Rockefeller, Jr., Abraham Flexner, and the other members of the inner circle of the Foundation showed their appreciation of Whipple's sound judgment and scope by putting him on the board of trustees of the General Education Board, a subsidiary organization engaged in furthering the cause of college and university education in the United States and in many other countries.

In the spring of 1934 Simon Flexner's long term as the first director of the Rockefeller Institute was drawing to a close. Appointed to its Board of Scientific Directors in 1901, he was soon chosen to organize the laboratories and the staff of the new Institute, and for more than three decades guided it wisely through its rapid rise to leadership in American medical science. Upon Flexner's successor would fall the heavy responsibility of maintaining the Institute's standards while leading it through a period of change and re-alignment that would inevitably follow Flexner's departure. The Trustees and the Board of Scientific Directors appointed a committee in January 1934, to seek a new director. The committee's long deliberations are veiled behind noncommittal entries in the Institute's Minutes; not until April 1935, did it present to the Board a list of possible nominees headed by the name of George H. Whipple.

Early in May Whipple received from Henry James, chairman of the committee, a letter hinting that he was under consideration and asking him to outline his ideas as to the administration of the Institute if the post were actually given to him. To this letter he reacted exactly as he had to President Rhees 14 years before when asked to think about the deanship at Rochester. In a two-page letter he stated good reasons why he could not consider the post and politely declined Mr. James's invitation to confer with him and another member of the committee.

Fortunatly for the peace of mind of his colleagues Whipple kept this tentative offer secret for three weeks. He discussed it at once of course, with Rush Rhees, who was frankly astonished by his reluctance to accept the appointment. No American medical scientist, Rush Rhees thought, could resist the claims of America's greatest medical research institution, least of all George Whipple, for whom it must have an intense personal appeal. His admired teacher and friend, William H. Welch, first president of the Institute's Board of Scientific Directors, had been the leading spirit in determining its character and policies, and the retiring director, the man Whipple was asked to succeed, had been Welch's most famous pupil. The Institute had worldwide reputation, a large endowment, the enthusiastic support of the Rockefeller family, a very distinguished staff, excellent laboratories.

Against acceptance, on the other hand, Whipple saw two strong reasons, one of them practical, the other rooted in his ideals and in his obligations to the enterprise he had begun at Rochester. He was now 57 years old, and the Rockefeller appointment meant retirement at 65; the trustees were not minded to leave Flexner's successors, as they had left him, in office to a greater age. The Institute, famous as it was, needed a good deal of redirection. Its policy of research without teaching, perhaps necessary in its earlier years to protect investigators from routine educational tasks, had led to isolation of its departmental divisions and to a degree of cloistered self-complacency that threatened to hamper its future development. Whipple would not have feared the task of reorganization, but in seven or eight years he could not hope to carry it to a satisfactory stage. Retirement at 65, moreover, might well cut off his own research program prematurely. To this practical reason for declining the offer he added a strong sense of obligation to the University of Rochester, and above all to the colleagues and friends who, confident in his leadership, had committed their careers to the School of Medicine and Dentistry. Furthermore, he had put his heart as well as his whole mind into the Rochester school, and the pain he would feel at leaving its future to others was more than he cared to face.

A rumor about this offer got into the newspapers on May 22, when the Rochester dailies and the *New York Times* carried a brief, unconfirmed report, without a stated source, that Whipple had been offered the directorship of the Rockefeller Institute.

The noted dean of the University of Rochester School of Medicine and Dentistry (said the *Democrat-Chronicle*) is on his way home from a vacation on the Pacific Coast, and could not be reached for comment. Prior to his departure he had told none of his associates about the offer. It is reported that he has rejected it, and credence is lent this report when it is recalled that the doctor has repeatedly indicated his reluctance to assume an executive position at the sacrifice of his research work.

Questioned by New York reporters about the story, Mr. James said that the Institute had several men under consideration, and that no one need be surprised if Dr. Whipple was one of them, but the position had as yet been offered to no one. Thus reported by the newspapers as an affair already settled, and by the Institute as not an offer at all, this proposal so momentous for both the Rockfeller Institute and the University of Rochester caused surprisingly little flutter in the Medical School and in the city. The Rochester papers did not see fit to take editorial notice of the honor paid an eminent citizen. They never knew that on May 28 John D. Rockefeller, Jr. wrote to Whipple conveying a firm offer of the directorship and proposing to take the overnight train to Rochester for breakfast with Whipple at his home to be followed by a thorough discussion. Whipple could not refuse this, but the plan had to be abandoned because of a brief illness of Mr. Rockefeller and instead Whipple went in early June to the Rockefeller estate near Tarrytown.

The two men, long acquainted through service on the board of the Rockefeller Foundation, could talk frankly, though Whipple found himself on delicate ground where he might easily lose the regard of a man for whom he felt deep respect and gratitude for his high-minded support of medical science. Rockefeller's most appealing argument was based on the relations he had enjoyed with Simon Flexner. "As a result of years of close and intimate association," he wrote the next day, confirming the conversation,

I have come to hold Dr. Flexner not only in highest esteem and regard, but also in truest affection. . . . Were you to succeed Dr. Flexner I might look forward to the same close, intimate, helpful, happy relationship with you. . . . That the head of this great Institute should be not only competent, on the medical and scientific side, but also truly human, approachable, and may I say, lovable, would mean much to me and all my family. While I realize that this personal feeling on my part toward you can properly have no material influence in the decision which you are about to make, I would hardly be human were it not to weigh heavily with me.

Whipple went on to New York City for an interview with Simon Flexner. Returning to Rochester a day later he wrote Mr. Rockefeller that his thoughts after the two talks "might properly be designated as chaos," but after a night's sleep and a review of the facts in the early morning he clearly felt that he could be of greater service to American medicine in his present position than as director of the Rockefeller Institute. Having made his decision, he went on with his work at Rochester in greater peace of mind than most men would have enjoyed after declining what the scientific world considered the top post in American medical science.

The Rockefeller Institute was unwilling to get along without Whipple's services in one form or another. About a year after he declined the directorship he was elected a trustee and member of the Board of Scientific Directors of the Institute. Here he felt more at home, as one of a group of medical and biological scientists, than on the more diverse and far more widely ranging boards of the Rockefeller Foundation and the General Education Board, from which he retired in 1943. Fellow trustees give the same report of Whipple as do those of the Rockefeller Foundation with whom he served: "He spoke up very seldom, and when he did, it was with very few words—and always to the point." While he was a member of the board the Institute passed through difficult times and great changes—the Second World War, with its inevitable disruption of the research program and diversion of energies; the retirement of a number of distinguished members of the Institute and the consequent new appointments to the staff; the harassing decision to close the Institute's Department of Animal and Plant Pathology at Princeton. Whipple was still an active member of the board in 1953, when the trustees and the Rockefeller brothers were considering radical steps which, under the presidency of Detlev W. Bronk, have converted the Rockefeller Institute from a medical research institution to a university-type faculty of biology and related sciences with gradually widening scope. Whipple had shared the feeling of most members of the board that the Institute, although still highly productive in medical research, was getting in a rut. In general he favored the proposed reorganization and redirection, and though as usual he spoke very little in the board's discussion of the changes, by a quiet word now and then (writes another board member) "he steered them on a good course, just as a good pilot on a ship's bridge, by giving the briefest and quietest suggestion for a very slight change of direction, often substantially influences the ship's movement."

George Whipple, as we have said, was more at ease under the responsibilities of a trustee and member of the Board of Scientific Directors of the Rockefeller Institute for Medical Research than as a trustee of the Rockefeller Foundation and the General Education Board. When in 1943 he reached the age of 65 and under the rules of the two international philanthropies retired from active service on their boards, he was not altogether regretful, for they had been demanding more time and attention than he was able to give them. Whether he was conscious of it or not, there were also other reasons for this sense of relief, deep-seated in the temperament he had inherited from his New Hampshire ancestors, who lived by a rule straight out of the New Testament: "Study to be quiet, and do your own business." Like them he was determined to mind his own affairs; he undertook the deanship at Rochester on condition that he would not be expected to spend time and energy on civic and professional activities outside the school. He knew, of course, that a dean's business includes minding the business of a great many other people, but this he accepted as a professional obligation. Now, as a trustee of the Rockefeller Foundation, he was called upon to deal with the affairs of farflung and distant nations. However important these undertakings, however useful the Foundation's leaders thought him in helping to organize them, he was happier on the Rockefeller Institute's board, which dealt only with medical and biological research; that was the business he best understood and had made his own.

In this as in many other manifestations of his character, George Whipple represents a typically American frame of mind often specially attributed to the Yankees of New England, but which in fact developed generally among early settlers in the new country. Men who lived in relative isolation on the frontier, struggling for a living against raw Nature and hostile aborigines, had to be self-reliant individualists, they had to be inventive and practical, they had to work, first, for survival and then for material progress. There was no time for idle talk or merely decorative arts, and no call to think about the problems of folk beyond the horizon. It was task enough to live and build on one's own homestead, and to stand by one's own family and near neighbors.

This is the kind of Americanism, born of the frontier and cherished in colonial and nineteenth century New England, to which Ralph Waldo Emerson gave ringing voice in his famous lecture "Self-reliance." This philosophy helped to shape the nation and still competes, in the minds and hearts of Americans, against the claims of a world outlook and the welfare state. It gave us leaders and heroes even as it bade each American to look first to his own affairs and his private responsibilities. Emerson could thrill his hearers with a challenge to supreme endeavor:

> We are now men and must accept in the highest mind the same transcendent destiny; and not minors and invalids in a protected corner, not cowards fleeing before a revolution, but guides, redeemers and benefactors, obeying the Almighty effort and advancing on Chaos and the Dark.

And yet in the same essay he chided some of his fellow countrymen for their misdirected charity:

> Do not tell me of my obligation to put all men in good situations. Are they *my* poor? I tell thee, thou foolish philanthropist, that I grudge the

dollar, the dime, the cent I give to such men as do not belong to me and to whom I do not belong. There is a class of persons to whom by all spiritual affinity I am bought and sold; for them I will go to prison if need be; but your miscellaneous popular charities; the education at college of fools; the building of meeting houses to the vain end to which many now stand; alms to sots, and the thousandfold Relief Societies;—though I confess with shame I sometimes succumb and give the dollar, it is a wicked dollar, which by-and-by I shall have the manhood to withhold.

In this philosophy of idealistic, self-reliant, home-centered individualism George Whipple was steeped from childhood. His ancestors for seven generations had been pioneer villagers and farmers, then for two generations country doctors fighting alone against disease without benefit of hospitals and consultations. Himself a pioneer in his own way as a scientific investigator, he too cherished the independence, the sense of personal responsibilty, and the will to be quiet and do his own business, that his Yankee forbears possessed. He brought with him into the modern era of spreading communications, world-wide scientific cooperation and international philanthropy, Emerson's conviction that to look out for one's self is prerequisite to looking out for others, and that Americans, as individuals or in organizations, and as a nation, should devote their time, money, and sympathy only to fully deserving causes, and preferably close to home.

A man with such principles as these cannot be classified as either a tory or a liberal. He is conservative because he holds to the well-tested ideal of individual responsibility and accountability, liberal because he believes that everyone must be allowed to carry that responsibility on his own shoulders. He will be severe—illiberal, if you like—only with those who fail in his opinion to accept and fulfill their personal trust. George Whipple's conservatism and his liberality have both been apparent in earlier chapters of this book telling of his attitudes as dean and professor. On the Admissions Committee he could be as essentially American as Emerson when, for instance, he opposed the acceptance of a rootless foreign applicant without a future in his own country; and yet could be broadly tolerant of students in any sort of mishap or misconduct if only they were serious about their work. Medical students, like other young people, sometimes get into bad scrapes; there are several Rochester-trained physicians now practicing medicine with good repute, who, if they cared to reveal their youthful indiscretions, could tell much about their dean's liberality, sympathy, and wisdom as a personal counselor in time of secret trouble.

As has also been said in earlier chapters, no dean of a medical school was ever more liberal in educational matters. To teach and to learn medicine is the business, Whipple thought, of the competent professor and the capable student, not of the dean's office or any committee. Each professor was allowed to conduct his courses as he chose; the students had the run of the laboratories day and night and were encouraged to study on their own schedules. At the end of the course, they knew, there would be a reckoning.

Just as he put the responsibility for learning upon the individual student, Whipple wanted the school to carry on its own business without interference by outside agencies. In the earliest days of the school, a rigid State law among other antiquated provisions required more hours of anatomy than either Whipple or the professor of that subject thought desirable. The dean solved this difficulty by blandly reporting to Albany a schedule in which part of the surgery course was classed as anatomy. He did not like the efforts of the Association of American Medical Colleges to influence the curricula and teaching methods of the schools. Necessary as its rules and regulations might be to keep the weak schools up to standard, they were a nuisance, Whipple thought, to sound institutions like Rochester. Writing to Simon Flexner in 1928 he said "There is an Association of American Medical Colleges which meets twice a year to talk over a lot of useless stuff relating to teaching." He consented only under protest to have his school join the Association, paid its annual assessment very grudgingly, and took no interest in sending a delegate to its meetings. When the Association, impressed by the general acceptance of the Seashore musical aptitude test, introduced a similar test of aptitude for the study of medicine, to be taken by all applicants for admission to the nation's medical schools, Whipple for several years accepted the reports on Rochester applicants without looking at them himself or showing them to the Admissions Committee. He had his secretary lock them up until a year after the admission of each successive class, when they were checked against the first year's actual performance, and again after graduation. The outcome, at least in the earlier years of the test, was that it was fairly successful, with a few notable exceptions, in picking out men who would go to the top and the bottom of the class, but it was not highly predictive as to prospective ranking of the general run of students.

George Whipple's views on politics and social problems are determined by his individual ideals. Like most up-state New Englanders and New Yorkers, he generally votes with the Republicans. Whipple's personal independence however, keeps him from being a strict party man. He vaguely remembers having voted at least once for Woodrow Wilson, probably out of loyalty to the commander-in-chief of World War I. In local elections he has often split his ticket or even voted the Democratic slate in favor of good government regardless of party lines.

Franklin D. Roosevelt's New Deal he considered the very antithesis of minding one's own business, and F. D. R. himself was the object of intense disapproval. Once during lunch hour at the medical school, when the dean made a vehement pronouncement on this subject, one of his table companions attempted to cool his wrath by remarking that after all the President was his own worst enemy. "Not while I'm alive," George calmly retorted. Along with his anti-New Deal sentiments went a profound distrust of organized labor, on the ground that union regulations force the surrender of personal freedom upon the laborer and his employer alike. During construction work at San Francisco in 1914, and at Rochester in 1923-1925, he was greatly vexed by the refusal of local labor leaders to permit non-union men to perform casual tasks, or to let a member of one union do a small necessary job in the jurisdiction of another. To an independent Yankee scientist it seemed absurd, as well as extremely annoying, that any able-bodied man might not tighten a nut or install a shelf, regardless of union affiliations.

Although George Whipple takes a firm stand on political questions, and in private conversation states his convictions with unmistakable vigor and frankness, he never associated himself publicly with any political group or movement until 1940. Under Franklin D. Roosevelt's leadership the nation was then moving with terrifying speed toward involvement in the Second World War. People took sides for and against intervention, for a complex variety of reasons. Some who opposed it were pro-German, some anti-British, some for peace at any price. Whipple was none of these, but he was pro-American and against foreign entanglements; he distrusted Franklin Roosevelt and the Democratic party's foreign policies. He found himself, therefore, in sympathy with "America First," the strongest and best-led noninterventionist movement, founded early in 1940 by General Robert E. Wood and a group of prominent industrialists and professional men, mostly Republicans and conservatives. To strengthen their position, General Wood and his associates sought for the national committee of America First men widely known and respected throughout the United States, among them Whipple. The stated principles of the movement to which these eminent citizens assented were that American democracy could be preserved only by keeping out of the European war; that no foreign power or group of powers could successfully attack the United States if the nation built an adequate defense for itself, and that Roosevelt's 1940 policy of giving Britain "aid short of war" weakened national defense at home and threatened to involve America in war abroad. Although Whipple, sharing these views, joined the movement and accepted appointment to the National Committee, he never attended its meetings. In a published history of the movement he is listed as an inactive member of the Committee.

As the international situation worsened, and American sympathies turned more and more to Britain and her allies, America First gradually lost the support of all but die-hard isolationists, whose extreme ideas began to dominate the organization. Whipple found their activities less and less to his liking, and before the end of 1940 sent in his resignation, as did, that year and the next, several other members of the National Committee. When on December 7, 1941, the Japanese Navy bombed Pearl Harbor, America First quietly vanished from the national scene.

George Whipple waited a long time before he again put his name to a public manifesto. When at last he chose to do so, the climate of world affairs had totally changed. New means of warfare achieved by physical science had made every one of America First's postulates obsolete or meaningless. Russia and the United States were threatening to resume, in the name of national defense, their pollution of the global atmosphere with ionizing radiation. American isolation was a dream of the past. A Nobel laureate, Linus Pauling, drew up an appeal by American scientists to the governments and peoples of the world, to abandon all testing of nuclear weapons. When Pauling's petition came to George Whipple's desk he would not sign it, for he thought it quixotic to trust the present leadership in Russia without international inspection of atomic installations. To the surprise of his friends, however, his name was published among the signers, through a misunderstanding which he had to correct by a statement to the newspapers. Four years later Linus Pauling circulated another and different document addressed to the United Nations and to all the nations of the world, urging the present nuclear powers not to transfer atomic weapons to any other nations, including those of the North Atlantic Treaty Organization or the Warsaw Pact group, and that all should aim at total disarmament under international inspection and control. This proposal, Whipple felt, made better sense than the earlier one. That the United States should alone control the atom bomb for the western world, pending its abolition, was fully in line with his Americanism; Russia's command of the bomb was an accomplished fact, to be accepted and reckoned with. On this practical, realistic basis, he put his name to the paper along with other men of pacific spirit, men of international ideals, even quixotic men hopeful that mankind will turn away from the path that could lead us to extinction, and aware that our nation has urgent responsibilities for the safety of peoples beyond its own borders.

CHAPTER

# 11

# THE SCHOOL GOES FORWARD

HAVING ORGANIZED the School of Medicine and Dentistry on a simple, workable plan and manned it with able men, George Whipple could expect it to go forward smoothly and to grow steadily in strength and in experience. During his first decade as dean, however, he faced two major administrative problems, both involving fundamental questions of professional education. They grew out of radical and—as things turned out—impractical stipulations of the two donors of the endowment. George Eastman and his personal advisers wanted the school to teach dentistry as well as medicine, and with equal scientific and intellectual standards. As told in Chapter 7, the other founding donor, the General Education Board, expected the school to adopt the so-called "strict full time" system of clinical teaching, under which the professors of medicine, surgery, obstetrics and gynecology, and pediatrics, together with a corps of associates, hold university appointments on full academic salary, all fees from private patients being paid into the hospital's operating fund. Each of these proposals bristled with difficulties; the dean, backed by his president, Rush Rhees, and supported by his colleagues, solved the one by finding a new and more broadly effective way of promoting dental science and education, the other by courageously doing as he thought best, against considerable pressure from the donor organization and especially from Abraham Flexner, its Secretary, for whom the strict full-time plan was a crusade.

Everyone who entered Strong Memorial Hospital by its main entrance saw carved in stone over the doorway, in one and the same panel, the words MEDICINE and DENTISTRY, an indelible pledge of the University of Rochester's intention to carry out George Eastman's wish by advancing dental as well as medical education. Yet this hope was unfulfilled for several years while medical teaching went forward at once. In the first enthusiasm for Eastman's ideas, the medical faculty proposed to teach the preclinical subjects—anatomy, physiology, biochemistry, bacteriology, and pathology—to dental students in the same classes with the medical students, as a full scientific preparation for their subsequent specialization in clinical dentistry.

The time, however, was not ripe for so radical a move, and indeed its wisdom is still disputed. Few if any predental students who applied for admission to the school were qualified to work alongside the well-prepared premedical students it was at once able to attract. The dental profession was, on the whole, doubtful of the scheme, and the Eastman Dental Dispensary, as we have seen, was not prepared for the necessary intimate cooperation. To establish a separate school of dentistry would only add another institution of less than university grade to those already existing. It would be as difficult to find dental professors qualified to teach at university level as to find properly prepared students. The Dental Dispensary as then manned could not have provided an adequate staff.

Uncertain how to fulfill Eastman's hopes, Rush Rhees and Whipple bided their time, meanwhile keeping in touch with leaders of the dental profession who were becoming more and more conscious of the need for broader scientific training than the dental schools were providing.

In 1921 the Carnegie Foundation for the Advancement of Teaching, well knowing what immense improvement in medical education it had touched off through Abraham Flexner's report of 1910, *Medical Education in the United States and Canada,* undertook to do as much for dentistry and asked William J. Gies, an experienced biochemist familiar with dental education, to make a similar survey of the nation's schools of dentistry. Taking five years for the task, Gies produced in 1926 an even bigger book than Flexner's—almost 700 pages of description, analysis, and criticism. Discussing the University of Rochester he referred to widespread disappointment that the School of Medicine and Dentistry had not yet done anything important to promote dentistry, dental science, or dental education. The paragraphs in which he puzzled over this seeming inactivity and suggested his own program for the school are no longer relevant, but a ringing statement in his "General Views and Conclusions" proclaimed a fundamental need that Rochester was soon brilliantly to fulfill under George Whipple's leadership:

Everywhere education is chiefly what the teacher makes it. The most immediate need in all the dental schools is a much larger proportion of able and inspiring wholetime teachers, who, devoting their lives to teaching as a profession, by their character and example would exalt the spirit of dentistry, by their conduct of the instruction would heighten the quality of oral health service, by their research would steadily extend the boundaries of dental knowledge, and by their scholarship would give to dentistry and to dental education the intellectual distinction now lacking in each. All desirable early improvements in dental education would follow their advent.

Here was a clear call to service worthy of George Whipple and his senior colleagues of the medical faculty, attended by no such uncertainties and doubts as the abortive plan for undergraduate dental teaching. For these men, to train investigators and teachers was a prime duty. They drew no line between medical and dental research; they had the equipment and were ready to begin. Within three years the Rockefeller Foundation opened the way. In 1929 a leading dentist, A. LeRoy Johnson, then of New York City, representing a group of dental educators who were anxious for action to implement the Gies report, took the problem of stimulating dental research to Richard M. Pierce, then director of the Foundation's division of medical sciences, and to Abraham Flexner. Both these advisers felt that a program of dental research could best be started at one or more universities where medical research was already flourishing, but where there were no dental schools to complicate the experiment in its first stage. The outcome was a grant of funds to Yale and to Rochester to support two quite different training programs. Yale's plan, led by Whipple's old friend Milton C. Winternitz, dean of Yale Medical School, was to admit selected graduate dentists to medical classes to work for medical degrees. Its vicissitudes and achievements have their own place in the history of American dentistry but need not be detailed here.

Whipple, believing that research can be developed in a concentrated research environment, chose to seek well-trained, scientifically-minded recent dental graduates, and also a few men trained in the basic sciences but specially interested in dentistry, and to put them into the preclinical departments of the medical school. There, as Harold Hodge, one of the first of them, has written, each of these men "was immersed in the department's scholarly activity and learned by association with those whose love of learning was outstanding." As the fellowship plan developed, it became the custom that each new dental Fellow, after being welcomed by the Fellows already at work and introduced to the facilities of the school, was left for weeks, or months if necessary, to attend classes, demonstrations, and seminars, to work in the library, visit laboratories and talk with various investigators as he wished. He was not pressed to choose a department with which to affiliate until he had plenty of time to find his way about and to discover which of the medical sciences interested him most. Once admitted to a department he was treated as a colleague, except that if his training in its field was inadequate he might take the regular course with the medical students. As soon as possible he joined the young assistants and instructors of his department in helping to teach the laboratory course, and began like them to carry on research in consultation with the department head, choosing a problem of dental interest related to the department's field. Dental Fellows were encouraged to work for a master's degree or the Ph.D., according to their qualifications, but were not permitted to seek a medical degree.

George Whipple, reminiscing in 1955 about the remarkable success of this program, ascribed it in part to good fortune. "Of course," he said, "there was something back of the luck." Behind it in the first place was his own shrewd planning, based on an incorrigible belief in the capacity of intelligent young people to make the most of a great opportunity, and in the second place the enthusiastic support of open-minded department heads who enjoyed their part in the experiment. Luck perhaps helped Whipple in securing a few men of special talent for leadership among the first dental Fellows, who quickly formed a kind of junior faculty of dental research. One of these, Basil G. Bibby, came from New Zealand in 1930, the first year of the fellowship program, joining the department of bacteriology, and remained for ten years until he was called to be professor of bacteriology and dean of Tufts College Dental School in Boston; in 1947 he returned to Rochester to succeed Harvey J. Burkhart as head of the Eastman Dental Dispensary. Harold C. Hodge, not a dentist but a Ph.D. in chemistry, came in 1931 from a professorship of that subject in Ottawa, Kansas, to devote himself, as dental Fellow, to research on the chemistry of the dental tissues. These men and other early Fellows organized a weekly seminar which served as a center of professional interest, moderating any sense the dental Fellows might have had of isolation from their own profession. These leaders also with their greater experience helped the new Fellows adjust to the unaccustomed freedom and responsibility of their posts, and were often consulted about the choice of research problems. Their own success as investigators showed that a medical degree is not the only passport to research in the medical life-sciences.

These were brave young men who committed themselves to the fellowship program in its earliest years, for no one could be sure that the dental schools wanted men trained in research on their faculties. Whipple felt obliged to warn them that it might take years to build up a demand for recruits of their type. "This is not a five-years plan," he said, "but a 25- or 50-year plan." But the situation changed more rapidly than anyone dared to hope, and within a few years the dental Fellows were being called to professional schools all over the country. New candidates, impressed by the success of the program, kept coming from many states and from Europe and the Orient. When in 1955 the former Fellows assembled to celebrate the 25th anniversary of the program, there were 58 "alumni," that is to say men who had held a dental fellowship for one year or longer. They came from 22 dental schools in the United States and 11 in other countries. Every one of the basic science departments of the medical school had received one or more of them as a temporary member, Whipple's own department, pathology, having trained 19, more than any other. Eighteen of the Fellows received the Ph.D degree and 18 a master's degree in science. From Rochester they had scattered to 14 dental schools in the United States and three in foreign lands. By 1955 five of the Fellows were deans of dental schools; 23 were full professors, and 13 not so long out were in other academic ranks. Three were associate deans; one was director of a dental institute, six were directors of dental research in various schools and industries, one a director of medical research. Two were officers in the U. S. Army Dental Corps, and five in the U. S. Public Health Service.

Nearly all of the dental Fellows continued to carry on research, and although the value of scientific investigations cannot be expressed by mere figures, their activity is indicated by their publication of more than one thousand research papers in 25 years. Even more valuable, surely, is the fresh outlook they brought to dental education. As Basil Bibby pointed out,

> They have shown that dentists can do high-grade research; they have established the fact that dentistry does have a scientific content which is worth the attention of good non-dental scientists; and they have demonstrated that research experience is valuable training for teachers in a changing profession. Twenty years ago, these ideas were completely strange to dentistry, but now largely as a result of the dental fellowship experiment in Rochester they are widely accepted, and many universities and governmental agencies are now offering dentists training and research fellowships in the medical sciences.

Under Whipple's deanship of the medical school the dental fellowship project was maintained with very little outside support, until its evident success began about 1955 to bring generous resources from the recently founded National Institute of Dental Research, in the form of grants for increased fellowship stipends and equipment. Two industries in the dental field have each created a new fellowship. The U. S. Public Health Service and the University of Rochester combined to erect and equip new laboratories and offices completed in 1958.

George Whipple's contribution to American dentistry, by developing and leading this bold program, was scarcely known to the general public, nor even (for a long time) to the dental profession, but the dental Fellows are proud to acknowledge it. "Doctor Whipple," said one of them, "more than any other man, brings to dentistry the grand tradition of the great teachers of medicine and science." When the Fellows proposed to acknowledge this debt at the opening of their 1955 reunion, Whipple characteristically asked that speechmaking be limited, but nevertheless man after man among their leaders rose to put into words their gratitude for his service to their advancing profession.

In the spring of 1930, when the clinical departments of the School of Medicine and Dentistry had been conducted for five years under the strict full-time plan, the heads of the departments of medicine, surgery, obstetrics and gynecology, and pediatrics expressed serious dissatisfaction with its operation. This system, the department heads said, however idealistic its basic aim of protecting their time for teaching and research under true university conditions, was not fulfilling that purpose. One great difficulty, especially for the senior professors, arose from the prestige of their university posts, which brought inescapable demands for medical care of private patients, among them influential citizens, civic leaders, and trustees of the University. The more the clinical professors' skill was recognized by the community, the less time they could save for study, research, and writing.

Unlike the older and larger schools, for example Johns Hopkins, which had accepted the strict full-time system, Rochester's full-time clinical staff was small and had only a few part-time practitioners associated with it with local reputation great enough to lighten the burden by attracting private patients. Because the professorial teachers were salaried representatives of the university, they could not turn away private patients without endangering public relations. The full-time plan, moreover, actually discriminated against the medical teachers as compared with the college faculty, whose members were permitted to charge consultation fees, some of them, especially chemists, physicists, and engineers, earning considerable sums in that way. The heads of clinics proposed that they and their associate and assistant professors should be allowed to collect fees for services to private patients under their care in Strong Memorial Hospital, to an extent that would not more than double their income from salaries. The strict full-time plan would thus be replaced by what has been called "geographic full time"; that is, the clinical teachers would conduct a limited amount of private practice, but only in the University's hospital, where they would still be at all times available as teachers and investigators and as physicians to the ward patients. Under these conditions they felt that they could limit their practice by declining private patients with less risk of offense, and could more reasonably ask their associates to carry some of the burden, since they too could charge fees.

The situation was complex and delicate. The General Education Board had given large endowments to several medical schools, including Rochester, on the premise that the strict full-time system, which the Board deemed essential to the improvement of medical education in the United States, would be given a thorough trial. As a matter of fact none of these schools had been able to install strict full time throughout all the clinical departments. Some of them had run into difficulties as had Rochester, and to the distress of the Board and of Abraham Flexner, chief exponent of its ideas, were trying or considering various modifications of the plan.

At Rochester a minority, at least, of the preclinical professors feared that doubling of their clinical colleagues' incomes would divide the medical faculty, hitherto united in true university effort, into two economically and socially distinct groups as was the case in older schools. On the other hand, a group of associate professors of the clinical subjects radically proposed that the university clinics should decline all private patients, giving medical care only to the poor. This, they thought, would not only relieve outside pressure on the professors' time but would also mollify certain physicians in the community who strongly contended that the University was conducting private practice of medicine in competition with them. Any such step would, however, deprive the students and house-staff of experience with patients of the middle and upper classes (financially speaking) among whom most of them would ultimately practice, and moreover would greatly reduce the educational influence which a university hospital should exert upon the community through its more enlightened citizens. A further complication of any scheme that would either abandon private fees or divert them to the physicians was a budgetary problem of considerable size, for these fees had been helping to carry the research expenses of the clinical departments, which the general budget would otherwise have to provide.

George Whipple, after careful reflection, concluded that the proposal of the senior clinical professors offered the only reasonable solution. Supported by a vote of the Advisory Board, he took immediate steps to put it into effect. The first hurdle was of course the trustees of the University, the second the General Education Board. Fortunately President Rhees, a shrewd diplomat as well as a keen executive, also approved the change and was willing to steer the negotiations. He saw to it that a statement drawn up by the hospital director and the professors of clinical subjects—"a clear but rather bald abandonment of our policy hitherto"—was redrafted in a more diplomatic tone and with more precise definition of aims. This proposal he put before the General Education Board, not directly through its Secretary, Flexner, who was sure to react violently, but by a skillfully worded informal appeal for advice to its president, Trevor Arnett; and finally he effectively explained the problem to the trustees of the University and won their consent. The change, voted by them in February, 1931, was retroactive to July, 1930.

Abraham Flexner, who learned of the impending action through Rush Rhees's letter to Arnett, was deeply disturbed. He felt that the University of Rochester, whose successful organization of a modern medical school he had sponsored and in which he took great satisfaction, was about to abandon a basic principle of the new era of American medicine, and that in favoring the new plan Whipple was rejecting the ideals of his own great teachers Mall and Welch. To a letter giving vent to these fears Rush Rhees replied, turning Flexner's argument against him,

It is a source of distress to us that we cannot see this question in the same light as you do, but I assure you, with all seriousness, that in the action which we have taken in response to the unanimous recommendation of our clinical chiefs, and after long and most thoughtful study, we have surrendered nothing of our determination to maintain a medical school of the highest order, and to protect our clinical men from the inroads of private practice upon the full discharge of their obligation for teaching and investigation.

Abraham Flexner was abroad when the change was voted. On his return in June 1931 he fired his last shot, a bitter charge in a letter to Rush Rhees, that the Rochester school had "admitted the thin edge of the wedge" that would ruin the university status of its clinical teaching, and was risking its right to be classed with the full-time institutions.

Obviously there is no perfectly satisfactory answer to the dilemma presented by the teaching of the practice of medicine at university level. George Whipple, upon whom the burden of this decision chiefly rested had, as always when faced with a policy decision, chosen the realistic rather than a theoretically ideal but impractical course. Flexner's fears, seen in the light of 30 years' experience, were not justified. The clinical teachers continued to be university professors in the fullest sense and the school holds its place in the front rank of American medical education.

As dean of the school, once the buildings were finished and in full use, and the department heads proving their competence, Whipple could devote more time to research and teaching. Other professors took over certain large specific tasks. Walter Bloor, associate dean, took care of screening applications and managed student loans. Later, when George P. Berry, and after him Wallace Fenn were appointed assistant deans, they directed the affairs of the growing postgraduate training program. Whipple, however, continued to take the lead in all matters of policy and in the administration of the school as a whole. When, about the end of the first decade, new wings had to be added to the staff residence and the nurses' dormitory, the dean was again busied with blueprints and specifications, as alert as he had been in 1921-1924 to build economically and efficiently. Another new building appealed deeply to his love of sports and his concern for the health of students and younger staff members. When after George Eastman's death it was found that he had left a further large sum to the University, in which the Medical School was to share, the Advisory Board asked for an athletics building with squash and handball courts and other facilities for exercise during the long Western New York winters. To George Whipple, former College Gymnast at Yale, this addition was a great satisfaction. He took special pains with the plans and watched the construction with a keen eye.

In the spring of each year when applications for admission to the school were flooding in, they stood in piles upon his laboratory table awaiting committee action. With undiminished care he went over the annual departmental budgets down to the last detail and pared them when necessary. In the fall he met each entering class on opening day and began to devote himself to the second-year course in pathology. His office and laboratory doors were open at all times to staff members for consultation. He never swerved from his determination not to let outside activities distract him from his own research and the school's business. If anyone complained that he did not give proper attention to the University's public relations or the city's medical interests, he paid no attention; he had told Rush Rhees that he expected such criticism and could take it, and when Alan Valentine succeeded to the presidency of the University he too honored Whipple's resolve to keep quiet and mind his own business.

George Whipple has written, in his *Autobiographical Sketch* of 1959, that he found routine administrative duties neither unpleasant nor very exciting. Teaching and research on the other hand brought satisfaction and pleasure. Research, he said, perhaps yields a greater sense of accomplishment, but teaching, a part of his life ever since his graduation from college, gave him more personal happiness than any other occupation. At Rochester he managed, in spite of all his other responsibilities, to lecture regularly and lead the laboratory work of the course in pathology. He was constantly teaching also at a more advanced level in his guidance of members of his department in training for professorial appointments in pathology and other laboratory subjects, or in clinical fields. These older men may properly claim to have been his pupils as much as the medical students, for there is no end to learning, and the best route to excellence in teaching and research is to work under a great investigator who can also teach.

Whipple's first departmental colleague teaching pathology at Rochester was Harry P. Smith, who had been one of his student Fellows in San Francisco. At first ranking as assistant professor, then associate professor, Harry Smith was appointed in 1930 to the chair of pathology at the University of Iowa and afterward moved to the College of Physicians and Surgeons of Columbia University. His successor as Whipple's senior colleague in the department, William

B. Hawkins, remained through the whole of Whipple's term of active service and is still with the school. Four other men have held associate or assistant professorships under Whipple: Ralph E. Knutti, now director of the National Heart Institute, from 1940 to 1943; Sidney C. Madden, at Rochester 1940-1946, now professor of pathology at the University of California, Los Angeles, and Charles L. Yuile and Roger Terry, both still with the department as full professors. From its organization in 1922 until 1955, when Whipple retired from the professorship, more than 230 men worked under his leadership in the department of pathology, as Fellows, assistants, instructors, assistant professors or associate professors. His *Autobiographical Sketch* lists 17 of these who by 1959 had gone on to full professorships or research posts of equivalent rank in various medical schools and research institutions.

In the later stages of Whipple's research career, as he broadened the scope of his investigations to cover many phases of protein metabolism, the number of persons directly engaged in research with him grew larger until he had at any one time a dozen or more associates of various ranks working in separate groups on three or four distinct problems. Between 1934 and 1955, about 75 men worked with him closely enough to appear with him as co-authors of scientific papers. In addition to his colleagues of the pathology teaching staff, he needed specially trained collaborators to help with the novel and intricate technical methods made available by the advance of biochemistry and biophysics, for example the use of radioactive isotopes. These experts might be drawn from other departments—biochemistry, radiology—as well as from the pathology staff. A need for clinical studies occasionally brought in men from the hospital. A growing number of visiting Fellows and medical students applied for training and research under Whipple's leadership.

His method of training younger people in research favored men of systematic mind and cooperative disposition, good team-workers willing to follow a strong leader while developing their own resources. His laboratory was no place for the maverick or the dawdler, but neither did it discourage originality and independence. In the deployment of the large manpower at his disposal, Whipple displayed masterly generalship. For each of his major investigations he formed a team with one or two experienced men at its head, together with two or three less experienced workers and usually a Fellow or medical student. The senior men were chosen for each project because of their personal interest in it and their command of special technical methods; the juniors were assigned to projects as they happened to be available.

Whatever the particular problem—blood regeneration, the metabolic role of iron, the physiology of the plasma proteins, red cell stroma formation, traumatic shock, blood substitutes, intravenous feeding, placental transmission—Whipple and his experienced immediate collaborators began with a careful briefing of the younger men on the specific phase of the problem on which they were to work and the methods to be applied. After the general plan was agreed on, he expected his senior collaborators to organize and direct the experiments. When the work required biophysical tools such as radioactive tracers, the specialist members of the team from the biochemistry and radiology laboratories planned the tests, Whipple and the other medical men supplying the physiological experience. Whipple liked to take part personally in experiments calling for his own special skills in physiological and surgical manipulation. Junior members of the teams—Fellows and students—helped in operations and other group procedures and carried out endless blood counts, hemoglobin estimations, nitrogen determinations and numerous other technical activities. When they needed advice they went to the older men. Once their skill and reliability had been tested they were given full responsibility for the data they turned in. Whipple met each research group for conferences at varying intervals, usually once or twice a month, at which he received the reports and tabulated data of his associates, commented on their results to date, and received suggestions for further steps, approving or amending them from his own knowledge and experience.

When the time came to publish the results of an investigation, Whipple usually asked the senior member of the group to prepare a first draft, under instructions to state the aim of the investigation succinctly, avoiding an extensive review of the preceding literature on the subject. He told the writer to put into the first paragraph or two a summary of the conclusions, and to repeat the conclusions at the end with brief comments upon their significance. When revising their drafts Whipple took particular pains with the introductory and concluding passages, to make sure that this formula was followed as it was in all his own singly authored papers. He never put his name down as co-author of a paper unless he had personally taken part in the basic research and supervised the writing of the article.

Because of his care in revising the key passages, a decided similarity of style runs through all the papers published by his research groups. Some of his associates learned to write in the same style and consequently their drafts required little revision by the chief. This makes it difficult to judge how much of any given article Whipple himself composed, but he made, at least, the final decision as to the wording of joint papers. One of his keenest co-authors, quizzed about this technique of mutual composition, replied that "concerning the opening paragraph of the paper I published with the dean—this represents essentially pure Whipple, inasmuch as he reduced my first draft of the opening paragraph to one-fourth of its volume and added the clarity which only he could be capable of." On the other hand, according to the same informant, Whipple, coming upon a somewhat high-flown phrase in his colleague's draft, first visibly winced at it and then on reflection adopted it to advantage. In line with this open-mindedness, Whipple was not above seeking advice on his own writing. Drafting an article of which he was the sole author, he often asked one of his senior colleagues to criticize its wording.

Whipple likewise listened with respect to the ideas of his colleagues about research problems, permitting them to test for themselves any reasonable proposal. When a member of his staff carried out successfully an investigation of his own, Whipple encouraged him to publish it independently. He insisted that once a year every research man owes it to himself, and to the institution that has supported his work, to review the past year's experiments and write them up. "You never finish problems," he said; "there's always something more you want to do, but never let either the desire for perfection or just laziness keep you from writing up what you have done, before it goes stale."

The Rochester school, and the dean who built it, won a strong hold on the loyalty and affection of its faculty. For almost a decade the group chosen by Whipple in 1922-1924 to head the school's departments and the hospital, remained unbroken. Then, inevitably, to some of them came calls they could not deny, from places to which they had prior ties of affection and duty. To those who were called away, as one of them can testify, this was a heart-rending experience. To George Whipple also each break in the ranks gave pain, for it meant the departure of a friend as well as the loss of an experienced colleague, and he did all he could by practical argument and personal suasion to avert the move; but he too knew what it was to be racked by such a decision and once the outcome was settled he calmly accepted it and never withdrew his friendship from the departing colleague.

Stanhope Bayne-Jones went to Yale, his collegiate alma mater, in 1932 as professor of bacteriology and Master of Trumbull College, thus taking another step in a long and distinguished career. He was succeeded by George Packer Berry of the Rockefeller Institute, who in turn left in 1949 to become dean of Harvard Medical School. Nathaniel Faxon could not deny the call of Massachusetts General Hospital when asked in 1935 to return to that venerable and distinguished institution as its director. Stout-hearted Basil C. MacLean took Faxon's place at Strong Memorial Hospital. George Corner returned in 1940 to his native city, Baltimore, and to the scene of his medical studies, to head the department of embryology of the Carnegie Institution of Washington. Karl E. Mason followed him as professor of anatomy at Rochester.

It was easier for Whipple to wish Godspeed to three rising young members of the Rochester faculty whom he had started on their scientific careers as student Fellows at the Hooper Foundation in San Francisco. Harry Smith, closest to him professionally, went to Iowa in 1930, as already mentioned, to be professor of pathology. Irvine McQuarrie, called in the same year to the chair of pediatrics at the University of Minnesota, was to have a notable career there. Stafford Warren, the dean's devoted friend and hunting companion, remained much longer at Rochester; long enough, indeed, to start a great new development there, but left in 1947 to organize a new medical school for the University of California at Los Angeles.

World War II upset the every-day life of the medical schools almost as much as World War I had done 24 years earlier, though the Armed Forces had learned to use medical institutions and manpower much more efficiently. A dean's role at such a time, Whipple thought, was to do all he could to hold things together and keep on teaching medicine while meeting the Armed Forces' needs as well as possible. Many of the younger men and some of the professors left for camps, war hospitals or hospital ships, or for the front. The students nearly all went into uniform as members of the Army Student Training Program, or of a Navy V-12 unit. Some of the senior faculty had research contracts for the Army, Navy, or Air Force.

One of these wartime projects, under the lead of Stafford Warren, grew into an immense addition to the school's activities which Dean Whipple could only watch benevolently as it expanded, his own task, as he puts it privately, being "to keep the Army and Staff Warren from tying up the whole school." In fact, he himself was at the bottom of the affair, for it was he who launched Warren on his career as a radiologist when at the Hooper Foundation in 1920 he chose the young student Fellow to join him in studying the damaging effect of x-rays upon living tissues. Later he had welcomed Warren to Rochester as a member of the department of medicine. In the simple early organization of the medical school radiology was placed, contrary to general custom in other schools, under internal medicine rather than surgery. Thus encouraged to make radiology something more than a handmaiden to the clinic, Warren developed his subdepartment into an active center of research in radiation medicine. In 1943, General Leslie Groves, heading the Manhattan Engineering District, as the secret atomic bomb development was called, needed an expert radiation biologist to study the health hazards of atomic energy research and to devise safety measures. Warren, picked for the job, first as a civilian consultant and then as a colonel in the Army, with headquarters at Oak Ridge, Tennessee, plunged into this momentous assignment with characteristic enthusiasm and drive. As an outcome of his service the University of Rochester was asked to set up under contract with the Manhattan Project a research and consultation center at the medical school. Housed in a building hastily put up in 1943 on the north side of Elmwood Avenue, this laboratory at the height of its activity employed 350 persons, many of them drawn from various departments of the School of Medicine and Dentistry and the College of Arts and Sciences. After the war it became a permanent department of radiation biology, formally initiated in 1948 under Harry A. Blair, and now occupies not only the original building with additions, but also a large new wing of the main building completed in 1950. Its investigations, supported by the Atomic Energy Commission, employ a staff of 50, with 70 graduate students—an astonishing sequel to the pioneer experiments in radiation damage begun by George Whipple and Stafford Warren in San Francisco in 1920.

The war brought the school new responsibilities in teaching as well as research. After demobilization many medical officers wanted to return to laboratories and clinics for a while to make up for studies interrupted by wartime service. George Berry, assistant dean, developed an agreement with the Veterans' Administration by which the school created fellowships largely paid for from funds appropriated by Congress for postwar training of veterans. During the four years of this program about 250 physicians each received a year's training.

Postgraduate teaching was not, however, only a wartime activity. From the beginning of the School of Medicine and Dentistry there have always been postgraduate students in the preclinical departments, many of them candidates for the Ph.D. degree, and from time to time clinical departments have conducted brief postgraduate courses and clinics. The dental fellowship program also is essentially a postgraduate school. George Whipple has thus seen the school he organized spread its influence far beyond the regular medical courses, to include postgraduate training for hundreds of doctors, dentists, biologists and biophysicists, on a scale too large for any one man to administer directly. It is a great achievement to have laid the groundwork for such a broad development, and to have built up a staff capable of handling it. Doctor Solomon Whipple, who in 1876 made his plea for better medical education in the United States, would certainly rejoice in the fullness of his grandson's accomplishment; but when George Whipple wrote that teaching has been his happiest task, and that he wishes to be remembered above all as a teacher, he was thinking especially of his own immediate pupils, the medical students who year after year in successive classes have gathered around him in the laboratory and the autopsy room, and those also of greater experience who have worked at his side in the research laboratory, daily companions in learning and discovery.

CHAPTER

# 12

# THE ROLE OF IRON IN THE BODY

SOME NOBEL laureates have found their investigations seriously hampered by professional and social distractions resulting from the sudden leap to popular fame. The Curies, for example, complained that they lost a year's research time after their award in 1903. Not so George Whipple, who knew how to avoid irrelevant demands upon his time, and had trained himself to take success as well as adversity as merely incidental to the day's work. As soon as he and Katharine returned from Stockholm after the Nobel Prize ceremonies he was again in his laboratory, continuing unfinished researches and following new leads that had developed from the study of anemia.

He was still reluctant to abandon the search for specific dietary factors in hemoglobin production. In spite of the consistently negative results of his efforts, recounted in Chapter 9, to pin this essential function to some one chemical agent or ingredient of the diet, the possibility lingered that such a substance existed and was merely eluding detection. Accordingly in 1935 Whipple and Robscheit-Robbins resumed cooperation with G. B. Walden of the Eli Lilly Research Laboratories in Indianapolis, who had aided them five years before in making the liver concentrate (Fraction No. 55) which, as narrated in Chapter 9, physicians had used with success in treating certain forms of secondary anemia. "With this background," wrote Whipple, "it seemed desirable to test similar fractions from spleen, kidney, and heart muscle. If such fractions showed unusual distribution of potency as compared with liver fractions a lead might be uncovered to indicate the value of these substances." This hope was not realized; when Whipple and Robscheit-Robbins tested the new factions that Walden prepared for them, the results again pointed to several factors rather than a single potent substance.

For years Whipple and his collaborators tested various amino acids for hemoglobin-building potency. In 1937 three of these, histidine, phenylalanine, and valine, proved to be definitely potent, though far less so than whole liver. These were the first organic substances clearly definable in chemical terms which were found to take part in buiding hemoglobin. By 1940 Whipple and Robscheit-Robbins had accumulated information on practically all the 20 or more amino acids known to exist in animal proteins, and were able to arrange them in groups according to their relative contributions to the total hemoglobin production.

In spite of his consistent principle of proceeding systematically toward the solution of research problems, Whipple was not unwilling to try an occasional shot in the dark, especially in a hunt as baffling as this one. Such a venture was suggested in 1937 by a pediatrician, Paul Gyorgyi, of Western Reserve University, who had noticed that the control diet of salmon bread, used in the anemia experiments, on which dogs built little or no hemoglobin, is remarkably deficient in one of the $B_2$ vitamins, lactoflavin or (as it is now called) riboflavin. Gyorgyi had been struck also by Whipple and Robscheit-Robbins's finding of 1927 that fish meat and fish liver, which also are practically devoid of riboflavin, did not promote the formation of hemoglobin. His deduction from these two observations, that riboflavin is essential to hemoglobin production, looked good enough to deserve a test. The fact that riboflavin had already been found useless in pernicious anemia was not relevant, since the dissimilarity of the dietary factors in pernicious and secondary anemia was by this time well established. The experiments which Gyorgyi, Robscheit-Robbins and Whipple now proceeded to do showed that riboflavin has in fact a small positive effect on hemoglobin production, about one-fourth that of whole liver. Although on this slight showing it could not be the long-sought specific agent, it had to be added to the accumulating list of contributory factors, including iron, copper, certain salts and salt mixtures, amino acids, certain proteins, and now even a vitamin. Evidently the building of the red blood cells and their most important and most complex constituent, hemoglobin, requires the participation of many substances in a series of synthetic processes by which the amino acids are joined to form globin and linked with heme, the iron-containing pigment. In a number of papers on the metabolism of hemoglobin in health and disease, published during the period 1935-1940, Whipple and several collaborators showed that the mechanism of hemoglobin-building is very complex, and may be upset in various ways by disturbances of internal metabolism. Doubtless some of the accessory factors—copper, salts, various body proteins and vitamins, are needed to keep the participating organs and tissues in good functional condition, whereas others serve to catalyze the chemical reactions carried on in the tissues, by which the actual ingredients of hemoglobin are put together. With this conclusion, George Whipple after two decades of unremitting work on this complex question went on to investigate other problems to which the study of experimental anemia had directed him.

One of these problems had to do with the role of iron, not only in the red blood cells, but in the whole economy of the body, Whipple's researches up to about 1937 had established two important facts about this essential mineral. One is that the body jealously conserves its stock of iron, accepting from the diet as much as it needs, but allowing very little to escape by way of the excretory organs. When, for example, in the ordinary course of events, iron is given up into the blood by disintegrating red cells, it is not excreted, but is at once used again by the bone marrow to build hemoglobin that goes into new red cells, or else is stored in the liver or spleen until it is needed for that or some other purpose.

In 1942 Whipple, with Walter O. Cruz, a visiting Fellow from the Oswaldo Cruz Institute of Rio de Janiero (named for his father, Brazil's distinguished medical scientist) and William B. Hawkins, associate professor of pathology, found an experimental method of disintegrating circulating red blood cells on a large scale, and thus of checking and extending what was known from previous studies about the fate of the iron-containing hemoglobin when set free in the blood. A chemical substance, acetylphenylhydrazine, known in the drug trade as Pyrodin, was known to destroy the red blood cells and was in use by physicians to treat polycythemia vera (Osler's or Vaquez's disease), in which there is a great overproduction of red cells. Cruz first worked out a careful description of acetylphenylhydrazine anemia to provide a basis for experiments; Whipple and Hawkins then joined him in producing the condition in dogs with bile fistulas. Following action of the drug, they observed a much increased output of bile pigment corresponding closely to the amount expected by calculation from the quantity of hemoglobin set free in the body by the destruction of red cells. Hemoglobin is made up of a pigmented portion (heme) combined with protein and iron. Evidently the heme of the destroyed red cells was being excreted as bile pigment. Yet examination of the blood showed that at the same time the dog was putting the iron back into new hemoglobin in the new red cells which it immediately began to produce in great quantity. The animal was, in other words, discarding the heme, which it could easily and (metabolically speaking) cheaply form in the body, but economically conserving and reusing its scanty stock of iron.

Whipple pointed out to physicians that it was illogical to treat polycythemia with acetylphenylhydrazine, because the hemoglobin set free by the drug is at once available to form undesired new red blood cells. On the basis of his own studies it would be more logical to remove surplus red blood cells by bleeding and to limit as much as possible the intake of foods which favor the rebuilding of hemoglobin.

The second cardinal fact established by Whipple and his group about iron metabolism is that the body will not accept from the alimentary tract more iron than it needs. Only when its stores are low will it utilize a new supply from the food or from drugs given by mouth. As Whipple put it in one of his papers, the body guards itself against too liberal an intake of iron because it finds the elimination of iron difficult, and cannot tolerate an excess of it. In his long experience with diseases of the human blood-forming tissues, for example hemochromatosis and the Mediterranean or thalassic anemia which he studied with William Bradford, he had seen evidence that a considerable excess of iron will harm those cells in which it is stored, for example in the liver, pancreas, and bone marrow.

Once aware of these facts, Whipple asked himself how the body manages to hold its stock of iron so closely. Where are the portals of entry that open to accept iron when it is wanted but close against it when the need is supplied? By what chemical and physical mechanisms is this control effected? Once iron is admitted to the body, by what pathways is it carried to the organs where it is used or stored? Whipple had been asking such questions since he first began to study the blood-forming organs and tissues. Some of them could be answered in a tentative way by the methods available up to this time. Two English physicians, R. A. McCance and E. M. Widdowson, after reading Whipple and Robscheit-Robbins's paper of 1936 on the utilization of iron in experimental anemia, and the Whipple-Bradford description of thalassic anemia, made iron-balance experiments on human subjects. They suggested in 1937 that the body does not conserve iron as it conserves many other substances, by limiting their excretion, but by a quite different method. Sugar, for example, is freely absorbed from the intestine, and is excreted only when the blood contains an excess of it. Iron, on the contrary (the English physicians supposed) is controlled at the site of absorption, that is to say, the lining of the intestine. Somehow the surface cells of the intestinal mucosa upon which food iron impinges must be able to accept or reject it according to the body's need.

To Whipple this seemed a very attractive hypothesis, but he was not able to prove it with current methods. He remarked in one of his papers that the metabolism of iron at first sight appears simple and easy to study, but any such notion, he added, was soon dispelled when one dealt with living organisms. He and one of his assistants, Robert P. Bogniard, in 1932 forcibly pointed out the difficulties they encountered when merely trying to assay the amounts of iron in various internal organs. Chemical methods of measuring the iron content of tissues were liable to serious errors. Analysis of an organ gave no accurate measure of the iron in the tissues unless the blood was first drained out of the capillary vessels, because the contained blood might well contain more iron than the tissue itself. Bogniard and Whipple had to meet this problem by an elaborate procedure for washing the blood vessels clear of blood. Iron exists, moveover, in many combinations and in many parts of the body, and in different states, some of it merely stored, some of it in active use in cellular tissues and in the blood. An experimenter therefore cannot simply administer an iron-containing food or drug and trace its distribution in the body, for it will at once become indistinguishable from iron already present in the organs and tissues.

A perplexing occurrence in Whipple's laboratory illustrates the difficulties that may arise in tracing mineral elements. For a number of years at the beginning of the anemia research, his laboratory kitchen baked the basal ration of salmon bread from ingredients mixed by hand. When the number of dogs to be fed on it grew larger, Whipple installed a machine which mixed enough dough at one time for 50 loaves of bread. Shortly after the introduction of this labor-saving machine, dogs on the basal diet, which should have produced very little hemoglobin, began to increase their production so much as to falsify the experiments. It took a good deal of detective work to discover that the increased hemoglobin production resulted from contamination of the bread mixture by iron from the metal surfaces of the machine and from the baking tins. When the machine was lined with monel metal and the tins replaced by stainless steel pans, the dogs' hemoglobin production dropped to the standard minimum level. This is only one example of difficulties of various kinds that long frustrated investigators' efforts to trace the metabolic pathways of iron, carbon, calcium, and in fact practically all the inorganic elements normally present in living tissues.

In the decade 1930-1940 the advance of "atom-smashing" physics suddenly broke through this technical barrier by providing a way of marking the atoms of chemical elements which are to be used in physiological experiments, so that they can be traced even in tissues where the same elements are already present. By bombardment with a cyclotron or other source of high-energy particles, physicists could produce atoms of iron, carbon, or any other desired element, exhibiting exactly the same chemical properties as before in test-tube reactions or in living tissues, but which had become radioactive and as long as they remained so could be detected by a Geiger counter or by their action upon a photographic emulsion. Such a radioisotope can, in fact, be recognized and its concentration in organs and tissues measured with far greater ease and accuracy than by ordinary methods of chemical analysis. This boon given by physics to biology at once revolutionized many phases of metabolic research. As George Whipple put it, grateful physiologists had been presented with a Rosetta Stone for the understanding of body metabolism. Whipple and two colleagues, Paul F. Hahn of the department of pathology, and William F. Bale of the department of radiology, were the first investigators to use radioactive iron in physiological research. When the National Academy of Sciences held its autumn meeting at the University of Rochester, in 1937, Whipple had an opportunity to discuss his hemoglobin problems with a group of distinguished physicists, including Arthur H. Compton of Washington University, St. Louis, William D. Coolidge of the General Electric Company, and Ernest O. Lawrence of the Radiation Laboratory of the University of California. Fortunately for Whipple's project, one of Lawrence's colleagues, Martin D. Kamen, had very recently discovered radioactive iron ($Fe^{59}$); Lawrence made its existence known to Whipple, pointed out that this isotope remains radioactive for a relatively long time, having a "half-life" of 47 days, which would allow ample time for prolonged study of iron metabolism with assurance that such iron found in organs, bones or body fluids is the iron introduced by the experimenter and not some other iron coming from red cell wastage or body stores.

Early in 1938 Lawrence sent Whipple a supply of $Fe^{59}$ produced by bombardment of ferrous carbonate with deuterons. With this the Rochester group began a series of beautifully planned experiments that rapidly won new insight into the problems of iron metabolism. Their first report, a brief note in the *Journal of the American Medical Association,* announced positive proof of the hypothesis that the absorption of iron from the alimentary canal is controlled by the body's need of it. This article carried the name of Ernest Lawrence as co-author with Whipple, Bale and Hahn. Kamen, who actually prepared the isotope for these experiments, was co-author of one or two early papers of the series.

Bale and Hahn shared in the investigation of iron metabolism during practically the whole decade in which this was one of Whipple's chief enterprises. Others who took part in the work as they passed through the various ranks in the medical school or in Strong Memorial Hospital were Herbert A. Claiborne, Robert A. Hettig, Anthony J. Izzo, Joseph F. Ross, Richard T. Snowman, Wellington B. Stewart, interns in pathology; Leon L. Miller, Lilly Research Fellow in pathology; Chauncey G. Bly, research assistant; John C. Wells, Jr., medical student; and Charles L. Yuile, whose internship in pathology, 1937-38, led to a permanent place in Whipple's department as associate professor of pathology. At any one time, three or four, sometimes a larger group, were actively at work on whatever phase of the general program was then current. In certain studies of iron absorption and storage in human patients, a young internist, William M. Balfour, and a gynecologist, Wesley T. Pommerenke, took part. Much of the research with radioactive iron, and that done later with radioactive lysine (tracer for proteins) was done under contracts with the Office of Naval Research and the Atomic Energy Commission.

The first full report by Hahn, Bale, Lawrence and Whipple confirmed once and for all the supposition that the normal dog absorbs very little iron from food or drugs in the gastro-intestinal canal, whereas the anemic dog promptly assimilates it. The peak absorption of iron by the anemic dogs occurs from four to eight hours after feeding, when the ingested materials are largely in the small intestine, which must therefore be the site of absorption. Contrary to a long-held impression of physicians and physiologists, these experiments gave no evidence that the large intestine is concerned with iron absorption. Measurements of radioactive iron in blood plasma and blood cells respectively showed that iron taken in by the stomach and intestine is promptly taken up by the plasma, and within a few hours—an astonishingly short time—it begins to accumulate in the red blood cells.

To study the excretion of radioactive iron it was necessary to flood the animal with that substance. To do this without impedance by the intestinal barrier, Whipple and his co-workers did not feed iron-containing compounds by mouth, but made up the iron in an aseptic, soluble preparation of ferric gluconate which they injected into the veins of several dogs. During the first few days a little of this excess of iron (about 2 to 8 per cent) spilled over, so to speak, and was excreted in the urine and feces, but the kidneys soon ceased to excrete it at all, and only traces continued to leave the body via the feces. In short, the dog has no effective means of getting rid of iron; to avoid an ever-mounting accumulation of this mineral the body must limit its intake with great precision. Further experiments of Whipple's group, in which radioactive iron in systematically varied dosage was fed to anemic dogs, revealed that as the amount is increased, the quantity absorbed rapidly falls. Thus the new method conclusively proved the hypothesis that the body controls its iron stores by regulating the intake rather than the outgo of iron.

This mechanism is quite unlike any other so far known to control the body levels of other minerals. To find out how it works was a problem calling for all the detective ability Whipple and his group could command. In 1942 and 1943 they carried out a long series of experiments that led to a full solution of the mystery. The first step was to recheck, with radioactive iron, the sites of absorption in the digestive tract. This they did by using well-known surgical procedures to isolate, in a few dogs, portions of the stomach, duodenum, and upper and lower small intestine (jejunum and ileum) in the form of small pouches cut off from the alimentary canal but open to the outside of the body, in which food samples containing marked iron could be placed, to be digested without displacement by intestinal peristalsis. Iron was absorbed, the investigators found, from all four of these sites, provided that the dogs were kept sufficiently anemic to need it.

The next important finding was that if an anemic dog is given ordinary iron by mouth a few hours ahead of a test meal containing marked iron, the first dose cuts down the acceptance of the second. If, however, the preliminary dose is given by injection into a vein, it does not block the subsequent absorption of marked iron from the stomach and small intestine. Evidently the blockade mechanism is located in the alimentary canal. When the lining (mucosa) of the stomach and intestine is saturated with iron, the body can accept no more of it from the food, but if the body's iron stores are drained by bleeding or by disease, the gastrointestinal mucosa is desaturated, the mucosal block is relieved, and the needed mineral is allowed to pass through the gastric and the intestinal linings into the blood stream.

Research as successful as this proves its success by raising new questions. Whipple now had to wonder what kind of chemical reactions within the living cells of the gastric and intestinal lining operate the control mechanism to which his experiments so clearly pointed. Just at this stage in his thinking two investigators at the Rockefeller Institute in New York City, the celebrated physical chemist Leonor Michaelis and his associate Sam Granick, published in *Science* a brief note calling attention to a peculiar protein, called apoferritin, which has a remarkable capacity to combine with iron in the ferric state. Struck by this report, Whipple built its findings into a working hypothesis to explain the mucosal block mechanism. He conjectured that the gastrointestinal lining must contain apoferritin or some similar substance able to take up iron from the food, to combine with it, and to hold it in the lining tissues until it is needed by the body. This need is signalled to the lining cells when the iron level of the blood is reduced by anemia, whereupon they release iron to the blood for transport to the organs and tissues where it is required.

Obviously Whipple's best way to test this ingenious hypothesis was to join forces with the Rockefeller Institute investigators. At his suggestion Hahn and Bale took up the problem in association with Granick, and with advice from Michaelis. In 1943 and 1944 they announced their solution of the problem. As Whipple had guessed, apoferritin is the key substance. Combining with food iron in the mucosal lining cells of the stomach and intestine, it forms ferritin, a complex protein-mineral compound containing 23 per cent of iron. When all the available apoferritin is tied up in this combination, the mucosa can take up no more iron. If then the blood stream calls for iron because hemorrhage or disease has reduced the body's iron reserves, the ferritin of the mucosal cells yields its iron to the blood, reconverting itself to apoferritin, which is able to accept more iron from the gastrointestinal contents. By this mechanism, essentially simple though operated by very complex proteins, the acceptance of iron is regulated exactly according to need. In subsequent studies both the Rockefeller Institute group under Granick and Whipple's Rochester colleagues clinched the matter by additional findings, the most important of which were Granick's demonstration that the amount of the iron-holding substance ferritin in the mucosa is greatest in the duodenum, i.e. in the upper part of the intestinal canal, and the parallel finding by Whipple and co-workers that the capacity to absorb iron also is highest in that part of the intestine.

Once admitted to the blood stream, iron is rapidly carried to various organs and to the cells in which it serves its physiological functions. Its pathway and storage places can be traced with the aid of radioactive iron. Quite early in their studies with marked iron, Bale, Hahn, and Ross found that iron is built into hemoglobin in the bone marrow with a rapidity previously quite unsuspected. Four hours after feeding a small quantity of radioactive iron to a fasting, anemic dog they found traces of tagged iron in the red blood cells, and within 24 hours it was there in considerable amounts. Even before these figures were published, two of the team, Miller and Hahn, had extracted pure crystalline hemoglobin from the marked cells and found it radioactive, thus proving that the tagged iron had not only reached the red cells but had been built into the molecules of hemoglobin within them. Once there, the workers of Whipple's group found, it is locked up for the lifetime of the red cell. Iron carried in the blood cells as an ingredient of hemoglobin does not exchange with that which is carried, for other purposes, in the blood plasma.

Whipple was not content to use only in dogs the almost magical new method of marking and tracing iron. Experiments on animals could of course be done with far better control than is possible with human subjects, but similar observations, even if incomplete, must eventually be made with human beings to exclude possible differences between the physiology of dog and man. Furthermore radioactive iron could be used to study disease states in human patients which could not be reproduced in experimental animals, for example pernicious anemia and hemochromatosis. For this reason, as soon as he had the methods in hand, he proceeded with his two chief associates in this work, Hahn and Bale, and two clinicians, Balfour and Pommerenke, to study iron utilization in hospital patients. In these tests, marked iron was easily and safely administered in the form of ferric ammonium sulfate, a familiar drug which for this purpose was specially prepared from iron chloride made radioactive by the University of California's cyclotron.

The most striking discovery made in these clinical tests was that pregnant women, in good health and not anemic, absorb iron from the alimentary tract two to ten times faster than nonanemic dogs and men, as freely in fact as anemic dogs. In pregnancy, the investigators concluded, the growing fetus robs the mother's reserves of iron and thus creates in her body a demand which lowers her gastrointestinal barrier and permits her to accept iron freely from her diet. An opposite but equally remarkable response of this control mechanism to a special physiological need occurs in diseases such as pernicious anemia, hemochromatosis, familial icterus, and thalassic (Mediterranean) anemia, in all of which a great deal of hemoglobin is set free by the breakdown of red blood cells but is not excreted, so that the tissues accumulate large stores of iron. In such diseases the iron content of the blood plasma of course remains high, even though that of the red cells is low. Consequently the gastrointestinal mucosa gets no signal to accept iron. The opposite findings in these contrasting conditions—pregnancy on one hand, iron-storage diseases on the other—reinforce the important conclusion confirmed earlier by experiments on dogs, that iron absorption is governed by the amount of reserve iron in the body rather than by the iron content of the red blood cells.

Radioactive iron also gave Whipple and his fellow investigators a tool for solving other problems that had resisted attack by ordinary methods. They easily proved, for example, the observation, contested by some workers, that whole red blood cells can pass from the peritoneal cavity into the lymphatic vessels of that region and thence into the blood stream. Marked red cells moreover permitted quantitative observations on the blood previously impossible to secure. Whipple's team were now able to calculate the total mass of the red blood cells, the ratio of the mass of red cells in active circulation to that immobilized in various organs such as the spleen, the total volume of the blood plasma and the relative volume of that portion of it which is actively circulated at any one time. These data were essential for the study of the plasma proteins which was now becoming Whipple's chief interest.

CHAPTER

# 13

# DYNAMIC EQUILIBRIUM OF PROTEINS

WHIPPLE'S INVESTIGATION of hemoglobin, whose elusive peculiarities were related to its protein structure, naturally led him to consider the whole subject of the proteins and their internal metabolism. This problem, he wrote, involves a vast chain of unknown reactions by which proteins entering the body in the food are accepted, broken down into amino acids, distributed to the organs and tissues, rebuilt into forms suitable for the body's use, stored or utilized; and when their physiological role is completed, are variously shifted, broken down and again rebuilt, or eliminated, in an unending metabolic cycle. The study of these vital phenomena is not only of intense scientific interest, but in many ways has great practical importance. Physiologists knew, for example, that the plasma proteins are necessary to hold water in the circulating blood, and when they fall below a certain level, as in some cases of nephrosis and nephritis, water passes from the blood into the tissues and a dangerous state of edema (dropsy) ensues. In the past biologists and physicians looked upon this water-holding (osmotic) action as the chief function of the plasma proteins, and did not seriously consider their role in the internal metabolism of the body. Surgeons interested in blood substitutes for perfusion after severe hemorrhage had even supposed that the blood plasma might be adequately replaced by inert materials such, for example, as solutions of gum acacia.

Only occasionally had physiologists and biochemists caught a glimpse of some of the more complex functions of the proteins of the blood. One such glimpse was obtained by Whipple in 1933-35, through experiments in which he was assisted by Frieda Robscheit-Robbins, with Floyd S. Daft and Russell L. Holman, junior members of the pathology department, and Earle B. Mahoney, a student Fellow. These investigators found that the plasma proteins have an important role in rebuilding body proteins whenever these are needed in any organ or tissue. In their experiments they studied the regeneration of hemoglobin under the most difficult experimental conditions. First they made their dogs severely anemic by repeated bleedings, then fed them a diet drastically low in protein. Even under such doubly unfavorable circumstances, they observed, the animal for a long time continues to build the desperately needed hemoglobin. It gets the necessary protein from the blood plasma, and the blood in turn draws upon the protein reserves in the body tissues as long as they last. In other experiments Whipple and his collaborators found that the protein of damaged liver cells also can be regenerated by drawing upon reserve protein in other tissues. A dog can even use plasma proteins from other dogs to build up the plasma proteins of its own blood, and this it can do whether the extraneous plasma is fed by mouth or administered by intravenous injections. There must be, therefore, a good deal of give-and-take between body protein and plasma protein, and between the proteins of various tissues, all of which seem to be in a state of adjustable balance with one another, or, as Whipple expressed it "dynamic equilibrium." The animal body, when deprived of proteins in the diet, can take them from its reserves, or even (in dire necessity) from the fixed tissues, to fabricate needed proteins of different character. This concept was to guide much of Whipple's subsequent investigation.

The dynamic equilibrium of body proteins is now a commonplace of nutritional physiology, but in 1934, when first announced by Whipple and his fellow investigators in a paper in the *Journal of Experimental Medicine,* it directly contradicted the current philosophy of nitrogen metabolism. The so-called "classical theory" proposed by Otto Folin of Harvard in 1905 held that the protein elements of the organs and tissues are relatively fixed and stable; while the proteins obtained daily from the food to meet energy requirements are in a state of flux as they pass through the processes of digestion to ultimate breakdown and elimination. On this theory the situation is something like that in an automobile factory, where part of the steel is built into the machines and changes only through wear and tear, while another part goes into the product, with practically no exchange of materials between the two uses. Whipple's findings could not be interpreted in any such way, for in the animal body, he perceived, the proteins of the machine and those concerned in daily vital processes undergo constant exchange and are in functional balance with each other.

Holman, Mahoney, and Whipple, in the first paper in which they used the term "dynamic equilibrium" to define their new concept, wrote that "the statement that blood proteins can be utilized freely in the body economy has a heretical flavor . . . We realize that these statements will be challenged but hope that the experimental data will be adequate to convince even the skeptic." There is no longer any skepticism on this subject, yet Whipple and his co-workers have never been given the full credit they deserve for their original discovery and proof of the dynamic equilibrium of body proteins, largely because their ideas were not placed before the scientific world with sufficient emphasis on their radical departure from accepted theory. The article of 1934, like all that Whipple wrote or edited, does not dwell upon the background of the investigation. Whipple was not primarily interested in the history of the problems with which he dealt. He took up each question as it currently presented itself, and when he had obtained an answer, aimed only to present the facts as he saw them. He taught his juniors, in fact, to avoid long historical introductions to their papers; really interested readers, he assumed, would be familiar with the previous state of the problem, or could look it up. Perhaps also Whipple did not wish to make an issue of his dissent from the views of Folin, a highly respected older man. In any case the 1934 paper, while admitting its novelty, did not explain to the general reader just what orthodox views it was refuting, and to this day most textbooks and reference books on the physiology of nutrition credit the theory of dynamic equilibrium to others.

In 1935 Henry Borsook and Geoffrey L. Keighley of the California Institute of Technology reported in the *Proceedings of the Royal Society of London* a series of ingenious dietary studies on human subjects, whose nitrogen and sulfur intake and excretion they carefully measured, with results that were incompatible with the classical theory. Their report clearly brought out their abandonment of Folin's concepts. Borsook and Keighley did not know of Whipple's recent work, which theirs, done by quite different methods and on men rather than dogs, so admirably complemented. Still another investigator, Rudolf Schoenheimer of Columbia University, reached similar conclusions a few years later, by yet another method of study. When in 1937 heavy nitrogen became available, Schoenheimer used it to label and trace amino acids in rats, and like the Rochester and Pasadena groups, concluded that his findings could not be reconciled with the concept of two independent varieties of protein metabolism. Presenting his work in a Dunham Lecture at Harvard, published in 1942 after his untimely death, Schoenheimer wrote that "the body constituents are involved in continuous chemical processes and there exists a close interaction between the food materials and the body components." Simply because these other investigators emphasized their dissent from older views much more explicitly than did Whipple, most compilers of textbooks of physiology, even when discussing the modern theory under the title Whipple introduced, "dynamic equilibrium of the body proteins," fail to recognize his priority in its establishment.

Since the circulating blood is the chief agent for transporting proteins throughout the body to maintain their dynamic equilibrium, the blood must continually be laden with proteins of diverse kinds, coming from various parts of the body, and destined to serve many functions. To analyze this complex metabolic traffic, Whipple thought, he should begin at its starting point, the acceptance of protein materials from the food. He had in fact begun such a study long ago in San Francisco in 1917-1919, when (as told in Chapter 5) Karl Meyer and Samuel Hurwitz awoke his interest in the serum proteins. At that time, needing dogs with the lowest possible level of blood proteins, in order to get a base-line from which to measure the body's ability to construct proteins, he prepared them by a procedure known as plasmapheresis, in which part of the blood is drawn off and replaced by a suspension of red blood cells in physiological salt solution. The animal thus retains a normal red cell count and normal oxygen-carrying capacity, but is hypoproteinemic; that is, its plasma proteins have been greatly depleted. Whipple had learned of this procedure from its inventor, P. Morawitz, in 1909, when working at the latter's side in Krehl's laboratory at Heidelberg. Morawitz's first use of it (in rabbits) was published in 1906. The name *plasmapheresis* was introduced in 1914 in an article by Whipple's revered teacher, John J. Abel, and two co-workers at Johns Hopkins.

In the San Francisco investigation Whipple found by feeding experiments on dogs made hypoproteinemic by plasmapheresis, that the body cannot recruit its plasma proteins directly from similar proteins in the diet, but must build them anew in the body from intermediate products (e.g. amino acids) which it obtains by partially digesting the food proteins.

Starting in 1933 where he left off in 1919, Whipple again used hypoproteinemic dogs to test the relative effectiveness of various dietary factors in the regeneration of plasma proteins, but this time he planned to keep the plasma proteins low for long periods rather than temporarily. The experimental procedure resembled that which he and Robscheit-Robbins had been using for a dozen years to measure the hemoglobin-building potency of various foodstuffs, except that now it was not hemoglobin that was to be chronically depleted, but the plasma proteins. This depletion was effected by repeating the plasmapheresis frequently enough to keep the blood proteins just above the level at which edema would disastrously set in. As in the hemoglobin studies, the dogs were fed on a basal maintenance diet. In this study, however, the diet was made deficient in proteins rather than in hemoglobin-building factors. It contained, in fact, no animal proteins at all, utilizing potatoes alone to provide the minimal amount of protein necessary to prevent edema and keep the animal in nitrogen balance. With skilled care, dogs prepared and fed in this way can be kept clinically normal, with good appetite, no anemia, and normal nitrogen metabolism. Once their reserve protein supply has been exhausted by plasmapheresis at weekly intervals for two to six weeks, they are in a steady state of hypoproteinema, producing a uniformly low, indeed negligible amount of plasma protein.

Readers who follow our narrative of Whipple's investigation of plasma protein formation, which in its many ramifications will occupy the rest of this chapter, should not let the printed page obscure their mental picture of these long-term experiments, done day after day by patient, vigilant, intent people handling a houseful of big lively dogs that had to be treated as if they were at one and the same time chemical machines, hospital patients, and pets. The animals were vaccinated against distemper and dysentery, and were isolated from other dogs in air-conditioned rooms with closely regulated temperature. Only aseptic methods were used in drawing blood and administering drugs and test materials intravenously and subcutaneously. Nor should the reader fail to appreciate the unending labor of assaying blood samples, counting red blood cells under the microscope, and a variety of other necessary technical procedures. The key operation of the whole program, measuring the output of plasma proteins in the successive samples of blood withdrawn to maintain the basic hypoproteinemia, called for much more complicated and exacting laboratory tests than did the assay of hemoglobin in earlier experiments.

For several years Whipple's principal co-worker in this project was Sidney C. Madden, a member of the pathology department trained at Stanford University and Johns Hopkins. The two leaders had the assistance of a number of young men, most of them taking part for a short time only while junior staff members or student Fellows. From 1933 to 1937 these included (besides Daft, Holman and Mahoney, mentioned above), Cyrus C. Erickson, Ralph E. Knutti, James B. McNaught, Paul E. Rekers, Howard B. Slavin, G. S. Waraich, and Francis M. Woods of the junior pathology staff; Clement A. Finch, Warren E. George, Joe W. Howland, Donald H. Kariher, Walter A. Noehren, W. George Swalbach, Philip Winslow, student Fellows; Virgil C. Scott, medical student; and Wesley T. Pommerenke of the gynecology staff.

Whipple's first dietary tests showed that the regeneration of plasma protein can be modified at will by food factors. On the basal maintenance diet, a dog of the size used at Rochester can produce only about two grams of plasma protein per week, whereas on a diet amply supplemented with liver or with casein (the principal protein of milk) it will make three or four times as much. Tests of various animal and plant products added to the basic diet showed that some proteins are very potent for producing new plasma proteins while others are poor in this respect. Beef serum proved the best of those tried; lean meat, milk protein (casein), and egg albumen were very good, liver somewhat less potent. Plant and grain proteins were well utilized, soy bean meal standing at the head of the list of vegetable proteins.

Subsequent experiments modified or rather, sharpened Whipple's concept of a general pool of body proteins in dynamic equilibrium, for he found that there is not quite a free two-way exchange between the blood proteins and the body's built-in stock of proteins in the organs and tissues. The plasma proteins readily go to build body proteins, but when themselves depleted cannot ordinarily reverse the process by drawing upon the body's built-in stock. The organs and tissues also hold, however, a reserve of loosely-bound protein material which serves for a time to restore plasma proteins after plasmapheresis. When these reserves are exhausted, the body proteins, as Whipple put it, "stand by, helpless to aid, while vital plasma proteins are depleted even to a lethal point."

The reserve stores, which are apparently of somewhat different nature from the fixed body proteins—Whipple thought of them as large molecular aggregates of proteid nature—are evidently formed from proteins consumed in the diet, which are broken down during digestion into amino acids and after absorption are rebuilt into loosely storable forms suitable to the individual species. The body does not make direct use, in the blood and organs, of proteins from other species. A dog, for example, cannot assimilate foreign plasma protein, e.g. horse plasma, if it is put directly into his veins, although he can readily utilize the plasma of his own species in that way. He can however use horse plasma given by mouth, rebuilding it into dog protein. This reworking of extraneous proteins is apparently done chiefly by the liver. When Whipple and his co-workers tested plasma protein formation in dogs in which they had made an Eck fistula, so that the blood coming from the intestines by-passed the liver, they found that these animals built plasma proteins at only one-tenth the normal rate.

A diagram from Whipple's Mellon Lecture at the University of Pittsburgh, May 18, 1938, clearly illustrates the traffic pattern of the proteins in the body which he had worked out by his experiments of the past two decades.

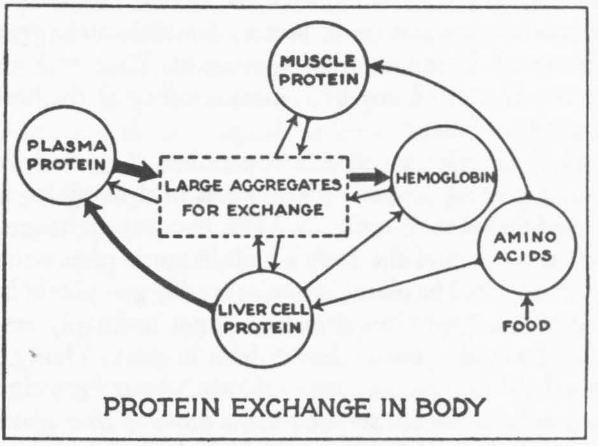



Diagram of protein exchange in the body. By courtesy of American Journal of the Medical Sciences.

From this diagram we see that the body gets its protein construction materials from the food, which when digested furnishes amino acids. These are synthesized in the liver and elsewhere into plasma proteins and ultimately deposited as fixed proteins in muscle and other cells, tissues, and organs; as hemoglobin in the blood; and as reserve proteins available for exchange and for restitution, in case of need, of the fixed and plasma proteins. The distribution and the utilization of protein materials in the body are kept in balance by the aid of the protein reserve stores. If the need to build new cell protein, new plasma protein, or new hemoglobin is greater than the diet can provide for, the reserve stock is depleted; if the need is less, the stores are rebuilt. The maximum and minimum limits of these stores are individually characteristic of each organ, tissue, and body fluid and are determined by factors yet to be fully understood.

Since, as the diagram reminds us, the whole process of protein metabolism depends upon amino acids derived from the food proteins, Whipple was now in a position to carry his analysis of plasma protein production a long step forward, by testing the separate potency of each of the common amino acids—20 in number—that occur in the animal and plant proteins. In this phase of the investigation (1940-1943) his chief aide was still Sidney Madden, now promoted to an assistant professorship of pathology. As the younger members of the research group went on to other posts, and the student Fellows one by one returned to regular medical studies, their places were taken by Leon L. Miller, Lilly Fellow in pathology; Eric L. Alling, Associate in radiology; A. D. Hengerer and John R. Remington, Assistants in pathology; Richard R. Woods, intern in pathology; Frederick W. Anderson, John R. Carter, John C. Donovan, Albert H. Kattus, Jr., Albert P. Rowe, Frederick W. Shull, Allen P. Turner, and Louis S. Zeldis, student Fellows.

As a basis for these tests Whipple and his group had extensive information from nutrition chemists and physiologists, who for years had been studying the respective values of the amino acids for general growth and maintenance of the animal body. In a first series of experiments Whipple added gelatin to the basic diet of hypoproteinemic dogs, choosing that particular protein because it was known to be "incomplete"; that is, it lacks tryptophane, one of the amino acids which are essential to animal nutrition, and is very low in two others, cystine and tyrosine. The outcome of this test, after some preliminary uncertainties, was definite and striking. Gelatin alone added to the basal diet caused very little increase in production of plasma protein. The further addition of any one of the three missing amino acids had little or no effect, but when gelatin was supplemented by cystine plus either tyrosine or tryptophane, the combined mixture became a potent stimulant of plasma protein production, as good in fact as beef serum, the best natural material thus far tested.

In 1938, when Whipple and his group were beginning these studies, an eminent nutrition chemist, William C. Rose of the University of Illinois, published a summary of his work of many years, done mainly with rats, to ascertain which of the natural amino acids are necessary for full nutrition and growth of the animal body. His list of ten essential amino acids is now familiar to all students of nutritional physiology. Generally speaking these amino acids which are indispensable for the rat have since been found essential for other animals including man. With this lead Whipple was able to make more rapid progress. He found, in brief, that his hypoproteinemic dogs were able to produce plasma protein abundantly when the basal diet was supplemented with all ten of Rose's essential amino acids. Tryptophane and tyrosine, which Whipple had already found essential for plasma protein production, were among the ten. Cystine was not, but this was explainable by the fact that it can be formed, in the body, from methionine, one of the essential ten. Whether or not any of the amino acids needed for general growth are not needed for plasma protein production was difficult to discover, because every modification of the supplementary diet caused internal shifts of protein which confused the experimental findings, but the available evidence strongly suggested that all ten are as essential to plasma protein production as they are to growth.

Mention of the two sulfur-containing amino acids, methionine and cystine, suggests a brief digression here to report a collateral investigation in which Whipple returned, with L. L. Miller and Joseph F. Ross, interne in pathology, to the field of experimental liver damage by chloroform poisoning which had first started him down the long road of his research on protein metabolism. In 1940 Miller and Whipple happened to observe that a dog anesthetized with chloroform suffers liver damage in proportion to the state of his protein stores in the liver and body tissues. A normal well-fed dog can undergo an hour of surgical chloroform anesthesia without liver injury. A dog that has fasted for three days, similarly exposed to chloroform, develops serious liver necrosis. If the protein stores have been depleted by plasmapheresis or a long-continued low protein diet, a dog can occasionally tolerate twelve minutes of light chloroform anesthesia but twenty minutes will be fatal. Again Whipple had reason, as he had 32 years before, to warn physicians against chloroform as an anesthetic, especially with patients in poor nutritional condition.

Thinking back to his early work he recalled an observation by John Howland and A. Newton Richards in their experiments which had first interested him in chloroform poisoning. They had described a marked increase in excretion of urinary sulfur in dogs after heavy chloroform anesthesia. To Whipple's prepared mind this observation now—in 1940—suggested that chloroform necrosis involved damage to proteins by which sulfur is set free. Since all the sulfur in animal proteins is contained in the two amino acids methionine and cystine, Miller, Ross and Whipple administered to protein-starved dogs, four or five grams of one or the other of these substances some hours before anesthetizing them with chloroform and saw a striking confirmation of Whipple's brilliant guess—the dogs were in fact completely protected against 40 minutes of chloroform anesthesia. A single large feeding of beef, or an injection of plasma protein by vein gave similar protection. Other amino acids not containing sulfur, alone or in various combinations, were not protective. Whipple had this discovery on his mind for some years, and two years later (1954) Miller and he found that methionine or cystine avert chloroform necrosis of the liver even if fed after the anesthetization. They suggested therefore that physicians should reinforce the diets of patients with damaged livers with proteins rich in methionine, among which casein is most readily available, or in emergency administer casein digests intravenously.

As Whipple expected, the mixture of essential amino acids on which depleted dogs successfully rebuilt their plasma proteins and hemoglobin was just as effective when administered by intravenous injection as it was when taken by mouth. In this finding he saw the possibility of an important clinical application in the intravenous feeding of human patients. For many years physicians had been trying to develop a satisfactory way to feed patients, in case of necessity, by other than the oral route. One of the great difficulties, in view of the fact that the body does not utilize foreign proteins except through digestion in the alimentary canal, was to supply sufficient nitrogen in the intravenous feedings. To give amino acids, rather than proteins, intravenously would avoid this difficulty.

When in 1941 the United States entered the Second World War the problem became a serious one for the medical services of our Armed Forces. Following wounds, burns, infections and major surgical procedures, nitrogen losses may be very large, too large in fact to be compensated by dietary intake of proteins. In these circumstances the human body's protein reserves may be so greatly depleted as to hamper recovery and wound healing. Also, in shock following hemorrhage, one of the pathological factors is a loss of plasma proteins. For this, of course, the best treatment is transfusion with human blood plasma, but it was difficult in war time to supply enough plasma for the fighting front, to say nothing of surgical patients at home who also needed it. Seeking substitutes for human plasma, surgeons experimented with digests of meat or casein in which the proteins were broken down, by digestive enzymes, into amino acids. Whipple, with his hypoproteinemic dogs, had a precise method of testing the value of such preparations for their power to restore the plasma proteins. As soon as he and his group found that casein by mouth could effectively support plasma protein formation, they tried intravenous feeding with casein digests expertly prepared by the Eli Lilly Research Laboratories. These mixtures, they found, generally kept dogs in full nitrogen balance and promoted plasma production as well as did casein by mouth.

Such digests, however, do not always succeed, as surgeons well knew who had tried them on patients. They sometimes contain by-products not safe for intravenous injection, and furthermore may not contain the essential amino acids in correct proportion. Whipple's group, moreover, experimenting with changes in the amino acid content of intravenous nutrients given to their dogs, had produced metabolic disturbances and toxic states. A mixture of pure amino acids in correct proportion would of course avoid these dangers. Having already fed such mixtures by mouth with entire success, Whipple ventured to test them on his hypoproteinemic dogs by intravenous injection. For this extensive experiment the famous chemical firm of Merck and Company donated generous supplies of the essential amino acids. Results were at once favorable, and with growing experience and constant improvement of the amino acid mixtures Whipple's group kept dogs in good condition on intravenous feeding alone for several months at a stretch.

This achievement with the experimental animals was dramatically emphasized by successful use of the mixture in the desperate case of a starving human patient in Strong Memorial Hospital. This was an elderly man on the surgical service with severe gastrointestinal ailments who could not retain food in his stomach. Under the supervision of Samuel H. Bassett, associate professor of medicine, the man was fed for two periods of three weeks each almost exclusively by an amino acid mixture injected into his veins, with resulting complete satisfaction of his nitrogen requirement and concomitant improvement in his general condition. Subsequently a number of other patients were similarly treated with favorable results, by a hospital group advised by Madden and led by Bassett.

Plasma proteins, however, are not the only essential protein ingredients of a blood substitute. A man who loses a great deal of blood suffers a shortage not only of plasma proteins, but also of hemoglobin. An ideal blood substitute therefore must be able to stimulate the production of both. In 1942 Whipple began to study this problem of "double depletion" experimentally. His immediate aim was to find the best possible blood substitute, but always in the background was the long-term objective of a better general understanding of the body's utilization and replacement of the proteins of the blood, and their interrelations with other body proteins. In the light of his concept, to which he frequently recurred in his published reports, of a body protein pool including the blood proteins, cell proteins, and reserve store proteins, with constant interchange by way of the plasma proteins, he expected the study of double depletion to tell much about the way in which the body reconciles the competing needs of these important elements of its vital economy. To help with this intricate project he formed a well balanced team of Freida Robscheit-Robbins, long his chief associate in the study of hemoglobin formation, and Leon L. Miller, the chemist who had taken part for two years in the group study of plasma proteins.

The dogs were bled at regular intervals to deplete both hemoglobin and the plasma proteins. They were fed on a basal ration in the form of dog biscuits containing no protein whatever. On this diet the plasma protein dropped to a low level without plasmapheresis. The ration contained corn starch, dextrin, baking powder, bone ash, salts, sugar, vegetable fats in the form of corn (maize) oil, cod liver oil, and hydrogenated cottonseed oil (Crisco). It was supplemented with iron and the necessary vitamins. It is not surprising that the dogs had to be conditioned to this diet, so foreign to canine tastes. Even when they seemed accustomed to it they sometimes rebelled and terminated the experiment by refusing to eat. They became, moreover, much more susceptible to infections such as pneumonia, septicemia and endocarditis, than they had been when depleted of either hemoglobin or plasma proteins alone. With patience and constant vigilance, however, they could be kept well and active for months.

Doubly depleted dogs, Whipple and his co-workers found, could make new plasma proteins and stay in nitrogen balance on a wide range of protein-containing supplements, including eggs and meat, and other animal products given by mouth such as beef plasma and digests of serum, hemoglobin, or casein. They could use dog plasma by vein to make new hemoglobin, and on the other hand made plasma proteins from hemoglobin digests given by vein, or from whole hemoglobin injected into the peritoneal cavity. Fed on the growth mixture of ten essential amino acids they built hemoglobin extremely well and also plasma proteins; on a slight modification of the mixture (replacing methionine by cystine) they considerably increased their yield of plasma proteins. They could even utilize globin, the incomplete protein fraction of hemoglobin, if injected intraperitoneally. This simple protein is constantly available in the blood stream through the breakdown of obsolescent red cells. That it can be rebuilt directly into new hemoglobin, Whipple had proved long ago. Now he learned that globin can also contribute to the production of new plasma proteins. To do this it must be supplemented, from the body stores, with those amino acids in which it is deficient. Summarizing all these findings, Whipple emphasized the remarkable fluidity with which, he had found, both plasma proteins and hemoglobin contribute directly to the general protein pool from which in turn are evolved, without waste of nitrogen, all the needed proteins of the tissues, the plasma, and the red cells.

In every experiment, whatever the effective supplemental diet, the doubly depleted dogs rather surprisingly produced more new hemoglobin than new plasma protein. Although Whipple pondered much about this, hoping that if explainable it might teach him how to change the relative yields of the two kinds of protein by appropriate changes of diet—something that might be very useful in treating metabolic diseases—such experiments as he could make at the time were not effective and he could only speculate as to the meaning of this preference of the body for hemoglobin. In 1949 and 1951 he and Robscheit-Robbins returned to the problem, and finally obtained, on selected diets, moderate changes in the ratio of hemoglobin to plasma proteins. They were hardly enough, to affect clinical practice.

The attempt to develop a practical blood substitute in the end baffled Whipple and his associates as it has thus far baffled everyone who has worked on the problem. The blood's complexity defies analysis. Whenever someone thinks he has within his grasp a combination of all the ingredients necessary to a safe and fully effective solution that can do everything that blood will do, some new difficulty arises. Whipple's doubly depleted dogs did astonishingly well, as we have seen, on natural food products given by mouth. Casein, lactalbumin, whole egg protein, liver protein were all adequate to maintain weight and keep the dogs in nitrogen balance for months on end. The dogs seemed to do well also when fed the growth mixture of ten essential amino acids. Whipple hoped that such a mixture, given intravenously, would form the basis of a blood substitute. Under the severe stress of double depletion, however, it failed, for while the dogs maintained a positive nitrogen balance for a time, they lost weight, sometimes as fast as if they were getting no nitrogenous food at all. For some reason the body could not, on this mixture, build all the blood proteins it needed and had to raid the cell proteins of its organs and tissues, which are normally not drawn upon by the circulating blood.

Evidently, then, whole proteins (eggs, liver, meat, casein, lactalbumin) contain something not present in the mixture of pure amino acids. This missing substance might conceivably be another amino acid not previously considered essential, an unsuspected trace element, an unknown vitamin, or something else quite unpredictable. Several students of nutritional physiology working with rats and mice had run into similar difficulties. When Whipple's group administered the amino acids in the form of protein digests, the dogs did well for long periods. The digests must have contained at least some part of the mysterious ingredients missing in the mixture of pure amino acids, but this did not suffice; the dogs did not retain the total nitrogen of the protein digests as well as they did that of whole proteins given by mouth.

Another difficulty of perhaps the same sort turned up in the case of gelatin, a simple protein tolerated by the body when injected into the veins, in which many investigators were at the time interested because it has many characteristics suitable for use in a blood substitute. As an incident in their own work, Whipple's group tried gelatin on doubly depleted dogs. They found that it could be administered intravenously for a few days without ill results and indeed contributed somewhat to the building of new hemoglobin and plasma proteins, doubtless supplemented from the body reserves with the three essential amino acids in which it is deficient. In the long run, however, it proved to be sufficiently toxic to impair the production of plasma proteins. Whipple's advice, based on these trials, that clinical experimenters should be very cautious about using gelatin in blood substitutes cogently contributed to its general abandonment.

By 1949 the blood substitute problem seemed less pressing than in 1942. The war was over and we had enough whole blood and plasma for our civilian needs. Whipple had interested himself in the practical side of the problem only as a war-time duty, in fact he made no contribution to it that was not also a contribution to knowledge of the underlying physiology and chemistry. The investigator of basic medical and biological problems, he always held, is under no obligation to work on practical applications. He should conserve his time and resources for front-line research, leaving it to the clinical practitioners to take up laboratory findings and put them to use. As a wise strategist in research, it was time, Whipple felt, to leave to others the search for a blood substitute, while he went forward with the investigation of fundamental problems.

Subsequent efforts to develop blood substitutes have taken other directions and the work of Whipple's group has not found application in that field. It has, however, greatly influenced important advances of another kind. One of these has to do with tissue culture. An experienced worker in that field, Philip R. White, at the Rockefeller Institute and later at the Jackson Memorial Laboratory at Bar Harbor, Maine, began in 1943 to develop a medium on which to grow animal cells, which should contain only substances of completely known chemical nature. The usual tissue culture media contain crude substances whose chemical nature is not precisely known. In this effort his laboratory achieved a high degree of success, culminating in 1959 in the report by his associate Charity Weymouth, of a stable, chemically defined nutrient solution in which mammalian cells will readily grow. White credits Whipple and Madden for the solution of essential amino acids supplying the nitrogen required in his and Weymouth's culture fluids.

Whipple's work has also helped greatly to advance the practical development of intravenous feeding of patients who for one reason or another cannot take food by mouth. The greatest difficulty with intravenous feeding has been that foreign proteins cannot be injected directly into the veins, because of the toxic and allergic reactions they set up. When Whipple's laboratory group demonstrated that nitrogen can be supplied by vein in the form of amino acids or even of partially digested protein hydrolysates, and when their clinical associates succeeded in keeping surgical patients in nitrogen balance for days at a time on such mixtures given by vein, they gave great impetus to the further improvement of intravenous feeding. Within the past two decades physicians and surgeons have advanced from the simple dextrose and salt solutions formerly used, to nutrient fluids containing all the essential ingredients of a complete diet. These improved fluids employ amino acid mixtures or protein hydrolysates similar to those pioneered by Whipple's laboratory. Although there are still difficulties involved in feeding human patients by vein, these are being overcome, and intravenous feeding has achieved a permanent place in medicine and surgery.

CHAPTER

# 14

# TRACING THE PLASMA PROTEINS

FROM THE Nobel Prize year of 1934 and until the 1950's Whipple constantly had three teams of investigators working side by side under his leadership, on the three great problems of hemoglobin formation, iron metabolism, and the utilization of proteins. To present a clear narrative of this multiple research program, it has been necessary to untangle the concurrent lines of research and discuss them separately. They were however closely related, each raising questions and suggesting methods of investigation relevant to the others. Since 1938, for example, Whipple's hemoglobin team had been using the radioactive tracer technique to follow iron in its metabolic course in the body. As he and his co-workers wrestled with the intricacies of plasma protein metabolism, they saw a similar need to mark the proteins and amino-acids in order to follow these substances through the traffic lanes of the body. Leads for such work were already available through the efforts of several investigators who had pioneered the use of isotope-labeled amino acids in physiological experiments. Hans H. Ussing of Copenhagen in 1938 labeled proteins with deuterium (heavy hydrogen) and by hydrolysing them obtained tagged amino acids for use in metabolic tracing studies. Rudolf Schoenheimer of Columbia University obtained heavy nitrogen ($N^{15}$) from the physicists in 1937, and in 1939 and 1940 published his extensive studies of protein metabolism in rats, already cited in Chapter 13. In 1939 Harold Tarver and Carl L. A. Schmidt of the University of California at Berkeley reported the use of radioactive sulfur incorporated in the amino acid methionine.

In 1944 Whipple started using $N^{15}$ with a team consisting of three Research Associates in radiology, R. M. Fink, Theodore Enns, and Charles P. Kimball; another worker in that department, Hannah E. Silberstein; and two of his regulars, William Bale and Sidney Madden. With the help of chemical specialists at the University of Maryland, the University of Illinois, and Eastman Kodak Company, the Rochester workers achieved the difficult synthesis of the amino acid, lysine, containing an atom of heavy nitrogen. They chose lysine because it is a relatively stable representative of the basic type of amino acid, not readily split by metabolic processes, and could thus be trusted, so to speak, to hold its marked element and not exchange it with any other metabolic substance. With this material Fink and his collaborators obtained preliminary data indicating, to Whipple's great satisfaction, that the plasma proteins are in constant and rapid exchange with a mobile pool of body protein.

Whipple also used lysine marked with $N^{15}$ in studies he made with David R. Hawkins and Roger Terry of his department, and Edwin H. Church, Robert E. Nye, Jr., and William E. Sandrock, student Fellows, on the dynamic equilibrium of the body's proteins. These experiments proved that even highly specialized proteins (fibrinogen and others) participate in the general turnover and metabolism of protein in the body.

Detection and measurement of heavy nitrogen is a difficult business. To measure radioactivity is far easier, and therefore Whipple was fortunate in being able by 1948 to obtain lysine tagged with radioactive carbon ($C^{14}$). This was synthesized for him at the University of Rochester under the direction of R. W. Helmkamp, professor of organic chemistry. The group working with it in Whipple's laboratory during the next decade and a half included as his leading associate William Bale of the department of radiology, who had already gained much experience with radioactive tracer work in the studies with tagged iron; Leon Miller, veteran of earlier experiments with plasma proteins; Charles L. Yuile, associate professor of pathology; and Frank W. McKee, then a junior member of the pathology department. Along with these at various times worked David R. Hawkins, Chester K. Jones, Robert D. Neubecker, and William G. Wilt, Jr., of the pathology department staff; Garson H. Tishkoff, Lilly Fellow; Baldwin G. Lamson, Fred V. Lucas, and Paul R. Schloerb, Veteran Postgraduate Fellows; Arthur E. O'Dea, Postgraduate Fellow; Samuel J. Chapin, Charles G. Cochrane, Rolla B. Hill, Jr., and Robert B. Hyatt, medical student Fellows (all the foregoing, in pathology); John A. Schilling of the department of surgery; Raymond E. Masters, research Fellow, and Leroy De la Vergne, graduate student in radiation biology.

In order to work with tagged proteins, the Rochester investigators needed first to build their radioactive amino acid (lysine) into plasma proteins. These are, however, impossible to synthesize in the laboratory. Whipple let the dogs do it for him, simply feeding them the $C^{14}$-tagged lysine. Their blood proteins soon contained $C^{14}$. Injecting plasma from these dogs into other animals, he and his associates using radiodetection apparatus noted the distribution of radioactivity throughout the body and the rate at which it disappeared from the circulation. The results indicated a surprisingly rapid turnover, from which the observers calculated that, as a whole, plasma proteins are utilized and replaced at the rate of at least ten per cent every 24 hours.

Further progress was limited by low radioactivity of the first batches of tracer material, but in a couple of years a lysine preparation 20 times more active was obtained, with which better quantitative measurements could be secured. When the investigators fed labeled dog plasma to dogs they found that it was rapidly incorporated into the tissues. By calculation from the rate of metabolic conversion of the marked carbon into carbon dioxide, they obtained proof or at least strong support of the long-cherished idea that ingested proteins, in order to be absorbed from the intestine, have to be broken down completely to amino acids.

Once they are absorbed by the blood, the amino acids, according to Whipple's concepts, go to the liver, are reassembled there into plasma proteins, and given back to the blood stream. Leon Miller and William Bale of the department of radiology, with two young associates, Chauncey G. Bly and M. L. Watson, used radioactive lysine to test in a technically beautiful way this concept that the liver is the chief seat of plasma protein formation. Their experiment was done with the rat's liver, removed from the body into a laboratory apparatus with which they continuously circulated through its blood vessels, an amino acid mixture including radioactive lysine. Analyzing the solution after its repeated passages through the isolated liver, they observed that it contained tagged plasma protein newly synthetized by the liver cells. By calculation they showed that the liver creates in this way from amino acids practically all the fibrinogen and albumin of the blood plasma and four-fifths of the globulin, in short almost all the total plasma proteins.

In one week, according to these quantitative studies of Whipple's group in 1949-1952, 30 to 40 per cent of the plasma protein taken up by the circulation is built into tissue proteins. How this conversion takes place was a much debated question among the few laboratories where labeled proteins and amino acids were being used in metabolic studies. Must the plasma proteins, if they are to be utilized in the bodily economy, first be broken all the way down into amino acids again in order to be rebuilt into tissue proteins? The findings of Whipple's group led them to conclude that the plasma proteins need be split only into their largest fragments, i.e. polypeptides, before being reconstructed in the organs and tissues.

In 1948-1949 Whipple introduced a novel method of studying protein shifts within the body, by experiments on dogs in which he brought about a condition of dropsy, or to use the more exact medical term, ascites. The method was one he had first used 40 years before in the Hunterian Laboratory at Johns Hopkins Medical School, to produce ascites as part of a study of liver function and its disturbances. By an operation which Whipple considered rather simple, but actually requiring quite elaborate equipment and considerable skill, he placed a band of pliable aluminum around the vena cava just above the diaphragm, where this great vein, carrying all the blood from the lower part of the body and the abdominal viscera, is about to pour its contents into the heart. When the vein is thus constricted to half its normal cross-section, the circulation is obstructed and as a result fluid containing plasma proteins accumulates in the abdominal cavity. By drawing off this fluid through a hollow needle, the rate of plasma protein production may be measured. The procedure is equivalent, in fact, to plasmapheresis. By adding radioactive lysine to the diet of his ascitic dogs Whipple and his fellow workers could follow the movement of plasma proteins in and out of the abdominal cavity.

Ascitic fluid as it accumulates in cases of dropsy, Whipple remarked, had generally been looked upon as a stagnant pool, containing proteins but not in free exchange with the general protein pool of the body His experiments with tagged lysine showed, on the contrary, that there is a rapid exchange of proteins between the two masses of fluid. Labeled plasma injected into either the blood stream or the abdominal cavity soon crosses the barrier from one to the other.

By varying the diets used in these experiments, Whipple secured evidence, important for physicians treating human cases of ascites, that a high-protein, salt-free diet markedly decreases the accumulation of ascitic fluid.

In the last phase of their study of plasma proteins Whipple and his colleagues investigated the protein content of that part of the body fluid which is found in all the organs and tissues, not in the cells, nor in the blood vessels, but in the interstices of the tissues—the tissue juices or "lymph." Observations with radioactive lysine revealed that this fluid holds a surprisingly large mass of plasma proteins, approximately equal to the plasma proteins in circulation in the blood. It constitutes a large stock of reserve protein available to the blood stream in time of need. During the first weeks of experimental depletion of the proteins by plasmapheresis more plasma protein is removed than can be accounted for by the drop in the total amount in circulation. The balance comes from the extracellular, extravascular reserve. Here, in large measure, lies the answer to the enigma that presented itself in the very first experiments, in the period of 1933-1935, on the regeneration of plasma protein, when Whipple found that the body holds somewhere, loosely bound and ready for use on demand, a reserve stock of protein not built into the substance of cells and tissues, so large that it is exhausted only after two to eight weeks on a protein-free diet.

At many stages of Whipple's long-continued study of the proteins he faced another enigma of general physiology to which he had to make a radical and even heretical answer. The protein molecule is very large, the molecular weight ranging from 45,000 in the case of egg albumin to over 6,000,000 in the case of hemocyanin. Molecules of such dimensions, physiologists have generally assumed, cannot pass the barriers that set off one element or space in the body from another—the membranous surfaces of individual cells, the walls of the blood capillaries, the lining membranes of the body cavities, the excretory tubules of the kidneys and many others. We have seen, for example, that the proteins of the food must be broken down into much smaller units, the amino acids, before they can pass through the intestinal lining into the blood stream. Again, the power of the plasma proteins to hold water in the blood by osmotic force depends upon the fact that water can pass through the walls of capillary vessels but proteins cannot. Whole chapters of physiology, pathology and internal medicine rest upon the acceptance of the principle, thoroughly tested by experiment, that the cell membranes and similar barriers of the body are semipermeable: electrolytes, i.e. the ordinary salts, and other substances of relatively small molecular size can traverse them, but not the very large molecules of the proteins.

Yet early in Whipple's study of the dynamic equilibrium of the body proteins he was forced by his experimental observations to accept the idea that protein molecules pass freely from cell to plasma and from plasma to cell. Summarizing his first work on hypoproteinemia with Madden, Turner, and Rowe, he cited two evidences of this: first, fibrinogen is formed in the liver cells and promptly appears in the blood plasma when needed; second, the dog can be kept in nitrogen equilibrium by plasma given intravenously. Evidently, therefore, the body cells can take in protein, as they need it, directly from the plasma, across the endothelial lining membrane of the blood capillaries and the surface membranes of the recipient cells. Whipple had no ready explanation for these facts. He could only suggest that the principles governing the passage of protein molecules through membranes must be fundamentally different from those relating to the electrolytes. Near the end of his active work in this field he was still convinced of the correctness of his deductions and still at a loss to explain them. "Whatever our concept of protein molecules," he wrote in 1949, "we are forced to the conclusion that protein does pass through cell surfaces readily, as part of normal protein metabolic exchange." This enigma still stands unresolved, a challenge to future investigators who venture to follow in George Whipple's footsteps.

An investigation carried out in 1949 made use of experience gained in all Whipple's researches since his Johns Hopkins days, on the formation of bile, blood cells, hemoglobin and plasma proteins. Through all those years he had been seeking a reliable, accurate answer to a question central to his work but impossible to answer with assurance before the era of radioactive tracer elements. What, he needed to know, is the life span of the red blood cell, from its formation in the bone marrow to its disintegration in the circulating blood? Many investigators have tried by various methods, and with varying results, to time the vital cycle of erythrocyte formation, their estimates ranging from 15 to 113 days in several species of animals. In 1937 W. B. Hawkins and Whipple attacked the problem with an ingenious but curiously roundabout method. Knowing that the bile pigments are formed from hemoglobin, they used bile-fistula dogs in which by bleeding or by poisoning with acetylphenylhydrazine they radically lowered the number of circulating red blood cells. Following any such crisis the bone marrow responds by putting out great numbers of new red cells. Until these new cells become senile, very little hemoglobin is set free in the blood and consequently the output of bile pigments is low. Since these cells were all formed about the same time, they become senescent and disintegrate at more or less the same period. Their breakdown *en masse* causes a conspicuous rise in the output of bile pigments. From five experiments of this sort on four bile-fistula dogs, Hawkins and Whipple worked out a life span of 112, 120, 126, and 133 days, averaging 124 days.

In 1949, Bale, Yuile, De la Vergne, Miller and Whipple returned to this problem with the aid of radioactive lysine. To doubly depleted dogs with a very low red blood cell count, they gave a generous meal of ground beef mixed with a half gram of tagged lysine, and continued a diet rich in proteins. The new red cells called forth by the regime contained labeled hemoglobin. By following the radioactivity of blood samples drawn at regular intervals until it fell to zero, they arrived at an average life of 115 days. Since their publication of this result, other workers studying human blood with radioactive tracers have obtained more or less similar figures.

The red blood cells are, practically speaking, tiny disks of a spongy substance known as the *stroma,* in whose meshes the gelatinous hemoglobin is packed. As early as 1922 Whipple recognized that this seemingly inert stroma is as essential to a healthy state of the blood as is the hemoglobin it carries. In his Harvey Society Lecture of that year he expressed the belief that in pernicious anemia there is a scarcity of stroma-building material and a surplus of hemoglobin, whereas in secondary anemia there is a shortage of hemoglobin in a normal stroma. More than 30 years passed, however, before he commanded the experience and the technical methods necessary to study the formation of the stroma protein in relation to the dietary proteins. When in 1950-1955 he took up the problem, his fellow workers were Robscheit-Robbins, Bale, Yuile, and Tishkoff. Finding by chemical analysis that the normal red blood cells of dogs contain a fairly uniform amount of stroma, they experimented with two types of secondary anemia, produced respectively by bleeding and by treatment with acetylphenylhydrazine, and found that although the hemoglobin of the blood cells was greatly reduced, the amount of stroma protein was increased. Even hypoproteinemia added to blood-loss (double depletion) did not reduce the stroma protein content of the blood; and an even more drastic condition, extensive sterile inflammation with loss of nitrogen in the urine, did not much decrease it. Evidently, the body will not normally produce hemoglobin without producing stroma to carry it, and therefore gives the latter also a high priority over competing demands upon its protein reserve stores.

The investigators next fed anemic dogs a full blood-regenerating diet which included protein labeled with $C^{14}$ lysine. They found that the protein got into the stroma somewhat sooner than into the hemoglobin, but from the time when regeneration of the red cells was complete, to the end of their life span, stroma and hemoglobin acted as a unit, not competing with each other for their protein content.

Putting together his conjecture of 1922 that pernicious anemia involves defective stroma formation—poor packaging, so to speak, of the hemoglobin—with the knowledge derived from Minot's work that Vitamin $B_{12}$ relieves the condition, Whipple deduced that the stroma is defective because of a $B_{12}$ deficiency, or in other words, that $B_{12}$ is specifically concerned with stroma protein formation. To test this hypothesis he procured a supply of Vitamin $B_{12}$ tagged with radioactive cobalt ($Co^{60}$). When anemic dogs were given a blood-regenerating diet containing this labeled vitamin, the isotope was soon found in the stroma but not in the hemoglobin of newly formed red cells. In another group of experiments normal dogs were first given radioactive $B_{12}$. This was found to be stored chiefly in the heart, stomach lining, liver, spleen, and brain. Subsequently dogs with ample stores of the vitamin were for several months subjected to repeated loss of red blood cells by treatment with acetylphenylhydrazine. When, finally, they were allowed to regenerate their red blood cells, the stroma of the new cells contained $B_{12}$, which must have come from the organs that stored it. This finding once more suggests that the stroma has a strong prior claim for the vitamin which is in some way essential to its formation.

Whipple's own estimate of this brilliant work, which powerfully supported his hypothesis of 1922 and came closer than ever before to an explanation of the nature of pernicious anemia, is a masterpiece of understatement. Referring to the specific dependence of the red cell stroma upon Vitamin $B_{12}$, which he and his colleagues had discovered, he wrote merely that "this response in dogs and the response to $B_{12}$ in pernicious anemia may have some points in common."

Toward the end of Whipple's active career in the experimental laboratory the problem of the transfer of protein across cell membranes, blood capillary walls, and other physiological barriers remained uppermost on his mind. One of the most remarkable and important of these barriers is that of the placenta, where the circulating blood of the mother and that of the fetus flow past each other in adjacent blood-vascular channels separated by thin walls of semipermeable tissue. Physiologists have long known that salts, sugar, and many other nutritive products including amino acids pass the placental barrier constituted by these thin walls. As for proteins, it was once thought that their molecules are too large to pass through the placental barrier, but advancing knowledge of immune reactions has shown that certain antibodies against infectious microorganisms and foreign proteins, which are themselves proteins, do pass from mother to fetus, at least in some species including our own. The human placenta readily permits the passage of such antibodies; a human infant at birth already possesses immunity to certain diseases against which its mother was immune. The dog's placenta, however, is one of those which are not permeable to such proteins. It offers, therefore, a critical test-object for studying the way in which the fetus gets from its mother's blood its supply of protein-forming nitrogenous material.

Whipple, armed with his radioactive tracer elements, attacked this problem in 1955 with Rolla B. Hill, Roger Terry, Fred V. Lucas, and Charles L. Yuile. They started the experiments by preparing labeled plasma as in previous work, from the blood of dogs given food containing radioactive lysine. This protein material, fed to pregnant bitches by mouth, was of course broken down in the stomach and intestines into amino acids and delivered to the placenta, where the amino acids passed into the fetal circulation. Further experiments showed that the fetus in fact gets most of its protein-forming materials from the mother in the form of amino acids derived directly from her diet. The mother can however also contribute to the fetus from her plasma proteins—and this means also from her protein reserves—by breaking them down to amino acids in the placenta, which contains a tissue (chorionic epithelium) adapted to that purpose. The fetus gets its supply of protein-forming material only partly by this means; most of it comes from the free amino acids of the maternal blood. Thus the acquisition of protein by the infant *in utero* is generously served by a double mechanism.

With William D. Woods and William B. Hawkins, Whipple studied the placental transfer of vitamin $B_{12}$, in which he had become specially interested through his discoveries about its relation to blood-cell stroma formation, a process as essential to the fetus as it is in postnatal life. He and his fellow workers found that $B_{12}$ readily passes through the placenta into the fetus, as would be expected from its moderately small molecular structure as compared with proteins. A store of it is laid down also in the placenta. Giving generously from her own supply to the fetus and placenta, the mother requires ample replacements from her diet. In this connection Whipple saw an explanation of the habit common to all maternal mammals, so far as known, except the human species, of eating the placenta (and in animals bearing several young at one time, all the placentas) immediately after giving birth. Nursing also draws $B_{12}$ from the mother, to supply the rapid production of new red blood cell stroma in the growing infant.

In 1956 Whipple summarized the findings of his investigations of the proteins in health and disease, in a little book, *The Dynamic Equilibrium of Body Proteins,* whose title suggests the main theme recurring in his publications since 1933. When he first began to study the plasma proteins, the idea that they are actively concerned in the general metabolism of proteins was scarcely credible. In little more than 20 years he had firmly established the concept he had been first to state, that the plasma proteins, formed in the liver and elsewhere from amino acids derived from food, constitute a mobile source of supply for the protein requirements of the body. He had demonstrated the existence of a considerable reserve of plasma protein-forming material, at least as large as the whole mass of circulating plasma proteins, that can be drawn upon by the blood stream to replace depleted protein. He had shown that proteins pass readily from plasma into cells and vice versa, as required, without loss of nitrogen. In health, the cell proteins, the reserve stock, and the plasma proteins are constantly in balance, exchanging with each other as may be necessary to maintain the state of dynamic equilibrium. This picture, patiently drawn up and substantiated by George Whipple and the 50 or more young men who at various times worked at his side, provides fundamental support for the whole modern theory of protein metabolism.

CHAPTER

# 15

# A MAN NOT OLD, BUT MELLOW, LIKE GOOD WINE

GEORGE WHIPPLE'S investigations proceeded steadily toward solution of the major problems he had set himself to answer. The School of Medicine and Dentistry continued to flourish. Generous additions to its resources came from wealthy people impressed by its contributions to the community—a fund for research in the medical sciences, an endowment for urological surgery, a large gift to build and operate a psychiatric clinic. Psychiatry, in the simple early organization of the school, was a part of the medical clinic. Now, in 1945, it was made a separate department. With as much concern, on Whipple's part, to find the right man as when the first professors were appointed, John Romano of Cincinnati was chosen to direct the clinic. The dean, looking from his office windows, could see the handsome new psychiatry building standing on a green lawn where 20 years before he had watched the pheasants coming out of a thicket to do battle with seagulls from Lake Ontario.

He kept up the steady schedule of work in the dean's office, in the classroom, and in the research laboratory, that had become the pattern of his life. Every year he allowed himself two or three trips to attend scientific meetings, one of them regularly to the Association of American Physicians, another to whatever gathering of pathologists or physiologists happened to interest him most; and faithfully attended the sessions, twice a year, of the Rockefeller Institute's Board of Scientific Directors. As in the past he managed to keep out of time-consuming community affairs. When in spite of this, the Rochester Municipal Museum in 1943 awarded him its Civic Medal he must have felt he had won a moral victory over the critics who complained of his seeming lack of community spirit.

Academic honors kept coming: honorary degrees from Western Reserve University in 1943, Buffalo in 1946, and two that perhaps meant most of all to him, from the universities he had served the longest, Johns Hopkins in 1947 and the University of Rochester in 1950. The next year the University of Glasgow summoned him to receive a doctorate of laws, with other distinguished guests, at the celebration of its 500th anniversary. He and Katharine sailed from Montreal June 8, 1951 on the *Empress of Canada* for Liverpool. After visiting Chester, Keswick, and the Lake District they went north to Glasgow for the convocation, carried out with brilliant pomp and circumstance. Resuming their travels they stopped a while in Edinburgh where, Katharine says, George was much less interested in historical architecture than in shopping for a proper Scottish salmon gaff. When they went on to the Highlands he found himself in the kind of country he loved best, a land of rugged mountains and brawling streams. Looking back upon this visit to Scotland he remembers it as the most enjoyable of his five trips across the Atlantic. Returning on the *Empress of Scotland,* he was back in his laboratory at the end of July.

In 1954 all the Nobel laureates in medicine were invited to meet at the old walled town of Lindau on the Bavarian shore of Lake Constance, for a conference on recent advances in medical knowledge. Again accompanied by Katharine, Whipple crossed to Le Havre on the French Line ship *Liberté,* on which when she was still the North German Lloyd's *Europa,* the Whipples had returned from Europe after the Nobel Prize award in 1934. Stopping a couple of days in Paris—a place George does not like—they went by rail to Lindau via Ulm.

A dozen Nobel Prize winners, not all medical, attended the conference, the most famous being Albert Schweitzer, whose poor health at the time kept him from very active participation. The others, besides Whipple, were Heymans from Belgium; Soddy from Britain; Butenandt, Domagk, Otto Hahn, von Heisenberg, and Warburg from Germany; von Hevesy from Sweden; Paul Hermann Müller and Reichstein from Switzerland. When George Whipple's turn came to speak, he talked about the dynamic equilibrium of body proteins in terms suited to the general audience of physicians and university students.

During the five days of the conference there was a lively round of hospitality, including a banquet, a "Bavarian breakfast" of beer, sausage, and cold cuts with sauerkraut, and—best of all for George—a medical students' party where he had a fine evening drinking beer, chatting with the young people, and at the last being photographed clinking glasses with a pretty girl who was president of the student group. After Lindau, the Whipples visited Heidelberg, where George had worked in 1909 in Krehl's laboratory, and then travelled by way of Cologne and Hamburg to Stockholm to renew acquaintance with Hilding Bergstrand and other friends at the Caroline Institute. The route home took them to Bergen, Stavanger, Kristiansand, and Amsterdam, thence to Paris and across to New York on the *Isle de France*.

At home, every autumn, Whipple kept up his pheasant shooting. Some of his outdoor companions departed, Bayne-Jones for Yale, Warren for Los Angeles. Jolly, brave Bill Wallace, who trudged across the fields with his friends, in spite of severe general arthritis, until he could no longer raise his gun, died in 1943. Several of the old crew, however—Bradford, Herman Pearse, George Hilleman—joined him as often as their busy lives permitted. In recent years younger men—Roger Terry of the pathology department and the surgeon John Schilling—have shot with him, and nowadays a companion of many years, Elmer J. Pammenter, can be relied on to accompany George whenever fine fall weather calls men and dogs to the open fields. The scene of the hunt has shifted from Garnsey's place on the western slope of Cayuga Lake to Oakfield, north of

Batavia, where a private sportsmen's club controls a large acreage. George has generally kept a bird dog or two; some years ago when one of his favorite dogs died, a group of former students of his, led by Howard Thompson and Roger Terry, presented him with a fine young dog appropriately named—in view of his speed and somewhat unpredictable ways—Rocket; but after putting up several seasons with Rocket's vagaries George decided that at the age of 80 he could not chase after an unruly dog as he did 20 years earlier, and therefore entrusted him to Pammenter.

In his later years George's favorite summer recreation has been salmon fishing in Nova Scotia, a sport he learned to love through the enthusiastic example of his old friend Edwards A. Park, longtime professor of pediatrics at Johns Hopkins. Ned Park's charm and lightly borne learning, combined with deep love of nature and out-of-doors life, make him a fishing companion worthy of Izaak Walton himself—and of George Whipple. Although Whipple and Park were classmates at Yale, they were not closely acquainted in college days, and lost sight of each other when George went to Johns Hopkins Medical School and Ned to Columbia University, College of Physicians and Surgeons. They met again in 1912 when Park became resident pediatrician at Johns Hopkins Hospital and roomed near Whipple in the staff quarters. Keeping up a casual friendship thereafter, they occasionally exchanged letters after Whipple went to San Francisco, and sometimes met at annual meetings of the Association of American Physicians. Visiting Park in 1927, when the rising pediatrician was again at Yale as professor in the medical school, Whipple learned that Park was as keen a fisherman as himself, and had a camp in Nova Scotia on the Margaree River, a noted salmon stream. Ten years later Whipple accepted Park's invitation to visit the Margaree and see for himself what salmon fishing was like. Delighted with the sport, he returned in the late summer of every year until 1957.

Near Ned Park's camp is an excellent small boarding house, in the possession of one family for 100 years, conducted by a popular hostess, Mrs. Ross Taylor, and frequented by friendly and interesting people. George Whipple entered into the life of this place as if he were a member of the family, even assuming the daily morning task of squeezing orange juice for the breakfast table. The country-side pleased him not only for its beauty but also because there was no ragweed to cause asthma, and above all because of the superb salmon fishing.

Ned Park, introducing his friend to a kind of fly-fishing that was new to him, had a good rod specially made for George and gave him a few dry flies of his own make, of the sort Ned had found the Margaree salmon would take. This was all George needed, for he brought to the Margaree his experience of many years fishing for brown and speckled trout in New England waters and for rainbow trout in California, Colorado, and Wyoming. He hooked his first salmon, a big one, in a pool near the camp. When it made several great leaps Ned started to coach his friend, but saw at once that George was an expert needing no advice.

Park, according to reports, is a very finished performer with rod and reel, with great accuracy and variety in casting the line, but somehow, Ned says, every time they fished together his companion got the bigger catch. George had his own perfectly controlled manner of casting, midway between an overhead and a sideways motion, and timed the cast so precisely that the impulse he gave the line would die out as the hook looped toward the water, just in time to make the fly settle on the surface of the stream and float free without drag.

"Fishing," says old Izaak, "is an art worthy of the knowledge and practice of a wise man." To this view George Whipple fully subscribed, putting his mental powers as well as physical skills into the sport, with the same thoroughness and calm judgment that made him successful in the laboratory. He employed the best guide on the river, a local character named Duncan Mackenzie, whose advice he freely took, and for whom he had real affection, but made his own independent study of the river and the ways of the salmon.

Whipple recorded in a special diary the events and results of each day's sport, keeping track of all the conditions of wind and weather that favored or hindered the fishing. Thus he learned which of the Margaree's pools were best under given conditions, and when to start and when to stop fishing. Ned Park tells of a typical day, when at George's suggestion they drove to the lower pools of the river. Stopping the car where the road runs an eighth of a mile from the stream, George produced a telescope and took a good look toward the pool, where he recognized some men already fishing there. Then he drove to another pool and reconnoitered it in the same way, and so to a third. Only after counting and identifying the men who had chosen to fish at each of the pools, comparing their skill and judgment, and checking wind, sun, and water, would he decide where to cast his own line.

Park especially enjoyed enticing the fish and getting a rise; playing and landing it were for him less exciting phases of the sport. Whipple on the contrary relished the long, tense contest with the tough and gamy salmon, in which he displayed exquisite skill, letting the fish run with the line and again reeling it in with patient judgment, never allowing himself to hurry or—as the fishermen say—"horse" the salmon toward shore. He not only enjoyed the combat but also wanted to land the fish, and took pride in making larger catches than did his rivals on the Margaree. To avoid losing a fish from his hook he would play it in his alert but careful way as long as necessary to outwit and wear it down, sometimes to the exasperation of other nearby anglers forced by the etiquette of the sport to avoid casting in the same vicinity while the contest was on.

When the great shiny salmon was landed and taken home, George would get out his diary and carefully enter every detail of the catch—the exact time of the first rise, how many times the fish leaped, the height of its leaps, how long it took to fight and land it, the conditions of weather and water. He noted also the varieties of dry flies that he found most tempting to the salmon, and when he had taken a fish with a given fly would use it again and again until it was so battered and worn that a more fastidious or less systematic sportsman would have discarded it long since. The art of making or "tying" dry flies, which appeals to the artistic sense of many fishermen, never interested George Whipple very much. Although he regularly carried the materials and a flymaker's vise with him to the Margaree, he found his friend Park was expert in the art and depended on him for fresh supplies.

Fortunately Whipple's sturdy frame was equal to the hard exercise of salmon fishing with its long walks and standing on the banks of the river, wading in the cold water, and tense battles with the big fish. During all the 20 years from 1937 to 1956 no illness kept him from getting to the Margaree. He remained very susceptible, however, to respiratory infections. The allergy to pollens, which had plagued him all his life, persisted and from time to time brought on an attack of bronchitis or even of bronchopneumonia. As a consequence of repeated treatment of these infections with antibiotics, he has become sensitive to penicillin, and must therefore avoid the risk of respiratory illness as far as humanly possible. Since the advent of air-conditioning he can be much safer and more comfortable in pollen season, living more or less constantly in the filtered atmosphere of his air-conditioned home and office, and driving from one to the other in an air-conditioned car. The safest course, however, is to get away in pollen season from a region so rich in trees and ragweed as Rochester is.

In 1945, at the age of 67, a series of minor illnesses that had gone undiagnosed for several years ended in a sudden and unexpected diagnosis and a major operation. Off and on in the past he had suffered some acute attacks of abdominal pain and fever that put him out of action for a few days at a time. If he guessed what they meant, he told nobody, and because these attacks happened to occur when he was away on vacation or at a scientific meeting, none of his medical friends observed them. Finally one occurred while he was staying overnight in New York at the Rockefeller Institute for a meeting of the Board of Scientific Directors. The resident physician of the Institute's hospital promptly diagnosed it as biliary colic. A hurry call to Columbia University brought George's quasi-cousin Allen O. Whipple, chief surgeon of the Presbyterian Hospital, to his bedside at 4 A.M., but the attack subsided sufficiently to permit his return to Rochester, where John Morton removed the gallbladder. Although George missed most of the pheasant shooting that fall and winter, he was ready for work in a few weeks and for the Margaree by midsummer.

Whipple was 75 years old in 1953 when he relinquished the deanship, turning it over to his successor, Donald G. Anderson, with so little fuss that the change passed almost unnoticed outside the school. The Alumni Association gracefully took note of it by awarding the retiring dean the Alumni Gold Medal "for his contribution to Medicine through his students, as an example to be loved and admired." The transition to full retirement was gradual; he retained the professorship of pathology two years longer, continuing his research and teaching, and was always available to colleagues young and old who wanted to talk over their scientific or personal problems. Some who had professed themselves afraid of him or mistakenly thought him unapproachable now saw only kindliness and the mellowing influence of ripened years and lessened responsibilities.

Time had dealt almost as lightly with his old faculty associates as with himself. All but one of the department heads he assembled in 1922-1924 were living, five of them still in Rochester. Samuel Clausen, professor of pediatrics, died in 1952, a victim of cardiovascular disease; his capable associate, William L. Bradford, Whipple's sometime collaborator in the study of Mediterranean anemia, and a frequent hunting companion, took Clausen's place at the head of the pediatric clinic. John Murlin, professor of vital economics, retired in 1945 and his department was combined with that of physiology under Wallace Fenn. Walter Bloor, biochemist, retired in 1947; Karl Wilson, obstetrician and gynecologist, in 1952; John Morton, surgeon-in-chief, in 1953. William McCann, professor of medicine, and Wallace Fenn were still in active service when Whipple retired, but after 1960 Dean Anderson presided over a totally new generation of department heads.

George Whipple's retirement from the chair of pathology was announced May 13, 1955 and took effect June 3. Any public recognition of this event by the University would have embarrassed him; any special tender of affection and regard by the faculty he had led for 34 years would have been superfluous, for he was to remain among them, an honored counselor and friend. Instead, Whipple himself marked the day by an action of great moment, designed to foster medical teaching at Rochester and to further the training of able students. He had begun to plan this step while he was still dean. Writing to Raymond L. Thompson, vice-president and treasurer of the University, in April 1953, he reviewed the story of his cooperation with the pharmaceutical firm of Eli Lilly and Company, of Indianapolis, beginning in the 1920's when his work on experimental anemia in dogs had resulted in the preparation of liver extracts with antianemic potency. As narrated in an earlier chapter of this book, the Lilly laboratories provided expert assistance in purifying the extracts, and put their product on the market for use by physicians in treating secondary anemia.

Although Whipple had deliberately chosen not to patent his discoveries in the name of the University, as had been done in similar situations at certain other institutions, the Lilly company, protecting itself by a patent on its own particular method of extraction, paid his laboratory generously for testing its preparations. As the sales, rapidly increasing, amounted within a few years to many millions of dollars, Lilly's fees for tests and for consultations with Whipple's staff enabled him to expand his departmental research program at no cost to the University and without detriment to current investigations, for the routine testing was actually useful in standardizing dogs for the continuing study of anemia. After paying salaries, wages, and the cost of materials and apparatus employed in the tests, Whipple regularly had a surplus at the end of each fiscal year. By 1953 the Lilly Fund, thus accumulated, amounted to nearly $700,000.

Whipple, who had thought long and deeply about the future use of this large sum, suggested to the trustees of the University through his letter to Thompson that after he gave up the professorship of pathology they should use the money for three purposes, all intended to perpetuate the work of research and education that he had himself started and carried on. First, he wished to set aside $250,000 to endow the chair of pathology. Second, he proposed to use $300,000 to create scholarships bearing the name of his wife, Katharine W. Whipple. This sum would provide 12 or more annual stipends of $1,000 each, four of them to be given to entering students, to attract to the medical school young men and women of exceptional promise; four to students already in residence, on the basis of need, ability, and promise; and four to students of the final year, to enable superior graduates with limited financial resources to accept internships in the best teaching hospitals rather than better-paid places in nonteaching hospitals where they would have less opportunity for further training and advancement. Third, Whipple wished to use $75,000 of the Lilly Fund to endow visiting lectureships in honor of the school's first three emeritus professors, John R. Murlin and Walter R. Bloor, and Samuel W. Clausen. It is an agreeable coincidence that Murlin had taught physiology and Bloor biochemistry, the sciences that had been of the most help in Whipple's own researches, and that Clausen represented pediatrics, the branch of medical practice he had in his youth seriously thought of entering. The balance of the fund he put at the disposal of the trustees for any future purpose similar to those he had designated. Laying these far-reaching proposals before the vice-president, Whipple asked that if they were accepted, there should be no announcement until after his retirement from the professorship of pathology. The trustees of course approved the whole plan, and put it into effect immediately upon his retirement in 1955.

When, years before, George and Katharine Whipple talked over plans for retirement, they thought of moving to a climate less rugged than that of western New York. For a while they considered various towns in South Carolina, not far from Charleston, Katharine's girlhood home; but when the time came George was reluctant to leave Rochester. "Most people are happiest," he said to some students who asked if he would move away, "when they are closest to the greatest number of their friends, and our friends are now mostly here." He and Katharine gave up the house at 320 Westminster Road, where they had lived since 1922, and took a pleasant small apartment in a modern development nearer the medical school. There George enjoys home-life in air-conditioned comfort, and in leisure hours tunes in a symphony or good band music on the radio, or loses himself in a novel of Joseph Conrad or some other favorite story-teller.

So far as his friends can see he might have gone on indefinitely working in the laboratory; as he always said, research is never finished, and there are plenty of problems about the plasma proteins still awaiting solution. In all good conscience, however, he could no longer maintain a large colony of dogs at the school, for space was limited and the new professor of pathology had a program of his own. He keeps his plain room in the original dean's suite, and has a secretary who knows her way about among his files containing 50 years' records of research and teaching. For five years more he met the second-year class once a week for a lecture or conference. Generally he discussed a current topic in pathology, but now and then, to the students' delight, talked about the history of pathology and what it had contributed to modern medicine. In the days of his active research he had always been too far in the vanguard to think much about the historical background of his work, but now he had time to recall for his young hearers the great pathologists he had known and the long era of discovery in which he had lived and taken part.

In 1960 he gave up the weekly conference because he thought he might be preventing some younger man from meeting the students in the allotted time. People keep coming and writing, however, to discuss their work, or to get him to pass judgment on a microscopic slide. He sees the autopsy material with William Hawkins and Roger Terry, and makes it his business to get acquainted, each year, with the new young men who join the department as Assistants and interns in pathology. He finds, moreover, always something to read in current journals, about scientific advances in pathology and physiology, better treatment of a baffling disease, a novel development in teaching, some new way to organize the medical curriculum. For the *Journal of Medical Education,* he has written several editorials based on his experience as dean and has published brief memoirs of three men he knew intimately who greatly contributed in their diverse ways to the advancement of medical education—Milton C. Winternitz, Alan Gregg, and Abraham Flexner.

At about the time of his retirement George Whipple, who had always enjoyed better than normal vision for distance and needed glasses only for reading, began having trouble with his eyesight. The field of vision became foggy and colors lost their brilliance. He soon knew he was developing cataracts. Fortunately the right eye did not cloud as fast as the left, so that he was never fully deprived of working eyesight. Albert Snell, Jr., Rochester-trained ophthalmologist, took him in charge and extracted the left lens in 1959, the right in 1960. Whipple approached the operations without apprehension—why not? the surgeon had been one of his own students—and was up on his feet the next day. The result was all that could be hoped for; without difficulty he can read fine print, use the microscope, drive his car, and sight a gun.

Before the operations clouding of his vision made salmon fishing in the Margaree a tricky business, and afterward the loss of accommodation that follows removal of the lenses impairs the judgment of close distances. This presents a great handicap in walking on rough ground and wading over rocks. A lifelong fisherman, however, does not give up the sport just because he doesn't care to wade in a river. There are bigger fish in the sea. Whipple switched to the west coast of Florida, where he can fish for tarpon from a boat. Each year since 1957 but one he has driven his car 1,200 miles from Rochester to Naples, far down the Florida peninsula, on the border of the Everglades—Katharine with him, enjoying the drive through her native Southland. They go in March or early April to avoid the pollen season in Rochester, and return in June in time for Commencement. He makes the drive in three or four days, unless he stops somewhere at a medical school to inspect a new pathology laboratory or to inquire what is going on in medical education.

Tarpon fishing in the western inlets is not the luxurious affair it is on the Florida East Coast, where they use big cabin boats with long trolling outriggers. In the Everglades people fish from a 15-foot open skiff with three seats; just George and the Captain, and occasionally an acquaintance of George's who goes along with them. They fish all day in the sun, and if it rains they get wet. In 1961, not long before his 83rd birthday, George wrote to a friend

> Fishing for tarpon in the Everglades is wonderfully exciting. I use flies and salmon tackle, which of course is very light for these big fish, but you don't care whether you catch them or not. The excitement may give you heart failure . . . you may have one on for five minutes or five hours before he breaks away.

During these recent years he has missed the Florida fishing only once, in 1957, when he and Katharine went on a Matson Line cruise to the South Pacific. He came back especially enthusiastic about Australia, where, he said, the people really take outdoor exercise, and the children are the sturdiest and handsomest on earth.

The modern world of science does not forget men whose discoveries set other people thinking and working. In 1957 the British Medical Association made Whipple a foreign associate member. In 1959 the European Society for Hematology sent a certificate of honor. In 1960 the International Association for Dental Research elected Whipple an honorary member, and in 1961 the American College of Dentistry awarded him a certificate of merit in recognition of distinguished services to the dental profession. The American Association of Pathologists and Bacteriologists had a special honor for him, the gift of its ceremonial gold-headed cane. This award, made only at intervals of several years to very distinguished older members of the Association, recalls a famous English symbol of eminence in medicine, now treasured by the Royal College of Physicians, a walking-stick carried in succession by five learned doctors of seventeenth and eighteenth century London. The recipients of the present-day American gold-headed cane—ten in the past 43 years—fully rival in eminence their English forerunners. That William H. Welch, Whipple's own teacher, was among them must have redoubled his pleasure in the honor; but its special value to him was that it came from close professional colleagues who could best appreciate his work, and from a society whose members, elected for their qualifications as investigators, include 25 of his former students, departmental colleagues, and research associates. He was in Florida at the time of the Association's annual meeting in April 1961, and at that uncertain period of the year could not risk a trip to Chicago to receive the cane in person. Explaining all this to a reporter and a photographer who journeyed from Miami to Naples to get the story for *Time* magazine, he told them he was glad he did not have to face the assembly in Chicago. "It would be embarrassing," he said. But when the handsome cane was delivered to him in Rochester, he proudly put it on display in his office, among the dozens of diplomas, certificates, and other testimonials he has there, to be seen and enjoyed privately by the friends whose affection and appreciation he has always needed more than public applause.

In 1962 there were two events calling him north during his Florida vacation season. The National Academy of Sciences summoned him to Washington on April 23 to receive its Kovalenko Medal, awarded every two or three years for especially notable achievement in medical science. A week later the President of the United States was to have a grand dinner at the White House to which all the American Nobel laureates were invited with their wives. The White House party was out, George Whipple told Katharine. It would mean waiting in Washington a week at the worst part of the pollen season. He did not enjoy such formalities anyway, and besides, he hated to miss the fishing. They could fly to the Academy meeting and back to Naples the next morning.

When the Academy and its guests gathered in its Great Hall for the annual evening session of awards and prize-giving, he was there. Fifty-four years ago, defending his choice of a career, he had written to Anna Whipple, "You have always advised me to set my ideals high . . . I assure you that in the minds of his fellow doctors, a pathologist (if of any ability) is held in the highest respect and honor." The doctors of medicine had long since recognized George Whipple's ability and given him their respect, honor, and affection. Now he found himself among his fellows in all branches of science, as one of eight distinguished men, six Americans and two from overseas, chosen for the honors of the year. When his turn came to stand at the rostrum, Detlev Bronk, president of the Academy, with warm acclaim presented him with the great gold medal and a scroll recording his skill as a pathologist, excellence as a teacher, leadership of an outstanding school, many important scientific discoveries.

For him that night the applause of the Academy, congratulations from many friends, a telegram of good wishes from associates in the Rochester department of pathology. On the morrow the plane to Florida, to long hours in the sun, evening walks on the sands of the Gulf; and one of these days, given a bit of fisherman's luck, another 100-pound tarpon on his line, strong and lively enough to test the skill of a wise old master of rod and reel.

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# PUBLICATIONS OF GEORGE HOYT WHIPPLE

## Key to Abbreviations

Am. J. Dis. Child. = American Journal of Diseases of Children
Am. J. Med. Sci. = American Journal of the Medical Sciences
Am. J. Path. = The American Journal of Pathology
Am. J. Physiol. = American Journal of Physiology
Am. J. Pub. Health = American Journal of Public Health
Am. J. Trop. Med. = The American Journal of Tropical Medicine
Ann. N. Y. Acad. Sci. = Annals of the New York Academy of Sciences
Ann. Surg. = Annals of Surgery
Arch. Int. Med. = Archives of Internal Medicine
Arch. Path. & Lab. Med. = Archives of Pathology and Laboratory Medicine
Bull. Coll. Am. Path. = Bulletin of the College of American Pathologists
Bull. N. Y. Acad. Med. = Bulletin of the New York Academy of Medicine
Calif. & West. Med. = California and Western Medicine
Calif. State J. Med. = California State Journal of Medicine
Fed. Proc. = Federation Proceedings (American Societies for Experimental Biology)
Gulf States J. Med & Sci. = Gulf States Journal of Medicine and Science
Johns Hopkins Hosp. Bull. = Johns Hopkins Hospital Bulletin
J. Am. Med Assoc. = Journal of the American Medical Association
J. Biol. Chem. = Journal of Biological Chemistry
J. Exp. Med. = Journal of Experimental Medicine
J. Infect. Dis. = Journal of Infectious Diseases
J. Med. Educ. = Journal of Medical Education
J. Pediat. = Journal of Pediatrics
Meth. Med. Res. = Methods in Medical Research
Minnesota Med. = Minnesota Medicine
Modern Med. = Modern Medicine
Nord. Med. Tidskr. = Nordisk Medicinsk Tidskrift
Perspect. Biol. Med. = Perspectives in Biology and Medicine
Physiol. Rev. = Physiological Reviews
Proc. Calif. Acad. Med. = Proceedings of the California Academy of Medicine
Proc. Inst. Med. Chicago = Proceedings of the Institute of Medicine of Chicago
Proc. Internat. Soc. Hematology = Proceedings of the International Society of Hematology
Proc. Soc. Exp. Biol. Med. = Proceedings of the Society for Experimental Biology and Medicine
Pub. Mass. Gen. Hosp. = Publications of the Massachusetts General Hospital
Resenha Clin.-cient. = Resenha Clinico-científica
Surg., Gyn. & Obst. = Surgery, Gynecology and Obstetrics
Trans. Assoc. Am. Physicians = Transactions of the Association of American Physicians
Yale J. Biol. Med. = Yale Journal of Biology and Medicine

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