SPECIAL ARTICLE

WALTER M. BOOTHBY, M.D. – THE WELLSPRINGS OF ANESTHESIOLOGY

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BOSTON

AROUND the turn of the century in this country the beginnings of specialization in anesthesia were apparent. More than a few physicians began to devote full time to this endeavor, and though nurse anesthetists were on the rise, several of the larger hospitals had appointed physicians to supervise anesthetic practice. This metamorphosis was reflected in Boston, as in other cities, but here perhaps could be discerned the outlines of anesthesiology – a branch of medicine with a clearly defined clinical responsibility, upon a background of its own scientific interest. While the spark may have flickered and died in Boston, to be kindled elsewhere, it is worth calling attention to this phenomenon for the lessons that it may carry for the present generation. Walter Meredith Boothby was a part of this phenomenon – and the subject of this brief biography calling attention to his scientific achievements. Known to an older generation as one of the innovators of the B.L.B. oxygen mask, few will recall that fifty years ago he was an anesthesiologist in the true sense of the term.

Walter M. Boothby was born in Boston on July 28, 1880, the son of Dr. Alonzo and Maria Adelaide Stodder Boothby. He attended Hopkinson's School on Chestnut Street, and entered Harvard College in 1898. One of his roommates at Craigie Hall recalls that Boothby was coxswain of the freshman crew. This roommate wrote that Boothby's later success was shown in his characteristics then: "He had a good mind and when he set out on a path, had the perserverance and determination to carry thru, regardless of how it affected his relation to others. To some this may have appeared as selfishness, but it was rather his determination to find the answer to his problem, that was the important thing."

Walter attended Boston University School of Medicine, where his father was professor of gynecology. After his father's death, Walter was admitted to the Harvard Medical School for the last year, having withstood the ordeal of taking all the examinations of the preceding three years. When he had graduated from medical school he spent a year in anatomy and obtained an A.M. from Harvard, in 1907. According to a remark in the *Twenty-Fifth Report* of the Class of 1902, it was his intention "to advance in the surgical line by doing research work." On the Third Boston University Surgical Service of the Boston City Hospital, he became successively house officer, junior intern, senior intern and house surgeon, thereupon opening an office for the practice of surgery at 508 Commonwealth Avenue in Boston. He was also anesthetist to the City Hospital, from April 1 to October 18, 1912.†

Boothby was for a short time assistant to Frederic J. Cotton, who at one time held appointments at the Children's, Boston City and Beth Israel hospitals. He had amassed a tremendous experience with fractures at the Boston City Hospital, culminating in 1910 with the appearance of his classic textbook, *Dislocations and Joint Fractures.* It is more than probable that Boothby's interest in anesthesia was stimulated by his association with Cotton. The majority of the papers on anesthesia that appeared from the Boston City Hospital were jointly authored by the two. That Cotton's name often appeared first may have been a manifestation of the professor-assistant relation, but, as is pointed out below, each took pains to give credit to the other.

One of the first papers pertaining to anesthesia did not carry Boothby's name as author.[1] In writing on the surgical importance of acapnia, Cotton commented, "I must confess it was my assistant Boothby who first called my attention to the literature on acapnia." He pointed out the remarkable constancy of the percentage of carbon dioxide in blood and tissues, about 40 per cent by volume. Loss of carbon dioxide could lead to respiratory failure under anesthesia, loss of venous tone, with bleeding into the splanchnic veins and development of shock, and loss of smooth-muscle tone. Several case reports followed, describing the benefits of carbon dioxide given to patients at the Boothby and Boston City hospitals. For the correction of air hunger and hyperventilation or for dilatation of the bowel during laparotomy, carbon dioxide was given either by inhalation through an inverted funnel (or by rebreathing from a simple grocer's bag) or by local surface application. Some patients did not do well and went to pieces if acapnia had progressed beyond the point of recovery of carbon dioxide balance. "My work on this problem is suspended until my assistant W. M. Boothby comes back from his Oxford trip. He is studying under J. S. Haldane of Oxford, the best methods applicable clinically to determine the presence or absence of a real acapneic condition in the given patient."

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†The Boston City Hospital, at its inception, had 5 operating rooms and 2 recovery rooms. Between 1910 and 1940 all hospitals in Boston employed nurse anesthetists. About 1910, Drs. Frank L. Richardson and Lincoln F. Sise, later joined by Dr. William Noonan, organized the first department of "etherizers" at the Boston City Hospital. Dr. Freeman Allen was supervisor of anesthesia at the Massachusetts General Hospital.

In the same year, 1912, a description of the Boothby–Cotton apparatus for the administration of nitrous oxide and oxygen appeared, a milestone for its technical innovations that now form the major ingredients of most modern apparatus.[2] The presentation (before a symposium on anesthesia of the Massachusetts Medical Society, on June 13, 1911) referred to the first use of oxygen with nitrous oxide by Andrews in 1868, and to Paul Bert's work on the use of nitrous oxide at greater than atmospheric pressures. Hewitt's use of nitrous oxide in England was cited, as well as Willis Gatch's procedure at Johns Hopkins, and Miss Hodgins's experience at the Lakeside Hospital in Cleveland under the direction of G. W. Crile.

The Boothby–Cotton apparatus was described as follows: "At the suggestion of Dr. Cotton and with the help of Dr. Albert Ehrenfried I had designed and built an apparatus." The apparatus incorporated high-pressure steel cylinders containing nitrous oxide compressed to 700 PSI (pounds per square inch) and oxygen at 2000 PSI. Pressure in the cylinders was reduced to 20 PSI before delivery. Connections were leak-proof, and there was provision for changing the tanks by means of a special casting of 4 yokes in pairs: 2 for oxygen, and 2 for nitrous oxide. The nitrous oxide reducing valve was surrounded by an electric heating coil to prevent freezing. Flow was measured by bubbling the gases through water, which also added moisture. For addition of ether, there was a large evaporating area with a three-way exit valve; this could be opened gradually so that the nitrous oxide could pass over the surface or bubble through it with the valve open wide. Gases were warmed by passage through an electric heater and delivered to the patient halfway between body and room temperature. Provision for rebreathing was incorporated by an inspiratory or inlet valve on the mask, the action of which could be partially or completely eliminated, and an outlet valve with a spring. Thus, each expiration could be rebreathed for smoother regulation of carbon dioxide content, to stimulate the rate and depth of respiration. "The latter would render more N_2O and O_2 available to the blood." Although Coleman, in 1868, had first suggested rebreathing, Boothby believed he was the first to suggest its importance in the uptake of anesthetics. He criticized Paul Bert's method as impractical, because the increased muscular action on the part of the patient to keep up respiration against positive pressure interfered with relaxation.

Cotton and Boothby described the technic of intratracheal insufflation according to the Meltzer–Auer method[3] and a simple introducer for a tracheal catheter, patterned after the Fell–O'Dwyer apparatus. Still another paper from the Boston City Hospital days disposed of the practice of warming anesthetic vapors[4] — "we have failed in the past to understand how quickly a gas warms or cools to the temperature of its containing tubes." Finally, in respect to safety during intratracheal insufflation anesthesia and the necessity for a safety valve, Cotton and Boothby[5] remarked, "We appreciate the dangers of emphysema and interference with the circulation (prevention of filling of the right heart). Pressure in excess of 10 mm. Hg. is unjustifiably dangerous. During light anesthesia the glottis contracts around the tube and raises the pressure. Spasm causes the danger!"

Boothby's transition from surgery to anesthesia and to basic research coincided with the appointment of Harvey Cushing as Moseley Professor of Surgery at Harvard and surgeon-in-chief at the Peter Bent Brigham Hospital, nearing completion in 1912. Cushing, it will be recalled,[6] had made significant contributions to the safety of anesthesia in his advocacy of the use of anesthetic records and in the routine use of blood-pressure measurement during anesthesia. He had also described from minute to minute monitoring of the circulation by means of continuous auscultation of cardiac and respiratory rhythm, by the use of a precordial stethescope, "accomplished by strapping the transmitter of a phonendoscope to the precordium." Now Cushing was to invite Boothby to become supervisor of anesthesia at the Peter Bent Brigham Hospital and director of the respiratory laboratory. In preparation for the latter, Professor Cushing obtained for Boothby a Sheldon Travelling Fellowship of Harvard University for the year 1912-1913. As a result, Boothby spent most of the year in Haldane's laboratory at Oxford, with visits to Joseph Barcroft at Cambridge and August Krogh in Copenhagen.

As a consequence of work done at Oxford, Boothby reported on, "The Absence of Apnoea after Forced Breathing."[7] In experiments performed on himself and others, sometimes using a body plethysmograph designed by Haldane and Priestley, Boothby failed to produce apnea with forced breathing. In a companion experiment, alveolar ventilation increased by 100 per cent with a rise of 0.22 to 0.23 per cent in alveolar carbon dioxide. On the other hand, oxygen want produced by rebreathing with a carbon dioxide absorber in the circuit, to an alveolar oxygen percentage of 5.46, did not affect respiration even though the face became blue, and tingling and giddiness arose.

Boothby began his service at the Peter Bent Brigham Hospital on December 11, 1913. In discussing staff organization in his first annual report from the Brigham, Cushing wrote: "In addition there is a supervisor of anesthesia who personally administers the anaesthetics in the more difficult and responsible cases and who happens to be the desirable type of man who gives his full time and has charge of a laboratory for the special study of respiratory problems." In his respiratory and metabolic studies Boothby had the encouragement of Francis G. Benedict, of the Nutrition Laboratories at the Carnegie Institute, of Professor Lawrence J. Henderson, of the Department of Biochemistry at the Medical

School, and of his chief, Harvey Cushing. Cushing had a considerable interest in the metabolic changes accompanying acromegaly.* Miss Irene Sandiford, who had just graduated from Radcliffe College, was appointed laboratory technician, later coauthor with Boothby of many of the papers written on basal metabolism. Dr. J. S. Haldane, of Oxford, visited the laboratory in 1914 (Fig. 1), trying to arrange for the members of the laboratory to participate in a scientific expedition to Pike's Peak, but the plans were interrupted by the war. An interesting group of investigators was associated with the laboratory, among them Dr. Maude E. Abbott, of McGill University, Dr. V. N. Shamoff, of St. Petersburg, Russia, Dr. Ernest Westcott, Dr. Frank B. Berry, Dr. Byron D. Bowen and Dr. Francis W. Peabody.

In his first paper from the Brigham,[8] a talk delivered before the Maine Medical Association on "Present Day Methods of Anaesthesia," Boothby reviewed the status of research work in the field, stressing pharmacology as it pertained to choice of anesthesia and dosage, mechanical problems relating to aeration of the lungs and physiologic problems involving the respiratory center. He warned against cyanosis and the use of positive-pressure breathing, especially in debilitated patients. He had found that the use of morphine, 1/8 to 1/4 gr., with atropine, 1/150 to 1/200 gr., half an hour before operation decreased the amount of ether needed. Although he disagreed with some of the tenets of Crile's "Anoci-Association Theory of Shock," he believed that procaine (Novocain), injected locally, helped to lessen the amount of anesthetic needed and prevented certain reflexes from exciting cerebral centers. He pointed out the value of intratracheal insufflation of anesthetics in operations on the head and neck and for intracranial and intrathoracic procedures. Boothby cautioned against doing artificial respiration so rapidly as to remove carbon dioxide. "Theoretically 4 per cent CO_2 would be desirable, the nearest approach being the use of expired air: in other words blowing into the mouth of the patient, not a particularly agreeable procedure."

Early charts at the Brigham reveal that Boothby was Cushing's "etherizer" for many intracranial operations. In his clinical work, Boothby found it safest to administer ether according to an accurate dosimetric technic; the Connell Anaesthetometer[9] (Fig. 2) was excellent for this purpose. The Connell apparatus was constructed so as to deliver a definite volume (and weight) of liquid ether with a definite volume of air, giving a mixture of definite percentage by weight of ether vapor in air. (The Anaesthetometer was still in use at the Peter Bent Brigham Hospital operating rooms as late as 1948; its heating element had even been fitted with an explosion-proof electric plug.) To be certain of its accuracy, Boothby and Miss Sandiford[10] employed the Waller Gas Balance to calibrate the Anaesthetometer. The Waller Gas Balance[11] for measurement of chloroform consisted of a translucent case containing a glass bulb of known volume. As mixtures of volatile anesthetics and air of varying densities were passed into the balance case, the glass bulb rose or fell. Having made corrections for barometric pressure,

*Basal metabolism was studied in acromegaly as well as the relation of the disease to hyperfunctioning thyroid adenomas and the development of exophthalmos. Although the findings were discussed in a correspondence between Boothby and Cushing over a period of twenty years the results were never conclusive enough to warrant publication.

FIGURE 1 *In the Respiration Laboratory at the Peter Bent Brigham Hospital, in 1914: Left, Professor John Scott Haldane; Center, Dr. Walter M. Boothby; and Right, Dr. Harvey Cushing.*

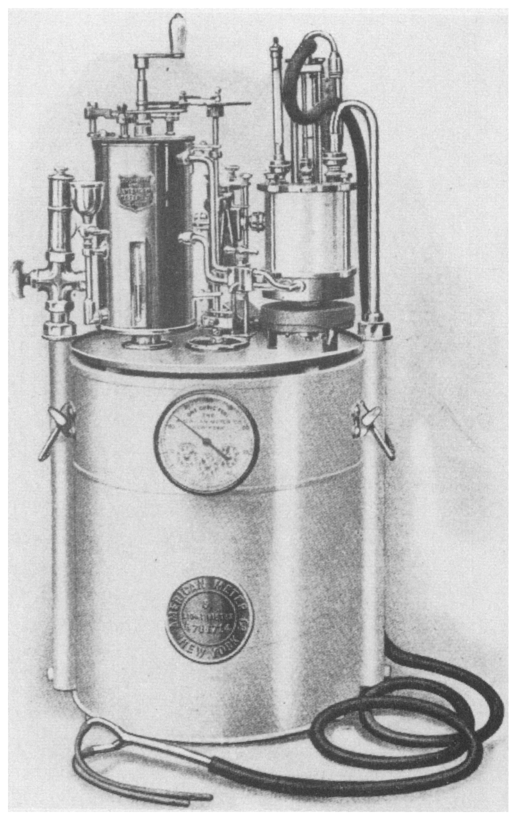

FIGURE 2. *The Connell Apparatus, Constructed so as to Deliver a Definite Volume (and Weight) of Liquid Ether with a Definite Volume of Air, Giving a Mixture of Definite Percentage by Weight of Ether Vapor in Air.*

for temperature, for the vapor tension of water and the alcoholic content of ether, Boothby and Sandiford measured the per cent by volume of ether in varying volumes of air and provided tables of corrections, so that the ultimate corrected tension of ether vapor delivered by the Anaesthetometer probably could be accurate to within ±0.2 mm. of mercury.

Thus prepared, Boothby wrote on the determination of the anesthetic tension of ether vapor in man, with some theoretical deductions therefrom on the mode of action of the common volatile anesthetics[12]:

> In order to determine ether tension it is necessary to establish equilibrium between the tension of ether in inspired air, alveolar air, blood and tissue — anesthetic tension is then equal to the tension of ether as delivered by the apparatus. . . . It is the custom at the Peter Bent Brigham Hospital to plot an anaesthesia chart on which are recorded the vapor tension of ether administered, the respiration, the systolic and diastolic blood pressures (determined by the auscultatory method) and the pulse rate. . . . [Fig. 3] There is a similarity of ether curves for all patients — regardless of age, sex, chronic alcoholism or in the newborn baby.

Apparently what Boothby was writing about is that blood levels of ether are approximately the same for the same surgical plane of anesthesia in any patient, provided a steady state has been achieved.

Another quotation from this article reveals Boothby's grasp of the factors involving uptake and distribution of anesthetics, which have been so thoroughly elucidated in recent years:

> Apparently the rate of saturation and desaturation vary with the relative mass of blood and the rate of circulation. In the same individual, different organs would be more or less quickly saturated and desaturated according to the proportional value of their blood supply. If ether were substituted for nitrogen, it is probable that the rate of saturation would be nearly the same (although the rate of diffusion of gases is inversely according to their densities, it seems probable that the anatomical perfection of the capillary system allows complete equilibrium to occur during the passage of blood through the capillaries, in either case).

Boothby was able to chart ether percentages during anesthesia because of additional experiments done.[13] He measured the tension of ether vapor delivered not only from the Connell Anaesthetometer but from the Richardson and the Woulfe bottles as well. An artificial respiratory system of mask, trachea and bronchi was constructed, with placement of thermisters at various points. A foot pump delivered a volume of gas measured in a Bohr 10-liter gas meter. In this manner, graphs were constructed, permitting the assessment of the percentage of ether vapor according to gas flow and temperature. Vapor pressure curves at different temperatures were supplied for ether:

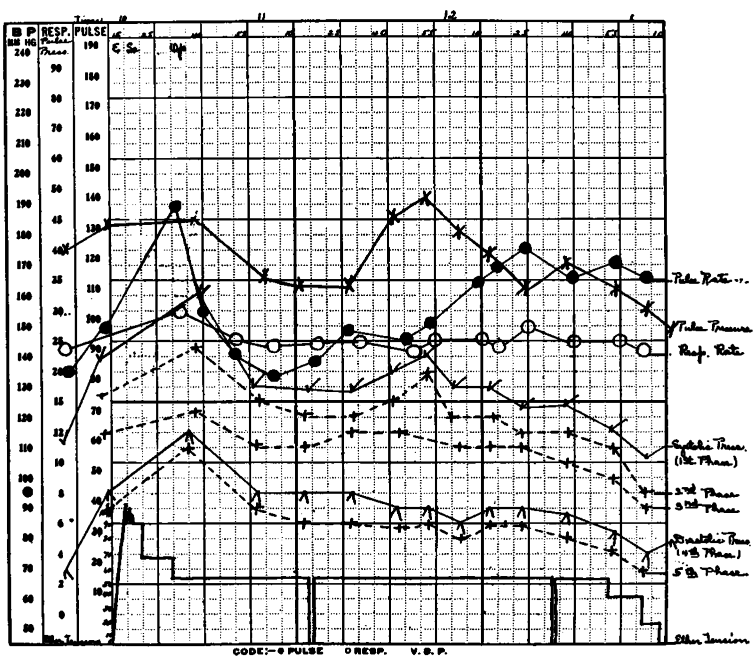

FIGURE 3. *Anesthesia Chart (Reproduced from Boothby[12] with the Permission of the Publishers).*

Name C.B.; Age 50; date of operation, September 6, 1913; lungs, negative; heart apparently normal; urine, negative; arteriosclerosis, none; operator, Dr. Cushing; first assistant, Dr. Bagley; anesthetic, Squibb's ether, Connell apparatus, Gwathmey mask and towel, cerebellar position; operation, extirpation cerebellar tumor; preliminary drugs, atropine sulphate, 0.5 mgm. s.c. at 9:40; blood pressure, Sys. = 110, Dias. = 70 (Tycos); stimulants, none; practically no bleeding. Tycos correction = —5 mm. (average).

Remarks: Induction accompanied by slight laryngeal spasm with coughing. It is especially noteworthy that "little ether" was needed for induction; as seen by the ether tension curve the higher tensions were given for only a short time. That is the patient came up to the anesthetic tension quickly; it was necessary to maintain the ether tension at 54 mm. throughout the operation. Perfect anesthesia. Anesthetist — Dr. Boothby.

> This curve can be made of practical use by placing a centigrade thermometer in the liquid ether of the vaporizing apparatus. At any given temperature of the ether, one may be sure that one obtains the corresponding ether percentage: then if one has a valve which will accurately shunt the air current so that one fifth or fourth, or third, etc. can be passed over the ether, and the rest around the ether, a close approximation of ether percentage which the patient is getting can be readily estimated.

Many of Boothby's measurements of ether tension were made in patients on whom Professor Cushing performed cerebellar operations, thus necessitating a prone position with the head supported by a special rest. These operations frequently lasted for three hours, and patients were placed in this position before induction of anesthesia. "It was therefore necessary so to administer the anaesthetic as to cause no excitement, struggle or scarcely a movement on the part of the patient."

In the short time that he was at the Brigham, Boothby's investigations became widely known, and his work on respiration and metabolism attracted the attention of Dr. Henry S. Plummer at the Mayo Clinic. As a result, he was offered the opportunity to establish a metabolism laboratory at Rochester, which he accepted in November, 1916. After war was declared, he sailed for France with the Harvard Unit in May, 1917. Upon arrival in England he was detached from the unit with orders to investigate methods of gas defense. As the Gas Service developed, he was made division gas officer for the First Division after its arrival in France. Later he became director of the Gas School at Gondrecourt.

The impact of Boothby's departure upon the anesthetic service at the Brigham was revealed in 1916 (in Cushing's absence), when Dr. David Cheever wrote:

> Two valued members of the staff have resigned to accept posts in other institutions – Dr. Walter M. Boothby who has become Assistant Professor of Medicine in the Graduate Department of the University of Minnesota at Rochester. This vacancy has not been filled and constitutes one of the pressing needs of the surgical service. A skilled anaesthetist to conduct difficult cases and to foster high standards and traditions among the successive groups of house officers is an indispensable factor in successful surgery.

In 1917 Cheever again remarked:

> A death occurred under ether anaesthesia administered for operation for simple hernia. In the absence of evidence to the contrary (which might perhaps have been obtained if the Medical Examiner had thought a post mortem examination advisable) it must be assumed that the death was due to ether, and this has led to a revision of the conditions surrounding the giving of anaesthetics. As in most general hospitals which have a graded system of intern service, this extremely responsible duty has been entrusted to the most recently appointed group of internes, with the delusion that under the general supervision of the operating surgeon it would be discharged with adequate satisfaction. Time and again the expectation has proved fallacious, though ill results are usually averted. Formerly Dr. Boothby, Supervisor of Anaesthesia, cared for special cases and gave instruction to internes, and after his call to the Mayo Clinic his work was in part performed by a trained nurse anesthetist until her departure with the Base Hospital Unit. We have now established the plan of entrusting anesthesia to internes during the second quarter of their terms of service, after they have acquired some clinical judgment and experience; they are instructed by two skilled nurse anesthetists, who themselves conduct the more critical cases.

Meanwhile, Boothby had organized the Metabolism Laboratory at the Mayo Clinic, and his name soon became familiar to every center of clinical investigation because of the standards of basal metabolism in health and its variations in disease that he had established. He and Dr. Plummer collaborated on studies of oxygen therapy, particularly for postoperative patients with anoxia. In the 1930's he and 2 Mayo Clinic associates, William R. Lovelace and Arthur Bulbulian, developed a mask for oxygen therapy. This came into wide use and was known as the B.L.B. mask. His earlier military assignments were the beginnings of thirty-five years of leadership in military medicine. His interests in respiration and oxygen therapy were soon directed to the solution of the problem of supplying oxygen to pilots at high altitudes. In 1939, in recognition of their research in aviation medicine, Boothby, Lovelace and Harry G. Armstrong were corecipients of the Collier Trophy, aviation's highest award.

Throughout World War II, many scientists came to Boothby for training; among them were F. J. W. Roughton and Charles A. Lindbergh. The studies on aviation medicine of the Mayo Aero-Medical Unit, which he had established, were eventually published in 6 volumes by the National Research Council. Of the several hundred papers that were written, in addition to those on thyroid physiology and disease, there were studies on insulin, on the parathyroid glands, on myasthenia gravis and on muscular dystrophy and many technical, scientific and clinical contributions to the field of inhalation therapy. Dr. Albert Faulconer, chief of the section of Anesthesiology at the clinic, recalls the later years:

> For a period of a year or two immediately following World War II, Dr. Walter Boothby made a practice of following very closely some of the investigative work I was doing in our physiology laboratories. At the time I was concerned with ether tensions necessary for anesthesia and methods for gas analysis. It was apparent that he had devoted a lot of thought to this field and I spent many stimulating hours in theoretical discussion with him. Dr. Boothby often spoke to me in glowing terms of the Waller balance and the Connell Anaesthetometer.

Walter M. Boothby died on July 3, 1953, in Albuquerque, New Mexico, where his final tour of duty had been with the Lovelace Clinic. One of his last papers, "Rate of Pulmonary and Tissue Gaseous Nitrogen Elimination as a Measure of Pulmonary Efficiency," was published posthumously.[14]

The anesthesiologist of today cannot help being struck by the many facets of Boothby's career that parallel those of anesthesia as it is now practiced. Although it was some fifty years ago that he delved into anesthesia, he was far ahead of his time in clinical and laboratory investigation — perhaps the first real investigator in anesthesia. His ideas on respiration, on uptake and distribution of anesthetics and on the need for dosimetric administration of anesthetics have gone essentially unchallenged. It is intriguing to speculate whether he would have remained in anesthesia today, with its greater challenges in the operating room, the variety of anesthetics and adjunct drugs now used, the broadening of interest in respiratory care, the teaching opportunities, the academic associations and the accepted practice of investigation in clinical and basic science. Possibly not, but the evolution of his career does suggest that anesthesiology must be broad in its interests, with a firm scientific background of its own, to appeal to the best minds. It must be broadly based in medicine to cope with the development and impact of new drugs and technics that will make the older practices seem primitive and perhaps to lessen the need for the anesthesiologist in the operating room.

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THE INVOLVEMENT OF RNA IN PROTEIN SYNTHESIS*

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In 1940 the work of Beadle and Tatum[1] established the concept that the genes carry out their function by controlling specific proteins. At approximately the same time Brachet[2] and Caspersson[3] independently concluded that ribonucleic acid (RNA) was somehow associated with protein synthesis. In the next fifteen years, several major advances were made: DNA was identified as the genetic material[4]; its double helical structure was elucidated[5]; it was postulated that DNA carries information as a sequence of nucleotide bases, from which a complementary copy can be made[6]; and the ribosomes, containing most of the cell's RNA, were identified as the site of protein synthesis.[7] The outline of the central dogma become clear: "DNA makes RNA, and RNA makes protein." That is, the genetic information is carried as a sequence of bases in the DNA; a piece of RNA is made with the use of the DNA as a template, in a process called *transcription*, and this piece directs the synthesis of a protein, its sequence of bases specifying the sequence of amino acids in the protein. This process is called *translation*, for the cell is translating the nucleotide language of the nucleic acid into the amino acid language of the protein.

As a result of a great deal of research in the past decade, this view of the situation has been filled out with many details, but the overall concept has remained essentially unchanged. The most important additions have been the identification of several types of RNA involved in protein synthesis and the elucidation of their role. We start by summarizing the process of protein synthesis, so that a coherent picture can be kept in mind during the discussion of each part. An excellent elementary source of background material is to be found in Watson's[8] recent book; several reviews have also been pub-

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