ACADEMIC MEDICINE

PRESENT AND FUTURE

ROCKEFELLER ARCHIVE CENTER CONFERENCE

ACADEMIC MEDICINE

(*Left to Right*) *Front Row*: Lehninger, Mastroianni, Tarlov, Avery, Bowers, King, McAnarney, Berliner, Kety
Middle Row: Hirsch, MacMahon, Sabiston, Ernst, Wolff, Haynes, Day, Robbins, Wyngaarden, Warren, Petersdorf, Motulsky, Lederberg, Choa, Rudbarg
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PREFACE

This book is a record of a conference that was held at the Rockefeller Archive Center in Pocantico Hills, North Tarrytown, New York, 25–27 May 1982.

Periodically it is important to evaluate the status of academic medicine and to forecast its future direction. This is particularly important today owing to increasing emphasis on the basic sciences at the undergraduate college level after the introduction of molecular biology into the college curriculum in the 1950s. During this period basic science became an important part of clinical studies, leading to an integration of basic research and clinical disciplines. For example, departments of obstetrics and gynecology in a number of institutions introduced research in basic reproductive biology; human genetics grew rapidly as both a basic science and a clinical discipline.

In the late 1970s United States government policy shifted rather suddenly from emphasis on more medical schools to a reduction in the number of schools and in student enrollment. At about the same time the Department of Health and Human Services, formerly the Department of Health, Education and Welfare, undertook a study of the imbalance of men and women in the various clinical specialities.

In the spring of 1981 Joseph W. Ernst, Director, and J. William Hess, Associate Director, at the Rockefeller Archive Center invited me to organize a conference on medicine. With academic medicine in mind, we invited leaders from the various disciplines considered of prime importance to that field. The caliber of the participants is mirrored by the excellence of their presentations.

The Rockefeller Archive Center, a division of The Rockefeller University, opened in 1975. It houses records from the University, The Rockefeller Foundation, Rockefeller Brothers Fund, the Rockefeller family, and other individuals and organizations associated with their endeavors.

The indispensable assistance of Dr. Ernst and Dr. Hess is greatly appreciated. Their personal attention and efficient management contributed greatly to the success of the conference. Additional appreciation must be given to their secretary, Mrs. Madeleine Tierney, who contributed much to

the organization of the conference. Thanks go also to Margaret Broadbent who guided and supervised the production of this book. Finally, I wish to express my deep appreciation to the participants, without whom there would have been no conference and no book.

JOHN Z. BOWERS, M.D.

New York City

THE INTRODUCTION OF WESTERN MEDICINE INTO CHINA

G. H. CHOA

I am looking forward to listening to the distinguished panel of speakers in the next two days when they will discuss the present and future of academic medicine. Meanwhile, I am going to talk about the past by giving you a brief account of the pioneers who introduced Western medicine into China, the clinics and hospitals they established, and the institutions of medical education they founded. Without these beginnings there would have been no academic medicine in China. Perhaps I should start with some geography first. China is the name by which we call the region as well as the country itself. Within the region, situated on the south coast and very near each other are the Portuguese territory of Macao and the British territory of Hong Kong where I come from. I will discuss the main events that took place in China and Hong Kong and the role of Macao as the portal of entry through which Western medicine was eventually introduced into China but where no significant development occurred. I should also explain that "Western medicine" is really "scientific medicine" as we know it. The word "Western" literally means

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GERALD H. CHOA began his medical training at the University of Hong Kong. During World War II he continued his studies at Cheeloo University in western China. He received his M.D. from Cheeloo University in 1945, and the M.B.B.S. from Hong Kong University in 1946 proceeding to the M.D. in 1960. After the war Dr. Choa spent an extended period of time in the United Kingdom, where he earned a diploma in tropical medicine from Liverpool and studied internal medicine at Birmingham and neurology at London. In 1949 he was appointed Lecturer in Medicine at Hong Kong University and in 1956, Specialist in Medicine at Queen Mary Hospital. He became Deputy Director of the Medical and Health Department of Hong Kong in 1967 and served as Director of Medical and Health Services of Hong Kong 1970–76. In 1977 Dr. Choa was appointed Dean of the new Faculty of Medicine, Chinese University of Hong Kong, and Professor of Administrative Medicine. He is a Fellow of the Royal Colleges of Physicians of London and Edinburgh.

"European" in the Chinese context, because after the thirteenth century, most visitors to China from the West were Europeans, especially the missionaries who subsequently figured so prominently in her history. The Chinese thus identified Europe as the West rather than the other western regions such as Central Asia, Asia Minor, and the Middle East, with which they had more trading than cultural contacts. Furthermore, apart from what they called European medicine, no other school from the West (for example, Indian medicine, which did find its way into China with the spread of Buddhism) had taken root.

The first contacts between China and the West were initiated by the Chinese who reached as far as the eastern end of the Mediterranean in a number of early expeditions. These took place during the Han dynasty, between 206 B.C. and A.D. 220. Probably no physicians accompanied the troops or the caravans that followed, and although the main items of import were new breeds of horses, some drugs or medicinal plants were said to have been brought back to China. However, Chinese medicine made at least one contribution to the West through the introduction into Turkey of the Chinese methods of inoculation against smallpox by traders either of Chinese origin or of other nationalities who learned the technique in China. Though this happened at a later period, it preceded Jenner, who performed his first vaccination in 1796, by at least a hundred years; in China itself the practice began in the tenth century. The first Western visitor to China whose name is known to us was John Alopen of Syria, a Nestorian monk. He arrived in Changan, the capital of the Tang dynasty, in about A.D. 635 and built a church there to preach his religion. This, incidentally, was the first introduction of Christianity into China. It has been recorded that a monk who came later and whose name was Sargis, was a physician, so presumably some medical aid had been available to the followers. The Nestorian Church lasted about two hundred years, and, with the demise of the Tang dynasty, it also came to an end. Its brief history was inscribed on a stone, which was unearthed long afterwards. The brothers Polo, Marco the elder, and Nicolo, first reached Peking in 1260, and again in 1275 with young Marco. They could not have had any knowledge of Western medicine to impart to the Chinese. Soon to follow was John of Montecorvino, a Franciscan friar and the first Catholic priest to set foot in Peking, where he arrived in 1294. According to Wong and Wu, whose *History of Chinese Medicine* remains the authoritative work on the subject, "it was quite possible that the works instituted by him, his helpers and successors, embraced some kind of medical undertakings," but there is no evidence that Friar John himself had ever studied medicine (p. 262, ref. 7). The consensus among medical historians is that the first Western physician to reach China was the Jesuit priest, Father Jean Terrenz Schreck, usually referred to by his middle name or as Terrentius.

Born in 1576 in Switzerland, Fr. Terrenz was widely known as a physician, philosopher, and mathematician in Europe before he joined the Jesuit Order rather late in life at the age of thirty-five. He had been a friend and fellow academician of Galileo, who was the sixth member elected to the Cesi Academy in Rome; Terrenz was the seventh. Fr. Terrenz started his journey to the East in 1618. En route, he collected plants, stones, animals, fish, reptiles, and insects on the shores of Goa, Malacca, Sumatra, and Cochin China and made first-rate drawings to accompany his descriptions. He left unpublished two volumes in folio containing these studies. He arrived in Macao in 1621, some sixty years after his illustrious predecessor, Fr. Matteo Ricci. A linguist who was well versed in the semitic languages, it was Fr. Terrenz who translated the Syriac inscription on the Nestorian stone monument erected by John Alopen's followers in Changan when it was discovered almost a thousand years later. He wrote a treatise on human anatomy in Chinese and apparently performed, on a fellow priest, the first autopsy or dissection in China. Otherwise his medical skill must have been largely wasted, for we know that he was assigned to work on the calendar in the years he spent in Peking where he died in 1630. Another Jesuit priest who came after Fr. Terrenz was Fr. Michael Boym who was reputedly a physician in the Polish Court. He translated some Chinese medical texts and literature into Latin and published his works in a volume entitled *Clavis Medica.* Concerning the influence of the Jesuits in the Ching Court, here is the story of Emperor K'ang Hsi's famous illness, quoted from Wong and Wu's book (p. 266, ref. 7):

> The Emperor K'ang Hsi (1661–1722) was attacked in 1692 by a malignant fever which was relieved by Frs. Gerbillon and Pereira administering some "medical lozenges which Louis XIV had ordered to be distributed to all the poor in his Kingdom." Later recurring symptoms of tertian fever appeared and defied the skill of the imperial physicians, proclamations were issued that anyone knowing of a remedy against this ailment should at once impart it to the Court. The missionaries possessed a pound of cinchona bark which had been received by Fr. de Fontaney from India. They offered this and three patients confined in the palace for experimental treatment were speedily cured by its action. Encouraged by this the Emperor partook the remedy with the same spectacular result.

Upon his recovery, the emperor appointed the priests as his personal physicians, much against their will, for neither Fr. Gerbillon nor Fr. Fontaney was a medical practitioner, the former being in fact a mathematician and the latter an astronomer. Later, more Jesuits who were trained in medicine, notably Brothers Bernard Rhodes and Jean Joseph Costa, arrived in Peking. Their skill was quickly recognized and they were appointed as court physicians.

We will now leave Peking for Macao, where the Portuguese established themselves in 1557. After that, Westerners would come to China by the sea route. Having disembarked at Macao, those who wanted to go inland had to wait there patiently, sometimes for years, before they could proceed. In 1569, the local branch of the Lisbon-based charity institution, the Santa Casa de Misericordia, was established in Macao. The works of charity supported by this institution included a hospice for lepers, an asylum for lunatics, and a civil hospital for men and women, the San Raphael, which, after repeated renovations and reconstructions, still exists on its original site today. It can claim to be the hospital with the longest history in China, though not the first, as we will see later. Let us skip two centuries and get on to the nineteenth when a new breed of missionaries who were qualified medical practitioners began to arrive in Macao to work in southern China rather than the north. They were more fortunate, for by then, foreigners were allowed to go to Canton. They could stay there for only about eight months each year, however, and they had to go back to Macao for the summer. The greatest of them was Robert Morrison, the first Protestant missionary in China. An Englishman, born in Northumberland in 1782 and trained at St. Bartholomew's Hospital in London, he arrived in Macao in 1807. He soon mastered Chinese and was so proficient that he was appointed official interpreter of the East India Company. It was missionary rather than medical work that actually occupied more of his time. He translated the New and the Old Testaments into Chinese, wrote a Chinese grammar, and compiled a Chinese-English dictionary. He saw how the medical man was allowed to practice his profession without interference in China and in so doing was able to gain easy access to the people. He became convinced that only through the professions of medicine and teaching could a mission in China prosper. However, he had to contend with the prejudice that the Chinese harbored against both Western medicine and the Christian religion. In the end, the clinic he ran in Canton had to close because of lack of support, and converts were few in spite of his efforts. In 1834, Peter Parker, the first American medical missionary, arrived in Macao. Born in Framingham, Massachusetts, he was a graduate of Yale's Medical School. He worked in both Macao and Canton, where he established clinics which attracted a large number of patients. He was the first in China to use ether anesthesia (1847) and chloroform (1848). He was more successful in his medical work because he performed eye operations and removed large unsightly tumors. He found that the local people would not take Western medicine for other ailments, but they would go to him because the traditional practitioners could not do anything about eye diseases and tumors. In the Gordon Museum of Guy's Hospital in London and in the Yale Medical Library, one can see parts of Parker's collection of oil

paintings illustrating cases of various types of tumors before they were removed by him. Indeed, unlike Morrison, he was so busy with bodies that he had not much time for souls. Parker later served as a diplomat in the American mission in China and was chargé d'affaires in the legation in Peking at one time. Apart from the medical missionaries, some ship surgeons of the East India Company also opened clinics in Macao and Canton. While practicing in Canton in 1805, Alexander Pearson became the first to introduce into China the European method of vaccination against smallpox. John Livingstone helped Morrison to operate a clinic in Macao in 1820, and Thomas Colledge opened an ophthalmic hospital in Macao in 1828. Colledge, in fact, found out before Parker that Chinese patients with eye diseases would consult Western practitioners more readily. Following the trail of Morrison and Parker, many other distinguished medical missionaries came to China, and in the words of one, they opened her door at the point of the lancet. After the Treaty of Nanking was signed in 1842, they could disembark at the treaty ports of Canton, Amoy, Foochow, Ningpo, and Shanghai and either open their missions in these places or go farther inland to others.

I do not propose to trace the history of hospitals in China and will now turn to medical education, because most of the hospitals founded by the medical missionaries were used in later years as teaching hospitals by various medical schools. As a matter of interest, the first hospital in China was opened by a physician, Isaiah, in the Court of Kyuk Khan in Peking in 1272. He was also a linguist and an astrologer, described by some as a European but considered as a Mussulman and not a Christian by others. Once having started hospital work, some medical missionaries took on local young men as assistants to train them as doctors. In 1838, a Medical Mission Society was founded, with Colledge as its president and Parker its vice president. The objectives of the society, as noted in a statement drawn up by Colledge, Parker, and Bridgman, were "to encourage the practice of medicine among the Chinese, to extend to them some of those benefits, which science, patient investigation and the ever-kindling light of discovery, have conferred upon ourselves" (p. 41, ref. 6). Parker actually initiated medical education in China by taking on an assistant by the name of Kwan Ato who joined him in 1836. I will tell you more about Kwan later. In 1865 in the Tung Wen College, a center of higher education established by the Chinese government in Peking, a course in Western medicine was organized by Dr. John Dudgeon of the London Missionary Society as its professor of medicine. This first official move was largely due to the broad-mindedness and far-sightedness of Li Hung Chang, viceroy, foreign minister, and prime minister, the most powerful mandarin in the last years of the Ching dynasty. Dr. Dudgeon wrote and translated a number of medical works for the students during his tenure. At about

the same time, at the Canton Missionary Hospital, Dr. John Kerr began to take in pupils. Dr. Kerr was born in Ohio in 1824, graduated from the Jefferson Medical College, Philadelphia, and arrived in China in 1854. The founder of the Republic of China, Dr. Sun Yat-sen, studied under Kerr for a year in 1886. These were the pioneer efforts; thereafter, many more national and privately funded medical schools and colleges were established in various parts of China. I will mention a few more and the personalities associated with them. For a country in which women had no place in society and no say at home, you may be surprised to hear that a medical school for women was opened in Canton as early as 1901. It was named after E. A. Hackett of Indiana, who was the generous donor. The reason for such an early start to train women doctors in China was that female patients, following the very strict rules governing social etiquette of the day, would not subject themselves to be physically examined by male doctors. The Peking Medical College was officially opened in 1906, with Dr. Thomas Cochrane, a graduate of Glasgow University, as its first dean. He was described as "a man with a stern, square face, dominated by a strong chin and steely eyes that hold one under withering scrutiny" (p. 7, ref. 1). The teaching hospital used was originally the Peking Hospital of the London Missionary Society, opened in 1861 by Dr. William Lockhart who studied medicine at Guy's Hospital. This medical college had had the financial support of none other than Dowager Empress Tzu-hsi, who donated the equivalent of £1,400. Later, the China Medical Board of the Rockefeller Foundation purchased the college which became the Peking Union Medical College, undoubtedly the most famous institution of medical education in Chinese history. The transaction involving land, buildings and equivalent, was completed in 1915, at an eventual cost of some U.S. $7.5 million, a huge sum of money in those days. Dr. Franklin C. McLean, who studied at the University of Chicago and Rush Medical College, was appointed as medical director at the age of twenty-eight. At this college, teaching was conducted in English; in fact, in all missionary medical colleges the students were required to possess an adequate knowledge of English. In 1906, the St. John's University was incorporated in Shanghai, with Dr. H. W. Boone as dean of the medical school. In 1909, a medical school was added to the Aurora University, an institution supported by the Catholic Mission where teaching was conducted in French. In 1912, Dr. Dugald Christie of the United Free Church of Scotland saw the educational efforts he started in Mukden developed into a medical college. In 1916, Dr. Edward Hume of the Yale Foreign Missionary Society became dean of the Hunan-Yale College of Medicine, later called the Hsiang-Ya Medical College, at Changsha, the capital of Hunan province. A man of deep religious faith, great strength of character, and considerable medical skill, he was another one of the

great pioneers. Both Hume's father and grandfather were missionaries who were based in India, and he himself, a graduate of Johns Hopkins Medical School, was working there when he was called to China. In his autobiography he wrote that it was the suggestion in the letter of invitation "to launch a university medical school" that made him decide to leave India (p. 20, ref. 5). At the age of twenty-nine, he arrived in China in 1905 when anti-Western feeling was high in the aftermath of the Boxer Rebellion. In the last few years before he left China in 1927, a period of civil war fought by opposing warlords in the province, his life was often in danger. Other well-known medical schools opened by medical missionaries included Cheeloo University in Tsinan, Shantung in 1909, and the West China Union University in Chengtu, Szechuan in 1914. Of the notable national medical colleges, the Tung Chi University in Shanghai, where teaching was in German, was opened in 1907, the National Chungshan University in Canton in 1926, and the National Medical College in Shanghai in 1927. National Chungshan was also known as Sun Yat-sen University, and its teaching hospital was the same Canton Missionary Hospital where Sun was a pupil.

To answer the question as to who was the first Chinese to practice Western medicine in China, we have two candidates, Kwan Ato and Wong Foon. Kwan was the nephew of the famous painter Lamqua who painted Peter Parker's interesting cases, and Parker obliged Lamqua by taking Kwan as his assistant at the Canton Missionary Hospital in 1836. It was said that thereafter Lamqua no longer charged Parker for painting his patients. In a report, Parker said that Kwan was a responsible and active youth, received five dollars per month wages, and was being trained to perform such eye operations as for pterygium and entropia (p. 318, ref. 7). Together with two others he was instructed mainly in English. By the time Parker was administering ether anesthesia, Kwan had become a very competent surgeon. In addition to performing eye operations, he had extirpated many tumors, extracted teeth, removed carious bones, and successfully treated dislocations and fractures, both simple and compound. When a medical school was installed in connection with the Canton Missionary Hospital in 1866, Kwan was appointed to teach practical and Chinese medicine. Also appointed to teach anatomy, physiology, and surgery was Dr. Wong Foon, who was the first Chinese to have taken a medical degree to practice Western medicine in China, but, being well ahead of his time, was not a graduate of a medical school in China. Wong Foon was born in 1827 in Kwangtung and died in 1879. He was a pupil in a school opened by the Morrison Education Society in Macao. Together with two others, he was taken to the United States in 1847. After attending the Monson Academy in Massachusetts for two years, he went to Edinburgh to study medicine from 1849 to 1856. Having

been under the influence of the Edinburgh Medical Missionary Society, he offered his services to the London Missionary Society after he graduated and was sent back to China. On arrival in Hong Kong in 1857, he opened a dispensary but removed it to Canton the next year. He worked for a while in the Canton Missionary Hospital, then he was in Hong Kong again, working in the Government Civil Hospital, but left for the north when he was appointed as medical adviser to Viceroy Li Hung-chang, whom I mentioned earlier. He found no interest in administrative work, so he returned to Canton where he was engaged in private practice for the rest of his life.

History does not tell us the real reasons why the medical missionaries did not accomplish in Macao what they did in China and then in Hong Kong. After the Union Jack was raised on the barren island of Hong Kong in 1841, there were military and naval surgeons who looked after the troops in the garrison, but the civilians were left uncared for. The medical missionaries soon came. Among the first was Dr. Benjamin Hobson of the London Missionary Society, who moved a general hospital from Macao to Hong Kong in 1843. Dr. Hobson, who was the son-in-law of Robert Morrison, and who graduated from the University College Hospital Medical School in London in 1839, should be given the credit for initiating medical education in Hong Kong. In his hospital he took on young assistants and he wrote a textbook in Chinese on anatomy and physiology which became very widely used. The government also appointed its first colonial surgeon in that year, whose duty was to treat the European residents and government employees. In 1872, a hospital for the Chinese was opened but the patients were treated by traditional practitioners whom they preferred. In 1882, Ho Kai, born in Hong Kong but having taken a medical and a law degree in England, returned home. He was the first Chinese to practice Western medicine in Hong Kong but he had few patients, such was the prejudice of the Chinese against Western medicine. Consequently, he gave up medicine and practiced law instead. This far-sighted man realized that to win over the Chinese to Western medicine, more hospitals should be built to offer Western medical treatment to the Chinese on a larger scale, and a medical school should be established locally to teach Western medicine to the Chinese. In 1887, the Alice Memorial Hospital was opened. Ho Kai had borne the cost of building this hospital which was named after his English wife, who unfortunately had died three years before. Six months later the Hong Kong College of Medicine for the Chinese was founded, with the Alice Memorial Hospital as its teaching hospital. Ho Kai was largely responsible for raising funds, drafting the constitution, and forming the administration for this college where he taught medical jurisprudence. The first dean was Sir Patrick Manson, often called the Father of Tropical Medicine, who

first arrived in the Far East in 1866. After practicing in Formosa and Amoy, where he studied the life cycle of the filaria and discovered the culex mosquito host in 1877, Manson came to Hong Kong in 1883. He left in 1889, two years after the medical college was opened, having handed it over to Sir James Cantlie. Among the first batch of twelve students admitted in 1887, only two graduated five years later. One of them was Dr. Sun Yat-sen, the founder of the Republic of China, forever the most distinguished licentiate of the Hong Kong College of Medicine. It will be remembered that Dr. Sun was attending the Canton Missionary Hospital under Dr. John Kerr, but he came to Hong Kong to join the college when it was opened. Here is another famous story. In October 1896 Dr. Sun was in London. Having fallen into a trap, he was kidnapped by members of the Chinese Legation and locked up in the basement of the building. He was to be smuggled out of the country, for there was a price on his head in China. Sun managed to persuade an English member of the legation to pass a note to his former teacher, Sir James Cantlie, who had by then returned to London from Hong Kong. Cantlie immediately informed the police; thus, in saving the life of his pupil, he had helped indirectly to found the Republic of China. The Hong Kong College of Medicine existed for twenty-eight years. In 1911, the University of Hong Kong was founded and the college was absorbed into its Faculty of Medicine. It was finally closed in 1915 when the last licentiate graduated. Ho Kai was again instrumental in founding the university, as much of the planning and organizational work was done by him. The China Medical Board generously endowed the three clinical chairs of medicine, surgery, and midwifery in the university in 1922, in addition to making gifts to the university's graduates of travelling fellowships in each of the clinical departments and the department of pathology. In spite of the many distinguished services Ho Kai rendered to the community in Hong Kong, especially in the areas of medicine, public health, and education, strangely enough, he is commemorated by our airport and not by some medical institution; the Alice Memorial Hospital, however, still exists today. Those of you who have been to Hong Kong will probably remember that our airport is called the Kai Tak Airport. Kai was Ho Kai, Tak was his friend Au Tak. They were the original co-owners of that piece of land on the Kowloon peninsula, named after them as Kai Tak Bund, on which the airport was built.

Some people may ask why Western medicine should be introduced into a country such as China which has, as part of her cultural heritage, a school of traditional medicine with a history dated back to 2900 B.C. To this question I have a short and simple answer ready. While Western medicine has gone through a scientific evolution and become what it is today, Chinese traditional medicine has remained abstract and empirical.

If scientific medicine is able to offer more benefits to mankind in both curing and preventing diseases, then it should be introduced to all nations and races. It was the spread of Christianity that started the incursion by missionaries into other countries and cultures. Whether that was right or wrong is perhaps debatable; but the motives of the missionaries were unquestionable. In China, the example of Matteo Ricci, who practically adopted the country by learning its language and living according to its social customs, was followed by most missionaries, both Catholics and Protestants. These missionaries often worked under very difficult conditions and suffered great hardship. Aside from religion, they wanted to teach the Chinese how to apply scientific methods in various branches of knowledge and skill. They succeeded in some instances: in astronomy they were able to show the Chinese, who were acknowledged experts, that their calculations and predictions were more accurate. However, the medical missionaries found the gap between Western and traditional medicine too wide to be closed, and they had to introduce to the Chinese something altogether new. To their credit, soon after they came, the missionaries began to organize training for the Chinese so that they could take over and carry on the good deed. It was a totally unselfish act, very much in the tradition of Hippocrates, and with the passage of time, it has eventually borne fruit. Let us not forget the pioneers, for we owe it to them that we speak the common language of medicine today and share the same aspiration of making medical education, and with it academic medicine, available to all.

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ADVANCES IN BIOCHEMISTRY AND THEIR SIGNIFICANCE FOR MEDICINE

EUGENE KENNEDY

The title I have chosen for this paper, "Advances in Biochemistry and Their Significance for Medicine," although grandiose, has the sole merit of having forced me to think in the most general way about the relation of biochemistry to medicine.

When I was working in the Ben May Laboratory for Cancer Research at the University of Chicago, my mentor Charles Huggins would occasionally challenge me to make an estimation of the number of patients who had been cured of some disease as a result of experiments carried out with a Warburg manometer. Since Huggins was, in fact, deeply committed to fundamental biochemistry as the most powerful approach to the future development of medicine, his query was a friendly one, but it made me aware of the troubling fact that the community was supporting fundamental research in biochemistry on the basis of a large number of promissory notes pledging the solution of major problems in medicine. Many of these promissory notes are still outstanding. Why is this?

There are in fact three levels of biochemistry that must be considered in relation to medicine. The first level is concerned simply with the

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EUGENE P. KENNEDY received a Ph.D. in biochemistry from the University of Chicago in 1949. After a year as a Fellow of the American Cancer Society at Berkeley, California, he returned to the University of Chicago as Instructor in the Ben May Laboratory for Cancer Research and the Department of Biochemistry, where he worked with Charles Huggins and Albert Lehninger. In 1960 Dr. Kennedy was selected to be head of biochemistry and Hamilton Kuhn Professor at Harvard Medical School. He was elected to the National Academy of Sciences in 1964, and he received an Honorary Doctor of Science from the University of Chicago in 1977.

chemistry of living cells. What are they made of? The contribution of biochemistry to medicine at this level has, in fact, been profound. The very phrase "blood chemistry" is, of course, one of the most frequently used by clinicians from day to day. It can hardly be doubted that biochemical analysis of the blood and tissues offers the single most important stream of quantitative information guiding the physician in diagnosis and treatment today.

This simple, but essential, aspect of biochemistry was not, however, what Charles Huggins had in mind. The great surge in biochemistry and molecular biology that has revolutionized biology since the 1940s is concerned with *what is happening* in cells. For example, we know not only the structure of the cholesterol molecule, and how to determine its concentration in tissues, but thanks largely to the work of Konrad Bloch, we know also in great detail how the molecule is built up, step by step, from simple precursors. Similarly, the biosynthesis of other major metabolites in the body—nucleic acids, proteins, carbohydrates, and lipids—has been worked out in great detail. Literally thousands of enzymes have been described that catalyze the intricate network of reactions charted in every textbook of biochemistry. What impact has this dynamic biochemistry had on the practice of medicine? As yet, surprisingly little.

We come then to the third level of biochemical investigation—how are biochemical processes controlled? And, indeed, it is here that the principal significance of *dynamic* biochemistry for medicine may be found. As we are all aware, the exploration of regulation at the genetic level is generating much excitement at the present time.

Protein Kinases in the Regulation of Metabolism and Cell Growth

I should like to consider briefly, and as a nonexpert, two aspects of the study of the biochemical mechanisms of regulation that appear to be of special promise and significance for medicine. The first of these is the posttranslational modification of enzymes in other proteins by phosphorylation. This topic has been the subject of recent admirable reviews by Cohen (1) and by Flockhart and Corbin (2).

Protein kinases were first discovered in liver in 1954 by Burnett and Kennedy (3). The classic work of Krebs, Fischer, and Larner in the period 1955–1970 established that the phosphorylation of enzymes of glycogen metabolism played an essential role in their regulation. Figure 1 summarizes these early findings. As is now well known, the enzyme glycogen phosphorylase is activated by phosphorylation on a serine residue in each of its identical subunits. The protein that catalyzes this phosphorylation (phosphorylase kinase) is itself subject to regulation by phosphorylation,

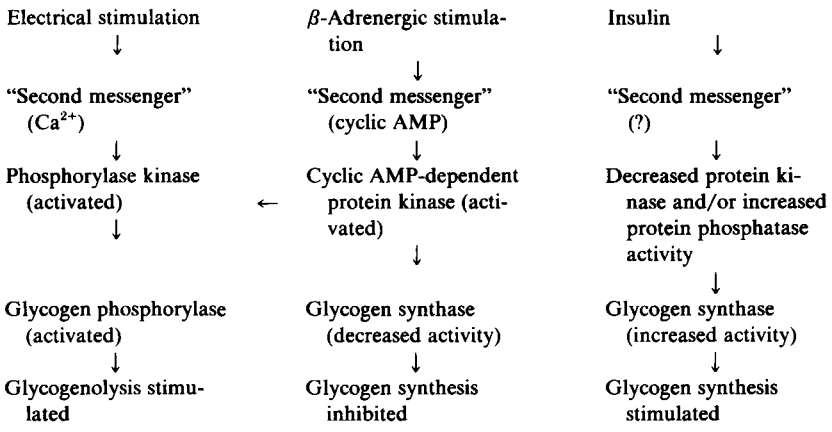

FIG. 1 Knowledge of the neural and hormonal control of glycogen metabolism in mammalian skeletal muscle up to 1970.

as part of a complex cascade of reactions, in which hormonal or neural signals are amplified and transduced.

The work summarized in Fig. 1 became one of the cornerstones of modern biochemistry, leading to the development of the concept of "the second messenger" and the recognition of the vital role of cyclic AMP and cyclic GMP in regulating protein kinases. More recent work has greatly extended the generality of the importance of protein kinases and has made it clear that the phosphorylation of proteins is one of the most general and powerful regulatory mechanisms functioning in mammalian cells. Table 1 from the recent review of Flockhart and Corbin (2) lists some of the properties of known protein kinases. Of these enzymes, kinases phosphorylating tyrosine residues (rather than serine or threonine) are currently attracting much attention. The transformation of cells in culture, both mammalian and avian, by the Rous sarcoma virus requires the function of the product of the *src* gene. This gene product has been identified as a phosphoprotein of molecular weight 60,000, designated pp60*src*. The pp60*src* protein appears to be a kinase that phosphorylates proteins on tyrosine residues. Untransformed, uninfected cells contain a protein closely similar to pp60*src* but at a much lower level than virally transformed cells, so that the possibility must be considered that the process of transformation is dependent upon the level of this protein kinase in cells. It is known that the transformation of avian and mammalian cells by the virus correlates with a five- to tenfold increase in the level of phosphotyrosine in cellular proteins.

TABLE 1
Purified Protein Kinases (February 1982)

Protein Kinase	Monomer Molecular Weights	Subunit Structure	Autophosphorylated Subunits	Km for ATP
cAMP-dependent type I	49,000 (R) 39–42,000 (C)	R_2C_2	C	3–15 μM
cAMP-dependent type II	54–56,000 (R) 39–42,000 (C)	R_2C_2	R,C	3–15 μM
cGMP-dependent	74–81,000 (E)	E_2	E	10–20 μM
Phosphorylase kinase	118–145,000 (α) 108–128,000 (β) 41–42,000 (γ) 17,000 (δ)	$(\alpha\beta\gamma\delta)_4$	α,β	200–400 μM
Myosin light chain kinase	77–125,000 (M) 17,000 (C)	MC	M	50–300 μM
Hemin-dependent eIF-2α kinase	80–95,000		+	
dsRNA-dependent eIF-2α kinase	67–70,000		+	
Casein kinase I	37–42,000	Monomer	+	13–200 μM
Casein kinase II	42–44,000 (α) 38–40,000 (α') 24–26,000 (β)	$\alpha\alpha'\beta_2$	β	4–10 μM
Viral tyrosine kinase I	60,000		+	
II	120,000		+	
III	85–142,000		+	
EGF-dependent tyrosine kinase	150,000 (E)		E	
Pyruvate dehydrogenase kinase	50,000			
Insect cyclic nucleotide-dependent protein kinase	180,000 (I)	I_2		86 μM
Rhodopsin kinase	50–52,000	Monomer		8 μM

From Flockhart and Corbin (2) with permission of authors and publishers.

Further dramatic evidence that the phosphorylation of tyrosine residues in proteins is involved in the control of biochemical events that lead to cell growth and multiplication has come from the finding that the receptor for the epidermal growth factor appears to be a tyrosine protein kinase. The epidermal growth factor stimulates the growth of a variety of cell types in culture. The finding that it activates a protein kinase that phosphorylates tyrosine residues reinforces the idea that the modulation of enzyme activity by such phosphorylation is crucial to the regulation of cell growth and proliferation.

Also, notable in the list of protein kinases in Table 1 is the double-stranded RNA(dsRNA)-dependent protein kinase. This enzyme phosphorylates the eukaryotic initiation factor eIF2α. Phosphorylation inac-

tivates the initiation factor and thus regulates protein synthesis. Treatment of cells with interferon greatly increases the amount of dsRNA-dependent protein kinase (4). This protein kinase may therefore play an important role in the antiviral function of interferon.

Receptor-Mediated Endocytosis

A second major development in the study of the biochemical basis of the regulation of cell activity has come from the work of Brown and Goldstein (5). In a series of elegant investigations, these workers have provided evidence for the model of regulation of cholesterol biosynthesis indicated in Fig. 2. In this model, low density lipoproteins (LDL), with their cargo of cholesterol esters, interact with specific receptors in the target cell. These LDL receptors are not randomly distributed over the cell surface. They are present in specific regions, described as coated pits, which can be visualized in the electron microscope. Coated pits cover only 2 percent of the cell surface of fibroblasts, but 50–80 percent of the LDL receptors are localized in these areas. As a result of the interaction of the LDL with the receptor, the complex is internalized, and coated vesicles appear in the cytoplasm. The fuzzy coat of these vesicles is composed predominantly of a protein of molecular weight 180,000, discovered by Pearse and her collaborators (6) and named clathrin. The coated vesicles containing the

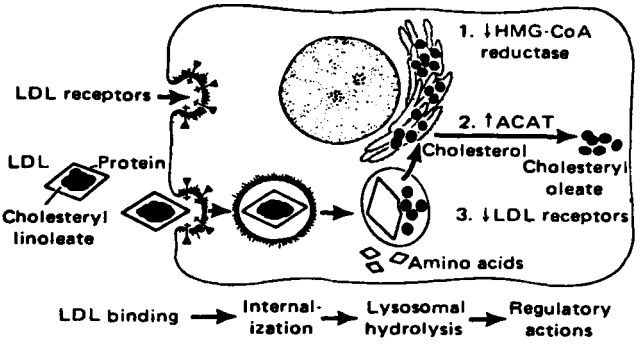

FIG. 2. Sequential steps in the LDL pathway in cultured mammalian cells. HMG-CoA reductase denotes 3-hydroxy-3-methylglutaryl-coenzyme A reductase; ACAT denotes acyl-CoA:cholesterol acyltransferase; vertical arrows suggest regulatory effects. Proposed mechanism by which LDL receptors become localized to coated pits on the plasma membrane of human fibroblasts. The sequential steps are as follows: 1) synthesis of LDL receptors on polyribosomes; 2) insertion of LDL receptors at random sites along noncoated segments of plasma membrane; 3) clustering of LDL receptors in coated pits; 4) internalization of LDL receptors as coated pits invaginate to form coated endocytic vesicles; and 5) recycling of internalized LDL receptors back to the plasma membrane. From Brown and Goldstein (5) with permission of authors and publishers.

internalized ligand rapidly fuse with lysosomes in which the apoprotein of LDL is hydrolyzed to amino acids, while the cholesterol esters are converted to free cholesterol, which is liberated into the cytoplasm. The cholesterol so made available to the cell can be used for cellular functions. The level of activity of hydroxymethylglutaryl coenzyme A reductase, the first enzyme in the biosynthetic sequence leading to cholesterol, is greatly reduced by complex feedback mechanisms still not clearly understood. As a result of this process of receptor-mediated endocytosis, the number of LDL receptors themselves is also down-regulated, further shutting off the entry of LDL and its cargo of cholesterol into the cell.

The development of the receptor-mediated endocytosis model appears to be of great significance, not only for an understanding of the mechanism of regulation of the biosynthesis of cholesterol, important as that may be to the clinician. It appears probable that a number of hormones, including insulin, the epidermal growth factor, and chorionic gonadotrophin, may be internalized as the result of the interaction of the hormones with specific receptors in the outer membrane of the target cell. Further, it seems likely that the coated vesicles that play an essential role in the LDL receptor-mediated system also may function more generally for the translocation of proteins through the cytoplasm (6).

It is clear from these two examples alone that an explication of the mechanisms of cell regulation at a biochemical level will be of the greatest significance to medicine. The task of the physician is much more difficult than that of other biologists, because the physician must not only understand what is going on in living systems, but must also intervene. Effective intervention is in turn dependent upon an understanding of the molecular basis of the regulation of cell growth and function, a pattern that is only now beginning to emerge.

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BIOCHEMISTRY IN BIOMEDICAL EDUCATION

ALBERT L. LEHNINGER

I should like to pass along some reflections on biochemistry and the medical curriculum, present and future. First, I shall examine briefly the state of biochemical science today and where it is going, at least as I see it in my crystal ball. Then I shall examine teaching of biochemistry in the undergraduate and medical curricula, where I believe we shall and must see change and progression. My viewpoint will in many ways be similar to that of Dr. Eugene Kennedy, since both of us have had the responsibility of departmental leadership and have survived many curricular twists and turns. But perhaps I can add another point of view, which arises from having written several textbooks of biochemistry, primarily for undergraduates, the most recent published just weeks ago. These efforts have led to many invitations to lecture and visit with undergraduates in a variety of colleges and universities and have given me, perhaps, a more comprehensive view of biochemical education.

ALBERT L. LEHNINGER completed undergraduate studies at Wesleyan University, Middletown, Connecticut, after which he earned a Ph.D. in biological chemistry at the University of Wisconsin. His early research was on the oxidation metabolism of ketone bodies and fatty acids. His more recent research is concerned with mitochondria and bioenergetics. He moved to the University of Chicago in 1945 to work under Charles Huggins for three years. This was followed by a year in Europe on a Guggenheim fellowship at Trinity College, Cambridge. In 1952 Dr. Lehninger was selected to be DeLamar Professor of Physiological Chemistry and Director of the Department at Johns Hopkins University School of Medicine. In 1963 he returned to England as Visiting Professor, Guy's Hospital Medical School, London, and in 1964 was again a Guggenheim Fellow in Europe. In 1978 he became University Professor of Medical Science at Johns Hopkins. Dr. Lehninger has received six honorary degrees in the United States and other countries. His textbooks of biochemistry are considered classics in the field.

At this conference I do not need to provide extensive data to support the conclusion that there have been extraordinary advances in biochemical science in the last two decades, as well as my view that there are many, many more advances to come. This already appears to be acknowledged in the program of this conference, since the traditional preclinical medical sciences are represented here by two biochemists and two molecular biologists. Although other preclinical sciences have also seen enormous progress, particularly immunology, endocrinology, and neurobiology, this has very largely been the outcome of the application of biochemical reasoning and methods. The new discoveries in gene and chromosome structure and the astonishing successes in cloning and study of recombinant DNAs are, of course, the most visible of the recent advances in biochemical science. But there have also been major but less heralded advances in other areas as well: in the biochemistry of membrane structure, in active transport mechanisms, in cell bioenergetics, in verification of the concept of the cytoskeleton and the identification of its increasingly numerous components, and in the regulation of cell metabolism, which, as Dr. Kennedy has pointed out, is accomplished by very sophisticated molecular mechanisms operating in principle like digital control networks. Moreover, powerful new biochemical or molecular tools have emerged: affinity chromatography, radioimmunoassay, high performance liquid chromatography, high resolution NMR, ENDOR and EXAFS, monoclonal antibodies, new x-ray methods, and new kinds of probe molecules that can reach into cells and indeed into enzyme-active sites, all of these powerfully aided by computer technology. The scope of biochemical research has also vastly broadened. Twenty years ago *Escherichia coli* cells and rat liver fractions were the major study objects of biochemists, but today, important new biochemical information and principles are emerging from molecular study of such exotic organisms as *Dictyostelium discoideum*, *Xenopus laevis*, *Electrophorus electrophorus*, and *Hemophilus influenzae*.

Another outcome of the last decades is the ever-tightening web of interlinking observations and interconnecting biochemical relationships. More and more often we see springing into view hitherto unsuspected relationships between very fundamental laboratory findings and clinical problems. Thus I find my own research at an interesting juncture. Most of my research has been concerned with the biochemistry and biophysics of energy transduction in the membranes of mitochondria of the liver and heart, an area of what we might call pure research, with little practical application to medicine. But in the last few years pursuit of this trail has led to study of Ca^{2+} and phosphate transport into respiring mitochondria, and, of all things, the salvage of Ca^{2+} from the exoskeleton of the blue crab *Callinectes sapidus* during ecdysis. These events, in turn, led us to

identify a substance, 3-phosphocitrate, first in mitochondria from the hepatopancreas of the blue crab and later in human body fluids, that is now of potential clinical interest, since it prevents pathological calcification of the kidney and other soft tissues in animal models. Moreover, the lead time between fundamental biochemical discovery at the laboratory bench and application in clinical medicine is becoming ever shorter. And I might add that, increasingly, we are seeing biochemical discoveries coming out of clinical departments.

I believe we are now in a transition period in biochemical research. The past decades have been largely focused on the biochemistry of cells, and, increasingly, on eukaryotic cells. What I foresee in the next twenty years—and the signs of this are already plentiful—is a rapid and extremely rewarding penetration of biochemical science into tissue and organ systems, and, indeed, into the dynamic biology of whole organisms. The new organismic or physiological biochemistry will surely be very complex; hard-slugging pick-and-shovel work may be needed before rich new insights emerge. Molecular endocrinology is already undergoing profound developments. The new science of "receptorology" will certainly continue to progress with the discovery of many new kinds of cell surface receptors and different kinds of molecular signaling between organs. Cell surface and connective tissue biochemistry, once and perhaps still a jungle, will be attacked with greater success. The regulation of eukaryotic gene expression and the molecular biology of tissue and organ development, although mysterious and complex, must inevitably yield to the new armamentarium of molecular biology. We can also see with some assurance further identification of neurotransmitter molecules and analysis of the molecular and cellular logic by which neurotransmitters and inhibitors function. Cancer cell biology and the genetics of transformation will surely begin to yield soon. And most important, biochemical sciences can be expected to penetrate much deeper into human behavior. Enrico Fermi once said he disliked making predictions, especially about the future. But I feel very comfortable predicting a new golden age in biochemical science, which I believe will bring far greater illumination to problems of human physiology and disease than we have seen in the past two decades.

Now let us have a look at the teaching of biochemistry to young medical students during whose active careers all these advances are likely to occur. Here I must express some disappointment in our efforts to bring to them not only the fundamentals of the *presently known* part of biochemistry (perhaps 3 percent of what there is to know?) but especially the excitement inherent in the biochemistry yet to come in their lifetimes. To get some perspective, let us stand back and look at biochemical education in the past and present. Two decades ago I was convinced, and I was not alone among biochemists then, that the study of biochemistry should not

be undertaken by undergraduates until after considerable grounding in chemistry, as well as physics and mathematics. I felt then that biochemistry should be a graduate subject, to be built on the firm foundations of classical chemistry. But today I have a very different view, although I cannot deny the importance of a solid chemistry base for serious in-depth study of biochemistry. Today I believe that basic biochemical principles must be taught very early to undergraduates interested in medicine or the life sciences generally, preparatory to study of the more organismic and systematic levels of biology, just as the quantitative study of physical science must begin with mathematics. The molecular logic of living cells (a term I have used in my books as a descriptor of modern biochemistry) is common to all forms of life. As such it illuminates all aspects of biological science. This is in fact now recognized, as the "old" biology gradually merges with the "new" biology. In parallel, a tremendous change has occurred in the levels at which biochemistry is taught. In the 1950s the center of gravity of academic biochemistry was in the basic science departments of medical schools. Relatively few colleges and universities offered undergraduate courses in biochemistry. But by the 1960s, when I began writing the first of my textbooks, the center of gravity in biochemistry instruction and research had already begun its shift into the arts and science divisions of universities. Undergraduate courses in biochemistry became a standard fixture in the curriculum. Moreover, undergraduate majors in chemistry or biology were often being required, or at least urged, to take a course in biochemistry. And in the last few years a third wave of biochemistry instruction has become evident, which in fact prompted my latest book: courses in biochemistry are now recommended or required for students whose primary interests are in widely diverse areas of life sciences, not only in zoology, botany, and microbiology, but also in applied areas such as nutrition, agriculture, forestry, food technology, home economics, environmental studies, marine biology, and oceanography, to say nothing of premedical and paramedical programs. Biochemistry is even taught as an honors course for seniors in some public and private high schools. On being invited to a Baltimore suburban high school to speak to a senior class in biochemistry, I was astonished to be met by over fifty students, each carrying my big book, who kept me busy answering questions for nearly three hours. Every year there are more than 17,000 new medical students in the United States, all of whom will take a required biochemistry course in the first-year curriculum. But, in contrast, it is estimated that 200,000 undergraduates in the United States are enrolled in biochemistry courses at any given time. Biochemistry is finally becoming, as long predicted, the basic language of the life sciences.

What has been most impressive to me on meeting many undergraduates

is the quite open understanding that many of them have about biochemistry—they *know* that biochemistry is the language of biology, and they find it exciting. Moreover, I have been enormously impressed with the sheer enthusiasm and deep interest in biochemistry, especially at its new cutting edges. I have found it a quite remarkable experience to watch college sophomores in biochemistry laboratory courses do cloning experiments, or measure H^+ ejection by respiring mitochondria, or simulate enzyme kinetics or metabolic cycles by computer—all with the greatest interest. And they look to new fields—to neurobiochemistry, to evolution, and to the mathematics and dynamics of cell activity, among many others. I have no fears about the future of biochemical research; there is extraordinary talent out there and a spirit of adventure.

Now let us look at the teaching of biochemistry in the medical schools. To be frank, I have been increasingly dissatisfied with the standard way in which biochemistry is placed and presented in the medical curriculum. Moreover, I believe it will become less satisfactory in the future and may not succeed in conveying to students the full future impact of biochemistry in medical science. Biochemistry is now taught in the first year and, in many if not most schools, at the beginning of the first year. And usually this is the only organized course in biochemistry in the medical curriculum. In the first two or three months of medical school, the new student is not yet settled. He has just recovered from the ferocious competition of his undergraduate years and is uncomfortably aware that more competition is yet to come, as he sizes up his new classmates. But there is another aspect of the first-year curriculum that is somewhat intimidating. Not only biochemistry must be mastered, but also, in rapid succession or simultaneously, with little opportunity for digestion and reflection, courses in cell biology, histology, gross anatomy, physiology, microbiology, medical psychology, and/or genetics, if not others. With the many new advances in these sciences, these courses have necessarily become increasingly compressed and concentrated; moreover, they are often taught in separate blocks, for sheer convenience. And as the first year goes along, medical students are often subjected, overtly or subliminally, to entreaties from the different preclinical departments as to the paramount importance of their respective disciplines in medical practice and research.

I believe there may be two fairly profound adverse consequences of these "first-months-of-the-first-year" anxieties. Although medical students can absorb large chunks of biochemistry very quickly and although they perform extremely well in examinations, I am not sure that they can see biochemistry for what it is in medicine today and what it will be in medicine of the future. Moreover, I am not sure that first-year medical students really find biochemistry to be "fun" in quite the same way that I have observed in undergraduate groups. If they do, it is "fun" in a

pressure cooker. If the present way of teaching biochemistry in medical schools is not adequate to convey the potential significance of biochemistry in the future of medicine, what is to be done? I believe there are two controlling principles. The first is embodied in the aphorism *"Repetitio est mater studii."* Constant repetition and reinforcement are, of course, the basis of learning and imprinting. Biochemistry cannot simply be dispensed in a single two-month shot; its principles must be repeatedly used and constantly reemphasized. Entering students who have already had undergraduate courses in biochemistry are, for the most part, not able to pass the final exam of a medical school biochemistry course (but then, neither are senior medical students!). Nevertheless, the undergraduate course has left a significant imprint. The second controlling principle is motivation and interest, which are not necessarily inculcated by rote learning or examinations. The intrinsic fun and excitement of biochemistry can stand on their own, if given a chance.

These principles of learning are age-old and apply, of course, to all aspects of medical education. Indeed, all of us here have a common problem: how to teach our medical students to teach themselves over a long-run future in which enormous advances in medical science are yet to come. Obviously, the teaching of biochemistry must be an ongoing thing. For some it begins in high school, for some in college. But it should be repeated and reinforced, not only in the first year of medical school, but also as an ongoing matter. Medical students will not be convinced of the worth of biochemical insights in medicine unless their subsequent teachers in the curriculum, especially their clinical teachers, employ the language and insights of biochemistry as essential components where these are appropriate.

Like many other professors of biochemistry, I have attempted over the years to introduce a second course in biochemistry, later in the medical curriculum. These attempts have inevitably foundered on scheduling complications and, of course, competition for time. Finally, a dozen years ago the opportunity arose to teach biochemistry to first-year students in two doses. Our first or basic course in biochemistry is taught in a nine-week block at the beginning of the first year. It officially assumes no previous biochemistry preparation, but since about 70 percent of our students have already had some sort of course in biochemistry or molecular biology, it moves along at a fairly brisk pace. Those students with a substantial undergraduate course in biochemistry attend the same lectures, if they wish, but have been put into an advanced ("Track II") section for twice-weekly intensive conferences. The second course in biochemistry comes in the last quarter of the first year, separated by several months from the basic course. It therefore comes after students have had the fundamentals of anatomy, histology, and physiology. The basic lingo has

been learned, and many human pathologies have already been touched upon, even though only lightly. The second segment of our course is required of all students and is taken concurrently with part of the physiology course. Coming in the last two months of the first year, when medical students are much more relaxed and comfortable with themselves and with the pace of the medical curriculum, our second course in biochemistry has been very well accepted. It has met two or three times a week for lecture and open discussion periods. As the vehicle, we have selected a series of major health problems, not the smattering of exotic genetic diseases that we, like many other biochemistry teachers, emphasize early in the year for their didactic value. These topics have varied somewhat but have included (*1*) the cluster of plasma lipoproteins-lipoprotein receptors-atherosclerosis-ischemia and bioenergetics, (*2*) the biochemistry of alcohol metabolism and alcoholism, including recent research on the isozymes and genetics of alcohol metabolizing enzymes, (*3*) some nutritional biochemistry problems, and (*4*) the biochemistry and molecular biology of cancer. We are not trying to teach pathology or diagnostic biochemistry. Rather we have tried to define the biochemical aspects of these pathologies and to outline current biochemical research approaches to an understanding of these conditions. Although we have given no examinations in this course, we have had excellent attendance and, indeed, student requests for more of the same. With much of the pressure off, it has been possible to convey some of the excitement of biochemistry in the study of major problems in medicine. What I wish to emphasize is that the disease problems we have selected also provide a very effective vehicle for review and reinforcement of basic biochemistry. Each of these series opens with a brief orienting description of the disease situation and its gross pathology. The biochemical aspects are then examined against the backdrop of normal biochemical function. Current biochemical research approaches to the problem are then examined. This has provided an extremely effective way of teaching "normal" biochemistry, while at the same time whetting interest in future developments. For example, in the four-lecture series on cancer biochemistry we examine the biochemistry and molecular biology of the malignant transformation and the role of reverse transcriptases in viral carcinogenesis. We then examine the enzymatic and regulatory mechanisms of glycolysis and respiration, the fundamental bioenergetics of cells, and expression of the genes for fetal isozymes and other anomalous proteins. The biochemical aspects of carcinogenesis by ultimate nucleophiles are also examined. Thus, this series of discussions on cancer biochemistry, presented nowhere else in the curriculum, brings back and reinforces basic biochemical principles in an active, pointed way.

Medical students today are keenly interested in nutrition, whereas ten

or twenty years ago they were totally unimpressed. We have discussed current investigations of the biochemical aspects of nutrition, as well as the interplay between nutrition and genetics. It is one thing to instruct students that many enzymes contain zinc, but the essentiality of zinc in nutrition becomes much more vivid through the story of gustin and the role of zinc in smell and taste reception. Zinc nutrition also brings into the picture the biochemistry of pollution via metallothionein and its role in buffering trace metal toxicity. But let me put another kind of bottom line on this experience. What has impressed me is that in this second part of our biochemistry course I have seen more of the spontaneous interest and enthusiasm that is so evident to me when I talk to undergraduate groups.

Finally, I should like to stress the salubrious importance of the tools and insights of biochemistry in the teaching and research programs of clinical departments. This is one of the important vehicles for reinforcing house officers' and young faculty members' interest in biochemical approaches. Biochemical insights can be brought into the research program of clinical departments not only by biochemists but also by clinically trained researchers and teachers. As a veteran of six years in a department of surgery, I can see a very great potential for biochemistry in clinical departments, which all too frequently is not fully developed or exploited. The major problem, of course, is the anomalous or dead-end situation of Ph.D. biochemists in the academic structure of clinical departments and the very fragile funding available for such appointments. Here is a problem that seriously threatens the continuity of biochemical teaching in the medical curriculum of the future. We must find ways to support careers for biochemists and, indeed, other basic scientists, in clinical departments, against the backdrop of increasingly scarce funds.

REPRODUCTIVE BIOLOGY AND MEDICINE: A UNIQUE MARRIAGE

ROBERT B. JAFFE

Since reproductive biology is at the cutting edge of contemporary scientific investigation, it is small wonder that individuals with the finest medical and scientific minds are electing careers in this exciting discipline. And the ability to translate basic scientific observations in reproductive and developmental biology into biomedical application is almost without parallel.

During this presentation, I should like to focus upon four major areas of reproductive and developmental biology. These are: (*1*) fertilization and the cell biology of embryonic growth and development; (*2*) biochemical genetics; (*3*) factors involved in the initiation of parturition; and (*4*) hypothalamic gonadotropin–releasing hormone. I shall discuss briefly the subject matter of the first three of these, fertilization and embryonic development, biochemical genetics, and the initiation of parturition, and point out their application to biomedical problems. I then will elaborate upon the fourth area, that of hypothalamic regulation of the pituitary-gonadal axis, and indicate in somewhat more detail how basic biochemical

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ROBERT B. JAFFE completed his undergraduate and medical education at the University of Michigan in 1957 with the M.D. degree, after which he served as intern and resident in obstetrics and gynecology at the University of Colorado Medical Center. He also spent one year as a U.S. Public Health Service postdoctoral fellow in endocrinology in the Department of Internal Medicine. In 1963–64 Dr. Jaffe was a postdoctoral fellow in reproductive endocrinology at Karolinska Sjukhuset, Stockholm. In 1964 he returned to the University of Michigan as assistant professor and in 1971 became full professor of obstetrics and gynecology. Dr. Jaffe moved to the University of California, San Francisco, in 1973 as Chairman of the Department of Obstetrics, Gynecology and Reproductive Sciences, and Physiology. He is also Director of the Reproductive Endocrinology Center at the University of California. Dr. Jaffe's chief research concerns endocrine aspects of reproductive biology.

and physiologic observations in this area are opening the door to a wealth of clinical therapeutic modalities.

Fertilization and the Cell Biology of Embryonic Growth and Development

It was appropriate that a January cover story in *Newsweek* entitled "How Life Begins" was subheaded "Biology's New Frontier." In that and other news magazines, as in many current scientific journals, the story of how fertilization and early embryonic development occur, and of the molecular mechanisms that underly these processes, is rapidly unfolding. Knowledge concerning cell, tissue, and organ biology is accumulating at an explosive rate. This new knowledge includes the process by which one of millions of sperm penetrates the ovum using digestive enzymes that alter the ovum's surface so that no additional sperm can enter; the manner in which cells communicate with each other; the various local and humoral factors controlling growth; the architecture and composition of the extracellular matrix on which cells grow and which influences their size, morphology, and function; and the choreography of nerve cell movement, communication, and interaction. Indeed, contemporary embryology, embracing as it does the sciences of genetics, molecular and cell biology, is emerging as one of the major syntheses of the life sciences. The biomedical correlates of this burgeoning field are multiple. The past few years have seen the advent of the successful fertilization of a human ovum outside of the body and the reimplantation of the fertilized ovum into the uterus. Although there remain some problems concerning this embryo transfer, success has been achieved, both in this country and abroad, with the delivery of apparently normal, healthy children. Since it is estimated that approximately six hundred thousand women in this country are infertile because blockage of their fallopian tubes prevents passage of sperm up the tube to fertilize the ovum and passage of the egg down the reproductive tract even though ovulation occurs, this procedure, when perfected, should offer help to large numbers of previously infertile couples.

Knowledge of normal development is a necessary prelude to understanding abnormal development. Since approximately 2–3 percent of newborns in the United States have an obvious defect at birth, ranging from cleft lips and palates to missing brain tissue, information concerning normal developmental processes is of more than academic interest, as it holds the key to understanding, and therefore preventing, the mechanisms that go awry in the congenital defects so frequently encountered. Three groups of teratogenic agents have been identified: microorganisms, such as the cytomegalovirus and rubella virus; physical agents, such as heat and radiation; and chemicals, including drugs, such as thalidomide and

anticoagulants, which cross the placental barrier. Understanding precisely how these agents produce their effects will inevitably help to understand the pathogenesis of congenital anomalies and the 70 percent of birth defects of which the causes remain speculative.

Biochemical Genetics

Some abnormalities, such as some biochemical and chromosomal defects, have clear genetic causes and can be diagnosed in utero. Prenatal diagnosis using amniocentesis now is practiced widely. Biochemical genetics and the new biology are making remarkable inroads into our ability to diagnose a variety of genetic disorders. Recently, our group has been sampling fetal blood from a vessel of the fetal side of the placenta through a fetoscope, to test for thalassemia and other blood disorders (1). The development of recombinant DNA technology heralds a new era in our ability to diagnose, and ultimately treat, a panoply of medical problems. Specifically, at our institution, Dr. Y. W. Kan (2) has developed a technique, using a restriction endonuclease, that permits the diagnosis of sickle cell anemia. Thus, instead of fetal blood sampling, all that is required is a sample of amniotic fluid, which does not need to undergo culture, to confirm the presence or absence of sickle cell disease.

With these refinements in diagnosis, the next step is intrauterine treatment. Recently, successful fetal surgery has been performed at the University of California, San Francisco (3). In individuals with congenital obstruction of the urethra, reflux of urine through the ureters can destroy the fetal kidneys in utero. A successful conduit to relieve the overdistended bladder by draining it into the amniotic sac now has been developed. This prevents kidney damage and allows the urethral blockage to be corrected successfully after delivery.

On the horizon? It should be possible eventually to replace defective fetal cells by stem cell implants, since intrauterine life is a time of relative immunologic privilege for the fetus.

The field of reproductive genetics, from recombinant DNA technology to intrauterine diagnosis to fetal treatment, is a burgeoning and most exciting one.

Mechanisms Involved in the Initiation of Parturition

It may be surprising that the cause of the onset of labor in women still remains elusive, although important strides are being made. In contrast, these mechanisms have been quite well worked out in other species, particularly the sheep (4). In the sheep, it is known that the fetus provides

the signal for the initiation of labor. More specifically, the fetal adrenal gland plays a key role in this process. Steroid hormones produced by the fetal adrenal cortex increase in amount in the last few days before delivery. This increase in adrenal corticosteroids induces the maturation of an enzyme system in the placenta, which increases the amount of placental progesterone converted to estrogen, thereby increasing the ratio of estrogen to progesterone. This increased ratio triggers the increased synthesis of prostaglandin, a key factor in initiating uterine contractions. And it is these uterine contractions that bring about delivery.

The question now being asked is the extent to which these mechanisms involved in the sheep mirror the situation extant in human pregnancy. There appear to be important differences and similarities between the two species. In an attempt to approach this question in a species closer to the human, we and several other groups have been studying the fetal rhesus monkey with catheters inserted into fetal blood vessels at the time of hysterotomy, following which the fetus is replaced into the uterus (5). This permits us to sample blood from and inject substances into the fetal circulation while the fetus remains in the mother's uterus. Using this preparation, we also monitor the fetal heart rate and intrauterine pressure. In addition, my colleagues have begun to monitor uterine muscle contractions. Recently, we found that the contractions of labor in the mother, which first are observed about ten days before delivery, occur (as obstetricians long have suspected) primarily at night. Preliminary studies suggest that these labor-type contractions correlate closely with a circadian nocturnal rise in fetal, but not maternal, adrenal steroids. Thus, there may be parallels between primates and sheep, and it seems plausible that the human fetus also may control its destiny and signal the time for delivery.

Why spend all of this effort on attempting to determine the cause of labor? Among other reasons, premature labor, with its attendant respiratory distress and hyaline membrane disease, is the largest single cause of neonatal morbidity and mortality today. While premature labor occurs in only 5–7 percent of all pregnancies, it is responsible for more than 75 percent of newborn loss. Understanding the causes of normal labor is a necessary prerequisite to the understanding of premature labor. It is likely that prevention of prematurity will follow on the heels of our final resolution of the cause of normal labor in women.

Hypothalamic Gonadotropin-Releasing Hormone

Finally, let us consider the role of the hypothalamus in the regulation of the pituitary-gonadal axis. It was less than five years ago that Drs. Guillemin and Schally received the Nobel Prize for elucidating the structures of the hypothalamic substances that regulate pituitary hormone

production. One of these, a decapeptide variously called gonadotropin-releasing hormone or luteinizing hormone–releasing factor, has the capacity to release the pituitary gonadotropins that regulate the function of the ovary in women and of the testis in men. It was found that these gonadotropins were not released in a continuous fashion but rather were released in a pulsatile, or episodic, manner (6). This, in turn, was found to be due to the pulsatile release of the gonadotropin–releasing hormone from the hypothalamus.

Subsequently, largely because of the pioneering studies of Knobil and his colleagues working with monkeys (7), it was found that, if the pituitary were exposed to continuous infusions of the gonadotropin–releasing hormone, pituitary function, and hence ovarian function, would decrease because of receptor desensitization, or down-regulation. In striking contrast, if the pituitary were exposed to pulsatile or episodic administration of gonadotropin–releasing hormone, then pituitary gonadotropin stimulation could be maintained. In a related manner, when female infant monkeys received pulsatile administration of the gonadotropin-releasing hormone, they went through menarche prematurely and began to have regular menstrual cycles (8).

We have made use of these observations clinically in a variety of ways. There is a large number of women who do not ovulate because there is derangement of the normal hypothalamic regulation of their pituitary function. This may be the result of stress, rapid weight loss or gain, competitive exercise, or other factors. As a consequence of the inability to ovulate, these women are unable to conceive. Recently, it has become possible to deliver, by means of a miniature programmed pulsatile pump (9) either carried in a handbag or worn on a belt under the blouse, the gonadotropin-releasing hormone with a pulse frequency identical to that in women with normal menstrual cycles. In this manner, this "substitute hypothalamus" can induce ovulation and pregnancy may ensue. We also have had success in inducing ovulation in this way in women with delayed puberty, using much the same principle as in the infant monkey.

Clinical advantage also is being taken of the observation that continuous exposure to the gonadotropin–releasing hormone, in contrast to pulsatile exposure, shuts down the pituitary-gonadal system. Long-acting analogs of the releasing hormone now have been developed. Their ability to turn off the pituitary-gonadal system should make it possible to develop an effective novel class of contraceptive agents that does not rely on synthetic estrogen and progestin to regulate fertility in women and men. Several of us are testing these compounds now, with promising results. There also are fairly common gynecologic problems in women, such as endometriosis, which should lend themselves to this type of hormonal system suppression. Finally, in dealing with sexual precocity (i.e., when

there are premature signs of puberty), which has severe emotional as well as physical consequences, the use of the long-acting releasing hormone analog shows promise as a useful therapeutic modality.

Thus, in all of these four areas, fertilization and embryonic development, biochemical genetics, the initiation of labor, and the regulatory factors of the hypothalamus, seminal advances in the explosive fields of reproductive and developmental biology have widespread application to biomedical problems.

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THE ROLE OF THE BASIC SCIENTIST IN ACADEMIC OBSTETRICS AND GYNECOLOGY

L. MASTROIANNI, JR.

In the past two decades, the field of academic obstetrics and gynecology has undergone significant change. In earlier years, the faculty in obstetrics and gynecology were looked to primarily for their clinical skills. Little else was either expected or encouraged. The discipline was looked upon as lacking intellectual challenge, and faculty role models who emphasized research and contributed to advances in this somewhat static and standard area of practice were relatively few in number. This concept of obstetrics and gynecology was supported by a lockstep system of residency training that emphasized technical skills and clinical judgment almost exclusively. In contrast to their colleagues in medicine, pediatrics, and surgery, academic obstetricians were not expected to have developed expertise in any of the basic science disciplines related to the specialty. With few exceptions, advances in reproductive biology and endocrinology came from departments of anatomy and physiology. The basic science underpinnings of this specialty were poorly developed. Only a relatively small group of investigators in basic science departments had elected to consider

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LUIGI MASTROIANNI, JR., graduated from Yale University in 1946 and Boston University School of Medicine in 1950. After four years of training in obstetrics and gynecology at Metropolitan Hospital in New York City and a year as Research Fellow in fertility and endocrinology at Harvard, he returned to Yale in 1955 as instructor. In 1961 he moved to the University of California as Professor of Obstetrics and Gynecology and Chief of the service at Harbor General Hospital. Since 1965 Dr. Mastroianni has been William Goodell Professor and Chairman, Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine. His major research has dealt with human reproduction and embryonic development.

the mysteries of uterine function, placental blood flow, fertilization and early development, and basic mechanisms of reproductive endocrinology.

More recently, progress in the areas which fall within the purview of the obstetrician-gynecologist has been rapid. The image of the specialty has gradually changed, and the modern department of obstetrics and gynecology has taken on a new and broader role in biomedical research and education. In large measure, this change in focus was spearheaded by a general recognition of the importance to society of the broad areas of concern implicit in obstetric and gynecologic practice. There has been a gradual realization that the well-being of each individual is influenced by the environment encountered during fetal life, labor, and delivery. There was also the evolving concept that every child should be a wanted child and the recognition that methods of contraception were vital to this goal. Broader issues of population, and concern for what has been termed the "population explosion," had the greatest influence on academic development within obstetrics and gynecology. It made sense to establish systems within academia in which the basic research aspects of contraceptive development could be addressed. It was apparent that this could be accomplished most expeditiously through obstetrics and gynecology with its traditional, heavy clinical emphasis. Additional programs had to be created, however, in order to develop the persons in obstetrics and gynecology with a research orientation. This could be brought about only if faculty were released from clinical responsibilities. To address this perceived need, opportunities for training in the basic sciences had to be created and a bridge established with other disciplines in which research talent was already available. The obstetrician-gynecologist could no longer rely for progress on histology, pathologic anatomy, and mechanical physiology alone. A blending of clinical and basic science efforts was essential.

In 1957, George W. Corner, an anatomist and a lifelong investigator in the field of ovarian endocrinology, physiology of the uterus, and embryology, addressed the membership of the American Fertility Society at its annual meeting. The title of his lecture was, "Laboratory and Clinic in the Study of Infertility" (1). In his opening remarks he suggested that such a title could easily be used before any society of specialists by simply substituting another specialty for infertility. He made the point that infertility carried a peculiar significance and that the relationship between laboratory and clinic in the field of human reproduction was unique. He suggested that whereas the clinician could ask fundamental questions, answers would not be forthcoming without observations on experimental animals. Conversely, while laboratory study furnishes general principles, the special physiology and pathology of human reproduction must be reexamined and fitted into the general format of our knowledge. He stated, "In this field beyond all others in medicine, the clinician and the

basic science investigator must work together to make laboratory findings useful in practice." He concluded, "So far as I know there is not a single women's clinic in the country that has the combined man power in both basic and clinical science now possessed by many of the medical clinics and by some of the surgical departments . . ." and suggested that "the women's clinics must find ways and means to close the gap between clinical and basic science investigation."

A number of models designed to encourage collaboration between the clinician and the basic scientist have, in the past several years, been adopted in departments of obstetrics and gynecology. The role of the obstetrician-gynecologist has been expanded, and the overall function of the female reproductive tract is receiving more comprehensive attention as a result. In addition, the talents of the nonclinician are increasingly utilized, and a team approach is emphasized. This trend has had a positive effect on obstetrics and gynecology. The basic scientist working within the framework of today's academic department of obstetrics and gynecology has introduced a variety of research areas within the department. These fields encompass a number of basic science disciplines including anatomy, physiology, biophysics and biochemistry, microbiology, pharmacology, and genetics, all of which enjoy departmental status in most medical centers, but are increasingly difficult to define as single entities. For each, a viable subspecialty is created simply by using the adjective "reproductive." Through this interplay, exciting new areas of research have been opened, and medical students find obstetrics and gynecology stimulating and a veritable gold mine for productive thought and research.

The experience of the Department of Obstetrics and Gynecology at the University of Pennsylvania will be cited as an example of the trend toward multidisciplinary research in reproduction. In 1965, the department had on its faculty two full-time biochemists but no fully salaried clinical faculty practicing in the "full-time" sense. The senior of the two biochemists, Joseph Touchstone, Ph.D., had previously worked with the clinicians in the department, and together they established the importance of estriol determinations in the evaluation of fetal well-being. Dr. Touchstone had been recruited by the late Professor Carl Bachman, who, although a clinician, was a consummate biochemist in this own right. As full-time faculty were being assembled, two additional Ph.D. biochemists were recruited, whose research focus was centered on fertilization. A Division of Reproductive Biology was established with a monkey colony and an electron microscopy facility. A pathologist, trained as a fellow in the Division of Reproductive Biology, was recruited to the obstetrics and gynecology faculty with a joint appointment in pathology to direct the electron microscopy facility. In time, a biophysicist and an additional biochemist were added. Since 1970, the number of basic science faculty has ranged between seven and nine. There are two additional faculty

members with Ph.D. degrees in social sciences who are part of a developing program concerned with the social and behavioral aspects of human reproduction.

With the exception of one tenured professor, who on expiration of a National Institutes of Health career development award is now being supported by departmental endowment funds, the salaries of the nonclinician investigators are derived principally from extramural sources. The largest segment of support is from the National Institute of Child Health and Human Development (NICHD), but there has also been a substantial investment from foundations including Macy, Ford, Rockefeller, and Mellon. Over the years, the department has raised funds—principally from patients—to create an endowment. The income from this fund is earmarked for the support of basic scientists. This income is now sufficient to support somewhat more than one full-time scientist, or equivalent, and is available for use during any funding hiatus, allowing the department to guarantee continued salary support for limited time intervals. Portions of the salaries of these investigators are derived from training funds. Their role in the training of investigators, both from the United States and abroad, has been substantial. Presently, Rockefeller and Mellon funds are used for this purpose. The difficulties associated with such heavy dependence on extramural sources are immediately evident, especially in the present uncertain funding climate. On the positive side, the confidence of NICHD in the ability of these investigators has been expressed in terms of continuous support. In the light of NICHD's stringent peer review system, this support serves as mute assurance of the quality of work of the investigators in the program.

NICHD support notwithstanding, one of the principal issues surrounding the creation of a faculty position for basic scientists outside of their own discipline is quality control. Is it possible to be sure that such faculty members are not "second-raters" who might not be able to make it in a purely basic science department? Can the obstetrician-gynecologist adequately judge the talents of a biochemist or molecular biologist? The fact is that he or she cannot, at least not without help. Input from colleagues in other departments within the institution and scrupulous peer review from outside are essential if quality is to be maintained. It serves no useful purpose to hire a less-than-talented "captive" biochemist who will serve as an indentured servant to the clinician. Such a course would be self-limiting and would soon be adjudged impractical as the individual failed to compete in the market place for funding. We have addressed the problem of quality control realistically, and from the beginning we have enlisted the aid of our basic science colleagues in the recruitment and evaluation of faculty. The majority of our investigators hold joint appointments in obstetrics and gynecology and in the basic science departments

represented by biophysics, physiology, pathology, and animal biology (School of Veterinary Medicine). They are active in the teaching programs of these secondary departments. They do, however, maintain identification with obstetrics and gynecology as their home base and occupy research space in the department.

A second recurring subject of discussion concerns the appropriateness of having such a large segment of faculty on "soft" money. This structure would not be tolerated in some other institutions, especially those with financial arrangements structured through state support. The alternative for us is to forego the presumed advantages of such a faculty or to build a financial base for continued support of some faculty at the tenured level. Unfortunately, all but a small percentage of the department's budget is "soft" and is comprised largely of funds generated from practice, extramural research, and training grants. Department endowment carries an increasingly small segment of the responsibility for faculty support, and this has been eroded by inflation. Central support from the dean's budget is minimal, as, understandably, the dean must deploy resources to cover long-range commitments principally to the faculty in basic science departments. The net result at the University of Pennsylvania is the inability to create tenured positions. Clinicians move into a recently created clinician-educator track designed for those who emphasize practice and teaching, and only a few attain tenured status. The basic scientists who elect to stay in the department move to a nontenured "research track," and this decision must be made after the initial three years of assistant professorship. They may, of course, take their chances within the tenure system knowing that, at this point, a tenured position for a basic scientist in a clinical department may be looked upon with disfavor. At intervals, the status of the research track is redefined, and there is repeated emphasis on the tenuous nature of these appointments. Presently, the department has one tenured professor, four research associate professors, and three assistant professors in the tenure track among its biomedical research scientists. The four research associate professors were appointed before the system was clearly defined but were aware that they were entering a nontenure track. As our basic science faculty has evolved, two persons have moved to tenured professorships in other schools, and those who have elected to remain have passed up opportunities to move to more financially secure positions. One of the assistant professors was recently moved to a tenured position as an associate professor in a basic science department but maintains close association, including geographic proximity, with obstetrics and gynecology. Thus, while the system appears complex, it is flexible and functional. The ideal arrangement would involve a commitment of endowment income for additional tenured positions, and presently we are working toward that goal. The principal

need at this time is continued interest of the private sector in interdisciplinary efforts within the discipline of obstetrics and gynecology, without which the program could not exist.

After more than fifteen years of experience with this interrelationship between basic science and clinical medicine in obstetrics and gynecology, let us evaluate the impact of this program on the department. The substantial research productivity of the basic scientists is easily judged in terms of the number of manuscripts published in quality journals. The continued confidence of NICHD in our programs also attests to the quality of their work. Could equal productivity be maintained in another department, for example, the department of biochemistry or physiology? One problem with centering reproductive biology in a basic science department is that most are not truly multidisciplinary. The interaction among people with various backgrounds in obstetrics and gynecology has resulted in some unique approaches to common problems. Furthermore, daily interaction with clinicians creates an awareness of the practical implications of research and allows almost immediate access to human clinical material for investigation. It would be most unlikely that a basic science department would have ready access to human follicular fluid, oocytes, granulosa cells, spermatozoa, endometrium, and the like.

Another equally important function of these investigators is training. They provide a ready opportunity for interaction with clinician-investigators, who during the course of subspecialty training, move into the already established laboratory programs of the basic scientists. Quality of training is assured when such fledgling investigators are in a position to witness the efforts of first-rate scientists functioning within the structure of their own specialty and not as guests in the laboratories of other departments. The net result has been the continuous development of investigators of promise who now occupy important positions in other universities throughout the country.

The basic scientists in this department have assumed additional responsibility for training investigators from abroad, many from third world countries. This effort requires special talent and dedication and, in some cases, a great deal of patience. There is the usual language problem; there is the lack of sophistication and background. Perhaps because our basic scientists are preselected for their interests, they have accepted this challenge with enthusiasm. This willingness has created an international flavor in the department which gives our program special significance with a missionary flavor. Of special note is a Rockefeller Foundation–sponsored program designed to train investigators from Latin America. This supports a full-time, or equivalent, basic scientist and, therefore, permits substantial input from this group into the training of our Latin American colleagues. Uniformly, our Latin American colleagues have

returned to waiting positions in their home countries and have, contrary to popular belief, been able to set up laboratories which function in applied research in the reproductive sciences. Investigators from abroad have also served to create visibility for the field. Over the years, many have attained positions of leadership at home and have found themselves in a position to exercise influence in governmental policy as it pertains to family planning and reproductive health. These programs involving cooperation between basic science and clinical medicine have resulted in the training of some seventy investigators from abroad, who continue to hold academic positions, several at the rank of professor.

To assess the impact of these arrangements on our academic program, the number of publications by members of the department from 1971 through 1980 was tallied. The percentage of departmental publications on which a basic scientist appears as senior author in the years 1971–73, 1974–76, and 1977–79 was 43 percent, 44 percent, and 36 percent respectively. In these intervals the percentage of the faculty who were basic scientists ranged between 25 percent and 30 percent. A large proportion of the publications of the basic scientists were coauthored by fellows or junior clinical faculty, providing objective evidence of ongoing collaborative effort.

The program involving basic scientists in obstetrics and gynecology has been modestly expanded to include the behavioral sciences. Behavioral aspects of reproduction have generally been neglected, and their implications in clinical and research approaches to both family planning and infertility have usually been disregarded. Interdisciplinary effort would do much to advance this important area. More rapid development can best be encouraged through the creation of positions in the Department of Obstetrics and Gynecology for individuals with backgrounds in psychology and sociology, as well as establishing leadership roles for psychiatrists, with joint appointments in obstetrics and gynecology. Concomitantly, obstetrician-gynecologists should be encouraged to seek additional training in the behavioral sciences. At the University of Pennsylvania, such interdisciplinary cooperation has been brought about through the establishment of an endowed professorship—The Stuart and Emily B.H. Mudd Professorship of Human Behavior and Reproduction. The programs of the Mudd Professorship are being developed along interdisciplinary lines.

The problems that such interdisciplinary programs in human reproduction now face are immediately evident. They are principally financial and will become more acute in times of economic uncertainty, as there is decreasing support for research in general, including reproductive biology and endocrinology. At this point, there are all too few obstetrician-gynecologists with a reasonable research background. The pressure to

generate funds from practice in academic institutions makes these persons an endangered species. Although the role of the basic scientist in their training is pivotal, systems must be developed to permit some clinician-investigators in obstetrics and gynecology to devote substantial portions of time to research. Central to this effort is the continued recognition of the importance of research and training in reproductive biology and endocrinology.

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PUBLIC HEALTH AND PREVENTIVE MEDICINE

ROBERT W. DAY

Opportunities for graduate education in public health, as in the other health professions, have expanded markedly during the past thirty years. Federal support has been of long duration, and continues, but in reduced amounts. The future for schools of public health appears promising.

This paper addresses several specific issues considered pertinent to the present and future of schools of public health. Material is presented describing the past and present status of the schools. Both curriculum and derivative descriptions of the thrust of public health graduate education are set forth in the context of a definition of public health.

Graduate public health education is a much-studied subject. The Milbank Memorial Fund Commission document, *Higher Education for Public Health* (1), published in 1976, provided descriptive, historical, and normative judgments about the field. Passage of the Health Professions Educational Assistance Act of 1976 (P.L. 94–484) codified reporting about the schools (2). These sources of information, when coupled with data collected by the American Public Health Association since the early 1960s, provide information about the schools (3). Other publications contain both normative and descriptive content (4, 5).

ROBERT W. DAY completed his undergraduate education at Harvard and at the University of Chicago. He took his medical training at the University of Chicago where he received his M.D. in 1956. He then attended the School of Public Health of the University of California, Berkeley, where he earned an M.P.H. in epidemiology in 1958 and a Ph.D. in 1962. After five years as a faculty member at the Berkeley school, in 1968 he moved to the University of Washington as Associate Professor and Head, Division of Health Services, Department of Preventive Medicine. In 1970 Dr. Day joined the new School of Public Health and Community Medicine, University of Washington, as Head of the Department of Health Services, and since 1972 has served as Dean of that school.

I will first briefly review the history of and give current descriptive information about these institutions. Figure 1 gives the location of the 23 presently accredited schools of public health. The schools are located roughly in proportion to the distribution of the population. Many of the schools are important to the region in which they are located. Regional functions include consulting and other forms of support to public health agencies, training of students from the region, providing continuing education, and conducting research and demonstrations on matters of regional importance. Among the 23 schools, 8 are located in private universities and 15 in public institutions. Fourteen of these institutions are members of the Association of American Universities (AAU).

Table 1 shows the year in which each school was established. Three predate 1940, 8 were established in the 1940s, and the remaining 12 are relatively new, established between 1960 and the present.

Figure 2 shows the enrollment trends in the schools, 1960 to the present. Total enrollments have more than quadrupled, and new admissions tripled during that time. Table 2 provides information on the range of enrollments for the schools, 1980–81.

Between 1930 and 1935 the several schools of public health graduated approximately 90 students per year. Between 1975 and 1979 this number had increased to slightly more than 2,700 graduates per year. Table 3 provides information on the proportion of graduates in each of the several specialties represented among the schools for the years 1961–62, 1971–72, and 1978–79.

The Association of Schools of Public Health, by contract with the federal government and through its own auspices, collects basic information on students, faculty, and the schools. The recent expenditure data is of interest. Between 1974–75 and 1979–80, approximately 38 percent of funds were received from the institution in which the school was located, 17 percent from federal training sources, and approximately 30 percent from federal research support. In 1979–80, total expenditures per school ranged from $2.4 million to $3.1 million. The comparable figures in 1960 were $240,000 to $3.1 million. In 1960–61, the average proportion of support derived from all sources for research activity was 40.4 percent. The comparable figure in 1979–80 was 35.1 percent.

Table 4 provides a ranking of the schools according to the amount of federal research expenditures, 1979–80, as a function of reported enrollments. Only those schools established at least ten years previously and which were members of AAU institutions were included. The schools were separated into four groupings, differentiated by an average of an order of magnitude.

Predicting future trends in enrollments and in research support is difficult. Certain areas of study and research, as well as practice, appear susceptible to changing public priorities.

FIG. 1. U.S. schools of public health, 1982.

TABLE I

*U.S. Schools of Public Health, by Year of Origin and Type of Institution**

Year Established	Number of Institutions		Total
	Private	Public	
1910–1919	3	—	3
1920–1929	—	—	—
1930–1939	—	—	—
1940–1949	3	5	8
1950–1959	—	—	—
1960–1969	—	5	5
1970–1979	—	5	5
1980–	1	1	2
Total	7	16	23

* Association of Schools of Public Health data collection project.

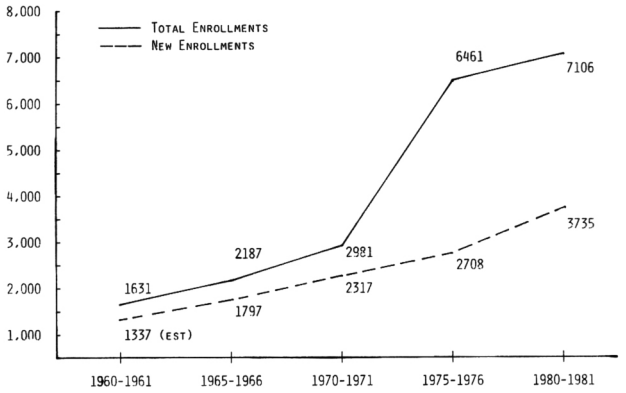

FIG. 2. New and total enrollments in schools of public health, 1960–1979. Adapted from reference 3.

The present 23 schools of public health are diverse in size and vary in the amount of research support received (range, from approximately one-third to less than one-twentieth of total expenditures). Both the number of schools and total enrollment have increased markedly. Support from the parent institution is generally small (range, from 50 percent for several of the newer and smaller schools to 10–15 percent for some of the more established, older schools).

The Milbank Report (1) defined public health as follows:

> Public health is the effort organized by society to protect, promote, and restore the people's health. The programs, services, and institutions involved emphasize the prevention of disease and the health needs of the population as a whole. Public health activities change with changing

technology and social values, but goals remain the same: to reduce the amount of disease, premature death, and disease-produced discomfort and disability.

TABLE 2

*Distribution of U.S. Schools of Public Health by Numbers of Enrolled Students and by Type of Institution, 1980–81**

Enrollment	Number of Institutions		Total
	Private	Public	
0–99	—	3	3
100–199	1	2	3
200–299	3	1	4
300–399	1	4	5
400–499	1	1	2
500–599	—	1	1
600–699	—	2	2
700–799	1	—	1
Total	7	14	21

NOTE: Two newest schools not included.

* Association of Schools of Public Health data collection project.

TABLE 3

*U.S. Schools of Public Health, Graduate Degrees Awarded by Specialization at 1961–62, 1971–72, and 1978–79**

Area of Specialization	Percentage Distribution by Year		
	1961–62	1971–72	1978–79
Biomedical and laboratory sciences	4.1	3.1	3.1
Biostatistics	4.6	5.2	4.7
Environmental sciences	13.0	15.2	15.3
Epidemiology	13.1	6.2	12.2
Health education	9.3	7.9	6.1
Health services administration	30.1	30.0	26.0
Nutrition	3.5	3.0	5.6
Occupational safety and health	6.2	0.1	0.7
Public health practice and program management	15.3	13.9	9.6
Other	0.8	15.4	16.7
Total	100.0	100.0	100.0

* Adapted from reference 3.

Briefly, the patterns of illness and mortality among the population in the United States have changed remarkably in the more than sixty years that have elapsed since the first school of public health was established at Johns Hopkins University. Life expectancy at birth has increased. Today

TABLE 4
*U.S. Schools of Public Health: Ranking by Federal Research Expenditures per Student, 1979–80**

Federal Research Expenditures per Student	Number of Schools
>$30,000	1
$13,500–$15,500	4
$4,300–$6,700	7
<$3,000	2

NOTE: Includes only schools established more than ten years which are members of the Association of American Universities.
* Association of Schools of Public Health data collection project.

the chronic diseases predominate. Technological advance has accompanied the development of a large number of well-trained and well-equipped health professionals. Public expectations of better health, certainly of less disease, are now coupled with various mechanisms by which the very high "sickness bill" is paid. The impressive advances brought about by biomedical research give the promise of even more and better treatments. The health care industry has become one of the largest and most pervasive in our society. Attention of the general public, and those elected as their representatives, has turned more and more to matters of personal and public health.

Amid these changes, the schools of public health have adapted to changing circumstances. The contributions of public health science are well recognized. Epidemiology and biometry focus on groups or populations as the object of study, complementing and supplementing both basic biomedical and clinical understandings of the nature of health and disease. The impact of the "first public health (epidemiological) revolution" is both understood and appreciated. The potential of the second such revolution, defined as the amelioration if not the conquest of the chronic ailments, now receives greater attention. This second era is rapidly being redefined as the time in which health will be promoted (6). The technology is imperfect. The approach is different. New knowledge is very much needed as are techniques by which that new knowledge can be applied.

Nonetheless, the concept that individuals can be healthier appears to have broad appeal. Epidemiological and other evidence suggest that life style and environment are important determinants of health outcomes. The sciences unique to public health offer important techniques for understanding associations between these factors and means of evaluating intervention measures.

Curriculum in schools of public health parallels the range of academic concentrations shown in Table 3. At minimum, the schools offer degree

programs in biostatistics, environmental health, epidemiology, and health administration. Most have concentrations in the behavioral sciences. Many provide instruction in specific program areas (e.g., maternal and child health, dental public health) and in public health aspects of broad fields such as nutrition.

While the schools have always stressed community-based preventive approaches, often environmental in nature, future curriculum will undoubtedly incorporate more emphasis on changing individual behaviors in directions increasingly understood to enhance health.

Federal support for graduate education in public health dates to 1956. At that time the Hill-Rhodes Act was passed, making available traineeship support to students. Several years later this authority was broadened to include institutional support, apportioned to the schools on a formula basis, the formula incorporating both a base uniform payment for each school that qualified, as well as varying sums depending upon enrollment. These support authorities were subsequently broadened to include monies for special projects that enhance educational programs—projects deemed to be in the national interest.

With the passage of the Health Professions Educational Assistance Act of 1976, schools of public health became eligible for capitation. Both the traineeship and special project authorities were continued. In the Reconciliation Act of 1981, capitation and traineeship authorities were continued and reauthorized for an additional three years.

Federal support to the schools and to their students has thus persisted longer, and was originated sooner, than that to other health professional schools. Congressional action reflects certain of the unique properties of education for public health. These include:

1. Many students enter careers in public health after having received basic training in one of the health professions or an allied field. The cost of further education is substantial.
2. There has been and remains a shortage of public health personnel. It is in the national interest to alleviate this shortage.
3. Many who elect public health choose careers that in general are lower paying than careers in the other health professions. This is particularly true of individuals with prior health professional training who subsequently specialize in one of the areas of public health.
4. Graduates of schools of public health carry out mandates of government at local, state, and federal levels (7). A supply of public health manpower is required to assure that legislative intent is effected.
5. The overwhelming majority of graduates of schools of public health are employed in the public sector, or in voluntary and nonprofit agencies and institutions (7).
6. There are few schools of public health. The schools represent a regional resource.

Additionally, the importance of public health—the preservation and the promotion of health—has been recognized as a public good. It is thus in the interest of government to assure a supply of competent and suitably trained individuals.

The future of federal support for public health graduate education is uncertain. However, the issues confronted by those trained in public health and practicing in this field are to a high degree intractable. Containing costs of health care, rationalizing the use of health care resources, and maintaining safe environments are problems that defy simple answers, relegation to private sector solutions, or technological mastery. When health promotion is added to the required maintenance of basic public health services, the need for schools of public health and their graduates will likely require some forms of continuing public assistance.

A significant proportion of training in public health takes place outside of schools of public health (1, 2). Residency training in preventive medicine is shared between the schools of public health, departments of preventive medicine in schools of medicine, health agencies, and industrial and military settings (8). Education for health administration is often conducted in joint arrangements between schools of public health and other institutions such as graduate schools, and schools of business, public administration, and medicine.

While the number of physician students in schools of public health averages slightly less than 10 percent, physician manpower in public health and preventive medicine is considered an important resource. For example, the Graduate Medical Education National Advisory Committee proposed this specialty as one of the few estimated shortage areas in 1990.

In 1979, residency training in preventive medicine was provided in 73 settings. The subspecialty of general preventive medicine was available in 21 medical schools, 7 schools of public health, and 5 federal facilities. Public health training was available in 9 health departments, 3 schools of medicine, 1 school of public health, and 1 military installation. Occupational medicine postgraduate education was available in 8 schools of medicine, 3 schools of public health, and 2 federally supported regional laboratories, while in-plant experience was available in 1 federal establishment and 9 corporate settings. The fewest training opportunities were available in aerospace medicine, 1 in a school of medicine and 2 under auspices of the military. All residency programs include an academic year offered by a school of public health or a department of preventive medicine.

One particular shortage area is physician faculty in schools of public health.[1] In 1977, 22 percent of faculty in schools of public health were

[1] William Bridgers, personal communication.

physicians, while in 1981 this proportion had declined to 19 percent. However, 80 percent of physicians in 1977 held ranks of professor or associate professor contrasted with 87 percent in 1981. This increased "aging" of the physician faculty in schools of public health is underscored by an examination of the number of physicians at the rank of assistant professor. In 1977, there were 50 in the 20 schools of public health, and in 1981 this number had declined to 30 in the then 22 schools reporting. Half of the schools had no physicians at entry-level rank. With such a trend, by or before 1990, it may be expected that there will be no physician junior faculty members in the schools of public health. Similarly, the numbers of physicians at the higher academic ranks will have declined. This trend points to a need for specific programs that will enhance the recruitment (and retention) of young physicians who enter academic careers in schools of public health. While data for the departments of preventive medicine are not available, a similar trend may emerge. The situation is particularly unfortunate when the new priority areas in public health are considered. Emerging emphasis on health promotion and health behavior, continuing and ultimately enhanced interest in the safety of the environment, and the need for those well-trained in medical sciences as well as public health who can assess health care technologies, and in other ways perform research and provide the intellectual leadership necessary in rationalizing the use of health care resources—all represent areas that require specifically trained physician manpower.

During the coming decade, both similarities in and differences between public health and medical school approaches to the emerging interests in health promotion may represent possible areas of conflict. Further, interest in health promotion is already evident and has often been of long-standing importance in the curriculum of several of the other health professional schools, e.g., nursing and social work. How such potential conflict is perceived and managed will have implications for relationships between the health professional schools and, importantly, for the research progress made in this emerging and high priority area.

The schools of public health have expanded markedly during the past several decades. Numbers of students, of graduates, and of schools have all increased. Rough estimates of future requirements for public health manpower currently show a continuing shortage. Future enrollment trends are difficult to predict.

The unique features of public health practice, and thus public health graduate education, have been and continue to be recognized by federal support. There is now some uncertainty about the continued availability and the form of this support.

The unique skills of graduates of schools of public health are in current demand. Quantitative disciplines, epidemiology and biostatistics, make important contributions in a variety of research areas. Management and

administration in the health care industry continue to occupy an important position in an expanding sector of the economy. Concerns about the environment and the workplace persist; research and practice skills are continuously required to maintain safe and healthy environments.

Of perhaps greatest importance is the recognition that better health can be achieved and certainly some of the major chronic diseases can be prevented through public health techniques. This recognition places increasing demands on the field for more research and for the application of existing knowledge.

In the remainder of this decade, emphasis on health promotion and disease prevention will have a major impact on the research and educational programs of the schools. The demand for better understanding of methods for promoting health will become an increasingly important object of federal research expenditure and very probably of reimbursement from third party insurers. Schools of public health, as well as some of the larger departments of preventive medicine, are in a very good position to lead in important aspects of this research. That clinical ties will be needed is certain. However, behavioral science techniques, study of population groups, particularly the longitudinal investigations, and demonstration and experimentation in large groups of individuals represent approaches for which public health science is uniquely suited. Relationships between schools of public health and schools of medicine will require careful attention, such that combined research and teaching efforts will be maximized and potential conflict minimized.

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EPIDEMIOLOGY IN THE MEDICAL CURRICULUM

BRIAN MACMAHON

The Role of Epidemiology

During the last thirty years there has been increasing recognition of the role of epidemiology in research leading to disease prevention. This recognition is seen in the strong support given by the National Institutes of Health to research and research training in the field—a support which, in some Institutes, has been preferential during years of constrained resources. We have seen, in part as cause and in part as consequence of this support, the capability to prevent 35 percent of cancer in this country and possibly more on a worldwide basis; demonstration of the ability to prevent a significant proportion of the consequences of hypertension; probably—though in indirect ways which we do not totally understand—the reduction of mortality from arteriosclerotic heart disease by about 25 percent from the high levels of the 1960s; and scientifically significant though numerically small advances in the understanding of the causes of congenital defects.

Yet epidemiology remains very much isolated from the broad world of

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BRIAN MACMAHON, Professor of Epidemiology and head of the department at the Harvard School of Public Health, was born in Sheffield, England, and completed his medical education at the University of Birmingham, England. After graduating in medicine, Dr. MacMahon earned a D.P.H. in 1949, a Ph.D. in social medicine in 1952, and the M.D. in social medicine, all from Birmingham. In 1952–53 Dr. MacMahon studied epidemiology at the Harvard School of Public Health under a Rockefeller Foundation fellowship. He joined the faculty of the State University of New York Downstate Medical Center, Brooklyn, New York, in 1955, first as associate professor and later professor of environmental medicine and community health. In 1958 he moved to Harvard in his present position. His major research interests are cancer and congenital defects.

medicine. It is seen more as belonging to public health than to medicine, and, unfortunately, these two are still perceived as separate and distinct. Apart from those in the federal government, strong epidemiology units in this country—and academic units in particular—are mostly based in schools of public health. The few that are in medical schools appear to operate in almost as much isolation from their medical colleagues as if they were in a separate school. Where groups have attempted to combine epidemiologic and clinical interests, it has often been deemed necessary to call the activity *clinical* epidemiology—as if to emphasize that it is not the hard-core stuff—and, indeed, all too often it is evident that it is not. It is my theme today that certain concepts that are basic to classical epidemiology, and on which a great deal of thought has been expended in the last two decades, are fundamental not only to etiologic research but also to the knowledge and understanding that are necessary for informed clinical practice. These concepts include the following:

—the notions of disease incidence and prevalence and their interrelationships
—the benefits and difficulties of longitudinal observations over time
—the difference between observation and experiment
—the role of selection bias in everyday phenomena
—the essence, detection, and treatment of confounding

I do not pretend that these concepts, or advances in understanding them, are unique to epidemiology. Certainly not. Indeed, epidemiology has drawn heavily on other sciences—notably statistics—for its progress. I do maintain, first, that in their simplest form these are concepts which should be an integral part of the intellectual equipment of the practicing physician, and which should be reinforced repeatedly throughout his training; and, second, that there has grown up in epidemiology over the last two decades a body of understanding of these issues which is not reflected in the research being published currently from many other academic departments. For example, clinicians, as well as epidemiologists, make longitudinal observations. But the clinical papers that take advantage of the formal analytic procedures that have been developed in the last two decades for dealing with longitudinal observations are in the minority. Let me try to indicate how these concepts enter into the everyday practice of medicine.

Diagnosis, Treatment, Prognosis

I suppose the three things that principally occupy the clinician are diagnosis, treatment, and prognosis.

Diagnosis. The question facing the diagnostician is the following: given a certain symptom or sign, or set of symptoms and signs, what is

the probability of the existence of disease, or of a specific disease? With sufficient experience—and many clinicians develop this over time—one can answer such a question directly, by counting or remembering the number of patients one has seen with similar symptoms and the number that were ultimately diagnosed with specified diseases. But the medical literature, which should provide at least part of one's experience, generally does not give us the direct answer to this question. Much more often than the probability of disease, given this symptom, it tells us the probability of this symptom, given this disease. Thus, we commonly see series of cases of disease X with the percentage of cases presenting with or exhibiting each of a list of symptoms. Bayes' theorem gives us the conceptual framework for getting from one probability to the other. It states that the probability (P) of disease (D), given symptom (S), is the probability of symptom, given disease, multiplied by the overall probability of disease divided by the overall probability of the symptom, or

$$P(D/S) = \frac{P(S/D) \cdot P(D)}{P(S)}.$$

While the probability of a symptom, given a disease, is clinically derived, the other terms in the equation are epidemiologically derived. The epidemiologic information must be provided in proper form and is essential, for example, to the algorithms based on Bayes' theorem which constitute the basis of most computer-aided diagnosis. The diagnostician who wishes to interact, as they say, with a computer must be aware of these relationships and the epidemiologic data on which the formula depends. Moreover, the practicing diagnostician, even if he never goes near a computer terminal, will surely be relieved to know that there is a formal basis for his intuition that he is most often correct if he diagnoses a disease that is common in the population, or that a symptom that is uncommon is more likely to lead to a correct diagnosis than one which is common, or that it is of no use to know for diagnostic purposes that 20 percent of hypertensives have headache, unless one knows what the prevalence is of headache in the population. Certainly these algorithms can be constructed intuitively, as they have been for centuries. But a clinician who relies solely on intuition in this age of information is shortchanging his patient.

A daily problem for the diagnostician is the definition of the limits of normal for biochemical and other clinical tests. A. L. Cochrane and others have stressed the rather obvious point that "normal" is better defined not in terms of so many standard deviations away from the mean of the population but in terms of lying beyond the point at which clinical malfunction either is evident at the time or is likely to appear after appropriate follow-up. A value that is the mean for a population—the

mean serum cholesterol or blood pressure for middle-aged U.S. males, for example—may well be one that is associated with increased probability of illness and that warrants a diagnosis and intervention. Conversely, an extreme value for some other population may not. Clearly, this point will not usually be a single point but a series of points associated with increasing probabilities of harm as the values increase or decline. Further, Cochrane draws attention to the need to define another point or points—those beyond which the probability of harm from the illness is greater than the probability of harm from the intervention that follows the diagnosis of abnormality. Intervention tends to follow diagnosis inexorably, and if the cost-benefit ratio of intervention is not favorable, it might be better to avoid the diagnosis of abnormality in the first place. How can these points be defined except by long-range epidemiologic follow-up studies which the practicing physician can interpret?

A third point on diagnosis is more frequently made. A diagnostician who inquires into the home, occupational, and social environment of a patient will occasionally be rewarded with a history that substantially raises his prior probabilities of diagnosing certain diseases. This is certainly true for the infectious, parasitic, and occupational diseases. It is less often so for other illnesses, but the possibility should not be ignored.

Treatment. An epidemiologic turn of mind seems most pertinent in the physician's evaluation of the experience of others in treating the disease with which he is now faced. He should be aware of the limitations of the experience of individual physicians and individual hospitals; not be surprised when the outcome for breast cancer patients is more favorable at a small community hospital than at a major medical center; be aware that the better known a physician, the more unrepresentative his patients are likely to be, biased either towards less favorable outcomes if he accepts all comers, towards more favorable outcomes if he is selective among those who wish to be treated by him. How many surgeons know that they can lower their stage-specific cancer mortality rates in all stages, including the worst, by staging their patients more severely—that is, moving them from a more favorable to a less favorable stage—even if their overall mortality does not change or even increases during the process? The prudent surgeon will classify his patients to the higher stage if there is any room at all for judgment in the matter; it will at least benefit his statistics if not his patients. This is a classic instance of confounding, a subject that has been explored in some depth in the epidemiologic literature recently. Problems of selection and confounding, of small numbers, of multiplicity of treatments, of failure to standardize treatments, of lack of controls, and of weighting of interpretations by prior intellectual commitments, make most of the literature on medical treatment valueless. For example, after two hundred years of scientific medicine and three decades of great

federal investment, we do not know:

—what the best treatment is for stage 1 breast cancer
—whether tonsillectomy is useful
—whether the cost-benefit ratio for the use of anticoagulants in infarction is favorable
—how useful intensive cardiac care units are
—how useful oral antiglycemic agents are

Perhaps no area of therapeutics needs more epidemiologic input than so-called secondary prevention—the matter of screening for and treating early disease. This area deals with questions of whether to screen and how frequently, for what conditions, in what subgroups of the population, and the impact of the available options when a test turns up positive. The issues involve intensely all the concepts I characterized earlier as being at the heart of epidemiology: the difference between observation and experiment, longitudinal observations, selection bias, confounding and, most of all, the interrelationships of incidence and prevalence and disease transition rates.

If the practicing physician is not going to undertake his own scientific evaluations of various therapies, he should at least be aware of the strengths and limitations of the evaluations he reads about.

Prognosis. For prognosis, the physician must understand the natural history of the disease. Clearly, longitudinal observations are required. The same kinds of methodologic problems that I listed in connection with evaluation of treatment—the limitations of individual experience and of numbers, selection bias, and confounding—apply here. As a consequence:

—misconceptions of the spectrum of a disease are common (as has been the case with cancer of the cervix, cancer of the prostate, and hypertension)
—estimates of prognosis may be too unfavorable because of selection of patients (as in multiple sclerosis)
—estimates of prognosis may be too favorable for similar reasons (as frequently happens for newly introduced surgical procedures)
—false associations between diseases are introduced through derivation of data solely from hospital, or, worse, autopsy sources

Conclusion

So much for the problem. It is a problem for which I personally see no clear solution. It is not addressed, in my view, by having schools of public health become the departments of preventive medicine of medical schools, for departments of preventive medicine also are frequently isolated and contained within their small and carefully delineated sections of the medical curriculum. For the same reason, I think that the issue is

incompletely addressed by strengthening epidemiology within such departments when no school of public health is available, although, naturally, I am not opposed to that. But somehow the epidemiology has to become part of the clinical departments—the departments to which students pay attention..

The most hopeful program that I am aware of is the clinical epidemiology program of the Milbank Fund. This program offers young trainees in academically oriented clinical departments the opportunity to undertake formal training in epidemiology—as, classically, many spend a year or so in a basic research laboratory. Although the program is called clinical epidemiology, the training is serious. Support is included for trainees to continue their epidemiologic pursuits on return to their clinical departments. Although Milbank has committed a relatively large proportion of its resources to this program, it is still on a scale that could be characterized as no more than a demonstration project. Early observations from this demonstration should soon be available, if they are not already, and, if they support the promise of the original idea, I hope that much broader support for such activities will be forthcoming.

PEDIATRICS: THE PRACTICE OF PREVENTIVE MEDICINE

MARY ELLEN AVERY

One of the attractions of working with children is the awareness of the long-term benefits from prevention of disease or from early detection and appropriate intervention. Although it is not glamorous to prevent disease and sometimes very difficult to document the extent to which it has happened, nonetheless we know, from a few well-documented illustrative examples, of the enormous benefit to society from the prevention of chronic or crippling illness. It does not always make news. As was noted on the editorial page of the *New York Times* recently, twenty-three hundred more babies were saved last year than the year before—if one compares national statistics in infant mortality. That, the columnist noted, was not news. What if twenty-three hundred lives had been lost that could have been saved? That, of course, would have made headlines. Thus, quietly in many ways, the improvement in perinatal care has resulted in a reduction in mortality and also in significant morbidity around the time of birth.

The advances in perinatal care have also permitted survival of more

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infants of very low birth weight than ever in human history. We have a new generation of human beings to welcome, to nurture, and to evaluate. The outlook for normal function improves each year; but even so, some known problems exist, and we assume others may emerge as our small patients age. What will a 600-gram infant be like as an adult? Perhaps we can generalize to say that the new pediatrics is creating new situations—the childhood precursors of adult problems are the other side of the coin of prevention.

Of course, the most dramatic illustrative examples of effective prevention come from immunization against some of the major infectious diseases. Although smallpox may not be free on the face of planet Earth at this time, we know that the polioviruses, measles, rubella, and the bacteria diphtheria, tetanus, and pertussis are, indeed, among us and that a diminution in the extent of immunity of the population will inevitably be associated with a recurrence of epidemics from these agents. One need only travel to other parts of the world to see paralytic polio, deaths from tetanus and even measles in 1982. Most of our own pediatric residents have never seen these diseases.

Another equally dramatic approach to prevention begins with screening for some of the hereditary metabolic diseases that can be detected in newborn infants. Phenylketonuria becomes the best known example; dietary intervention can prevent the profound mental retardation that was so common in the infants whose phenylalanine levels reached excessive heights. More recently, screening for congenital hypothyroidism has revealed deficiencies in as many as one in four thousand births. The recognition of this problem and its subsequent treatment within days after birth prevent the mental retardation that was associated with delayed diagnosis of cretinism.

Pediatrics brings into sharp focus a consideration relevant to all clinical medicine, the need to consider the genetic susceptibility of the individual to environmental influences that tip the balance from health to disease. Increasingly, as we learn how to distinguish human individuality with tissue typing, we have at hand the means to designate some individuals at risk of insulin-dependent diabetes mellitus, for example, when they encounter another influence such as some viral illnesses that affect pancreatic islet function. We can easily imagine providing each newborn infant not only with information about inborn errors of metabolism but also with a list of odds that a given illness may strike at a later age on the basis of knowing the genotype that is associated with a predisposition to disease. Not every child with a family history of early onset coronary is at risk; however, some are at great risk which could be lessened by dietary precautions taken from an early age. The most difficult assignment will be to convince the individual to avoid harmful exposures. The role of the

pediatrician is to know the individual child not only in terms of growth and development but also in the expanded terms of the new knowledge that can be gained from a more complete definition of genotype. When this and other new knowledge is applied through prenatal diagnosis, as in the case of Tay-Sachs disease and other disabling illnesses, parents have the option of abortion as a means of prevention. Perhaps we will see the time when some of these disorders can be treated in the neonatal period by genetic engineering.

Another domain of preventive medicine, although only recently coming into ever sharper focus, is the early recognition of behavioral disorders or specific learning disabilities that can lead to school dysfunction. Michael Rutter made a cogent point when he entitled his book *15,000 Hours*, recognizing that that is the amount of time children are obliged to spend in school in our society. In the past, we were tempted to label children who were not able to meet normative expectations as dumb, lazy, low I.Q., or distractible or hyperactive. None of those labels was very discerning of the dysfunction a child might have, nor did they take into consideration cataloguing strengths as well as weaknesses. More refined assessment of children's abilities usually brings into focus specific areas of weakness and often some remarkable compensation that promotes talents by which the child can negotiate success in other areas. Adults have many options for ways to spend their time. If you do not like to dance, you do not have to go dancing. Alternately, if you are a good athlete, you can emphasize athletics, and if you are a good mechanic, you can display your skills. If you have difficulty writing, you can avoid a career choice that requires it. Children, on the other hand, are forced into a common mold in our educational system and only recently has the coalition of parents, educators, psychologists, and pediatricians directed their efforts toward identifying the needs of the individual child and bending the system to acknowledge those needs in a way that obviates some of the frustrations and motivates through positive reinforcement. It is our belief that emphasis on this kind of attention to the needs of children will reduce the level of frustration that is associated with school dropout, rebellion, and the violence we sometimes associate with juvenile delinquency. We believe careful evaluation of school dysfunction should prevent some social and educational maladaptations.

Let us reflect on the promise of treatment of many of the disabling disorders characterized only by clinical description in the past. For example, the advent of bone marrow transplantation has permitted the cure of some of the severe forms of immunodeficiency, including the Wiskott-Aldrich syndrome, agranulocytosis, some of the Hurler syndromes, and Gaucher's disease. When it is possible to cross the HLA barrier and widen the pool of donors, many more children with hereditary

metabolic diseases will become candidates for bone marrow engraftment. We foresee at least a decade of this kind of treatment being a central responsibility of major medical centers where the teams of immunologists, clinicians, students of metabolic and infectious diseases, and chemotherapists can increase the success of this major intervention. At some point, one expects that gene transfer will be possible in some of these situations. Although for the most part the disorders are rare, on a national scene they become significant. They are tragic for the affected individual. If one begins to think about gene transfer for the hemoglobinopathies and, perhaps, cystic fibrosis, it becomes apparent that when we finally understand the nature of the defect we will be very busy indeed.

We have not adequately considered the impact of the new knowledge on medical school or residency curriculum. Much time is devoted to the more traditional teaching of empiric approaches to disease once it has occurred. Little time is given to a discussion of strategies for disease prevention, probably because illness prevented does not appear in our hospital wards where most clinical teaching takes place. Only a diligent student inquires extensively about the family history and considers risk factors in the environment. We do well when we encounter an acute infectious process, and we usually try to protect family contacts. We do less well when we engage in genetic counseling and all too often ignore associated conditions in relatives. Only this past year did one of our house officers pursue the possibility of renal disease in relatives of infants with Potter's syndrome. Her findings of previously undetected hydronephrosis and other genitourinary problems in some of these relatives brought them to medical attention, and taught us that ultrasound examination of relatives should become a routine part of good medical care for these families.

A set of questions that should be asked at every encounter with a sick child is: why is this particular child ill at this time? what could have been done to prevent this illness? what are the risks of a recurrence? what does this illness mean to this family? When those considerations were applied by another of our residents to an infant with tyrosinemia, the full dimension of clinical pediatrics emerged. The child was from New Hampshire but of French-Canadian ancestry, and with the help of the parents who had not initially known of similar problems, an extended family tree was drawn up which revealed relationship to a kindred, well known to Quebec physicians, with other children who had died in infancy of tyrosinemia. Early intervention with dietary restrictions brought the patient through a stormy infancy. Now at age three years, cirrhosis is advanced and only a liver transplant carries promise of cure. The coordinated efforts of the pediatrician, the family, townspeople, and even NBC news have been mobilized to identify a possible donor. I leave you in suspense, the shared suspense we all have as we await the outcome.

For the house officer concerned, the issues of newborn screening, genetic counseling, care of a child with chronic illness, provision of emotional support to a family, mobilization of community resources, and identification of a pioneering approach to treatment have provided a memorable experience. In my view that experience is a model of the best way to educate a young physician. The science is essential; without it we are in the medical Middle Ages. Commitment to a patient over a period of time is all too unusual but equally essential if we are to teach responsibility for an individual for whom we are to provide the best possible care. Whatever the outcome for the child with tyrosinemia, the family knows a caring physician, and the emotional strain they must endure is alleviated by their trust in their child's doctor. This kind of optimal physician-parent-child relationship is surely the best means of prevention of family disruption by serious chronic illness.

I have touched only briefly on some of the ways in which we practice preventive medicine. I would like to philosophize briefly on the impact of modern obstetrics and pediatrics on child health in general and what it means to women in particular. I would suggest that the reduction in perinatal mortality and the expectation that most babies will be born normally and survive childhood has in fact been one of the greatest, if not the greatest, medical contribution of our generation. Think for a minute of the implications for women in their own lives. No longer need there be 137 million births per year on planet Earth, 85 percent of which are in the developing countries. Not long ago a woman was expected to have multiple pregnancies in order to assure the survival of a few children. Even today in some parts of the world, most women anticipate that nearly all of their adult years will be devoted to childbearing and child rearing. There could be little time for any other consideration when infant mortality was high. Now it is possible to choose the time at which one wishes to have a family, to expect that two living children will emerge from two or perhaps three pregnancies, and to assume that childhood is a relatively safe time of life. Women can now anticipate another thirty to forty years of adulthood during which careers can be planned and creative activities of sorts other than the perpetuation of the human species can be carried out. We can call this the prevention of the need to produce large families in order to have a few surviving offspring.

In conclusion, I think pediatricians can be very proud of the accomplishments of the last decades. I think they can also anticipate powerful new tools to transform the lives of a group of patients who would otherwise have been severely handicapped. The accomplishment of these latter goals will require collaboration with the basic scientist and attention to the transfer of information from the laboratories to the bedside in a scientific manner. It will also require liaison with individuals who are concerned about children, such as parents and teachers and all who work

to reduce the adverse effects of an environment that is poor in respect to the ability to meet financial needs as well as emotional needs. This becomes a societal responsibility. I have never heard anyone in political life claim to be against children, but I have certainly seen many illustrations where the needs of children have taken second or third place to other perhaps better articulated and better heard needs of a voting public. We have come a long way, but to paraphrase the poet, we have promises to keep and miles to go before we sleep.

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DISCUSSION

DR. JOHN BOWERS: Are there any comments or questions?

DR. KENNETH WARREN: I would like to agree completely with Dr. MacMahon. I don't think statistics in epidemiology should be thought of as a discipline unsuitable for medical schools or solely for schools of public health. This attitude and its effect on medical schools have concerned us at the Rockefeller Foundation, since we played such a role in the creation of the schools of public health. Medical school administrators felt that public health was being taken care of outside of the medical schools and that this area was no longer their concern.

I also agree with Dr. MacMahon's point about departments of preventive medicine. Their members think that to give a token course in epidemiology to medical students that may last two weeks or a month in the first two years is virtually useless, and that everything must be done to get the concept of epidemiology into the clinical years, because those are the years when the student is directed largely toward individual-based medicine, does not think in terms of a population basis, and may get a distorted viewpoint about medicine, working in a tertiary health care facility. If you could make epidemiology an important discipline in the clinical years, which would go into the house officer years, it would have a very important effect.

We also think that epidemiology—if the biochemists will forgive me—is as important a basic discipline for a clinician as are biochemistry, immunology, and physiology. The pathway to becoming a "young Turk" member of the American Society of Clinical Investigation, using epidemiology and basic science tools, should be as important as pathways of using a bioscientific–molecular biology approach. We feel this is very important, and with Kerr White, we are attempting to do something about this in the Rockefeller Foundation.

DR. ARNO MOTULSKY: I would like to comment about the trend towards increasing demedicalization of epidemiology. In the olden days most epidemiologists were physicians, and the contact between clinical medicine and epidemiology might have been easier. Nowadays most epidemiologists, in my experience, when looking at data about disease, really don't know what it's all about. (And this is true for Ph.D.s.) To bring epidemiology in contact with clinical medicine may become increasingly difficult. What can be done?

DR. BRIAN MACMAHON: I think that was a short-term experiment which is coming to an end through the forces of the marketplace, and which has been only partially successful. There has been in the last twenty years or so a tremendous demand for epidemiologists, which couldn't possibly be met from the recruits from medicine. Much of this demand was in industry and in other places where knowledge of the biology of disease was not so important. My thought is that the people who have been turned out as Ph.D.s in epidemiology have done quite well, better than if they had gone into other alternatives. They have benefited society more than they would have if they had taken other routes. But I think the marketplace is pretty well saturated. People are now looking for M.D.s who are

trained in epidemiology. I agree that they have tremendous advantages over the person who does not have the biology.

There is another encouraging trend, and I don't know whether it is local or not. But we are seeing more physicians coming. There is a kind of program that I suggested which the Milbank Fund is interested in. That kind of program has been requested by clinical departments in the Harvard area. We have this year ten applications from M.D.s for our doctoral program, whereas normally we have one or two a year. These applications all came from the current class. Whether this is the beginning of a quickening interest on the part of M.D.s, which would make it unnecessary to train other people, I don't know. But I hope so.

DR. ROBERT PETERSDORF: I would like to address the issue of the residency in preventive medicine. This issue is particularly pertinent because it involves one of the shortage areas that has been pointed out by GMENAC. I recently had occasion to review some proposals put forth by some very distinguished schools of public health for residencies in preventive medicine. The best you can say for them is that they will prevent medicine. These proposals combined what I think most of us would consider to be the worst clinical training with a sort of pseudofellowship experience in public health and epidemiology.

As Dr. Day knows, I strongly support M.P.H. degrees in public health and good hard-nosed training in public health and epidemiology. But what I think is a pedagogic malformation in graduate education is the residency in preventive medicine. Only good clinical training followed by good investigative training can provide the proper pathway for people in epidemiology and in public health.

DR. ROBERT DAY: I will respond to that briefly. I won't argue with you because I don't know what you have seen. Public health is the one specialty that is non-hospital based. Therefore, it has always had difficulty, precisely for that reason. There is now specific federal support for residencies in preventive medicine.

To answer your second point, some residencies do include a clinical year. Three years are required to become board eligible, one of which is academic, one clinical, and one supervised practice. In Washington, we have the biggest residency in the country, but there is almost no one who hasn't completed a primary care residency on his own, so that we get, I think, people who are quite clinically competent to start with. I am very much opposed to most schools of public health offering that clinical year, since they have to gerrymander it out of other residency programs, as far as I can tell.

Third, preventive medicine residencies are primarily in the aerospace area, which is almost entirely a military occupation. I think there is some question that it may have been the back door into a clinical practice that has turned out to be rather lucrative in some areas and has been in very short supply with regulatory demands. It is now picking up quickly.

I won't say the traditional public health officer is disappearing entirely, but certainly the numbers are very short. When you look around, and I have had occasion to, for people to fulfill what has been a rather interesting career, you don't find very many. The more traditional general preventive medicine is a grab bag—that is probably the area you are referring to.

PETERSDORF: I am referring to all of them.

DAY: I would agree that a major overhaul is needed. There is the problem of

lack of financial support. These residency programs are all having difficulty attracting good residents because of inadequate stipends.

MOTULSKY: May I ask about the role of the Johnson Program?

DAY: That support has been tremendously helpful, but it is small. It accounts for only a very small proportion of our total residents, but it is certainly helping to pull up the average.

PETERSDORF: That is a fellowship program. I object to the term "residency."

I am much more encouraged by what Dr. MacMahon is saying, that he has ten applicants who are well trained coming out of residency programs. I think that is like taking a fellowship in basic science, and that is great. But to call them "residents" and to gerrymander clinical programs—this is what I object to. I know you don't have that in Seattle, although it was proposed by some of your distinguished colleagues in the state of California and was simply unreal in terms of quality control.

WARREN: I would like to comment on the question of epidemiology in medicine. If we are going to try to change the situation of getting clinical or hard-core epidemiologists in medicine, we have to emphasize the quality of the effort. The people that come into this field have to be as good as anyone. At meetings, they have to participate on an equal basis with the people doing recombinant DNA and RNA studies and molecular biology.

There are a few clinical epidemiology programs that are of true excellence. One of them is at McMaster in Hamilton, Ontario, where epidemiology is a fundamental discipline of a new type of medical school called a community-based medical school. It is an interesting concept. The Department of Epidemiology has twenty-nine people in it, and it pervades the whole medical school. It has both hard-core epidemiologists and clinical epidemiologists. I would like to suggest someone I consider to be an absolutely outstanding role model in this area—and I know only about four in the world—David Sackett.

Building on a research grant provided by the Dana Foundation, we at the Rockefeller Foundation made possible what may have been the first division of clinical epidemiology in a department of medicine in the United States, at the University of Pennsylvania under Paul Stolley. I think this unit is an outstanding example of that discipline. All of these clinical epidemiology programs are offering two-year training programs. In Dr. Stolley's department, the residents are on the ward, involved with epidemiology every day.

I am a little distressed because unfortunately for financial reasons the Rockefeller Foundation couldn't carry through as much as we had hoped on epidemiology. Another foundation has now put a lot of money into the field. I am a little distressed because the way it was done, as far as we can tell, was to say to some of the larger private medical schools in the East, "Are you interested in clinical epidemiology, because if you are, we will provide you with the funds." As far as I can tell, every one of these schools said they were interested, and six or seven programs were started, all organized in different ways. I don't know what the outcome is going to be, but these programs may dilute the quality of the effort. That quality is absolutely essential in establishing the importance and position of this field.

DR. FREDERICK ROBBINS: I wanted to comment on Dr. Avery's presentation,

which I thought was excellent. But, Dr. Avery, we are talking about academic medicine, and the relation between the academic world and the practice world didn't come through very clearly in your presentation. It is in the *practice* of pediatrics where the preventive medicine you were talking about should be applied, and this is where the real problem lies. The economic situation and the way we finance the whole system underlies everything we have talked about. Public health is not attractive because it does not pay well.

Pediatricians work like the devil and make a reasonable living, and it is very difficult for them to practice the idealized preventive medicine system that you talk about. That is a problem for the academician to worry about, and it is most acute in pediatrics. I don't know, but I suspect it is a problem in obstetrics and gynecology, and it certainly is plaguing psychiatry. I think it is a very critical situation.

We can talk about education all we want, but if the system won't accept it, then we won't get very far.

WOMEN IN ACADEMIC MEDICAL CENTERS IN THE UNITED STATES: AN UPDATE

ELIZABETH R. MCANARNEY

Even though it can be debated whether women in academic medical centers in the United States fared better, worse, or the same as their male colleagues in past years, what is clearly indisputable at the present time is the marked increase in the number of women at all levels (medical students, residents, and faculty) during the last twenty years in the nation's academic medical centers. It is too early to appreciate the full impact of the increased number of women on the administrative structure and the overall milieu of the nation's academic medical centers, as those changes often take decades and possibly even generations to occur.

Background

The history of women in medicine has been a unique one in the United States. The first medical school, which opened in 1765, excluded women. In 1849, Dr. Elizabeth Blackwell was the first woman to graduate from an American medical college (1, 2).

The first medical college for women opened in Philadelphia in 1850

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and was followed by many others. Those medical schools were somewhat short-lived, and by 1910, only two survived. By 1910, however, there were 13,687 women physicians in the United States (2). Gradually, during the late 1800s, women began to gain access to some all-male medical schools. By 1944, only 9 percent of the nation's medical schools were enrolling men exclusively. Jefferson Medical College was the last institution to exclusively enroll men (3). The last medical college to become coeducational was The Women's Medical College of Philadelphia, which accepted its first male students in 1970!

From the early 1900s to the 1960s, the percentage of women graduating from American medical colleges ranged from 2.6 percent in 1910 to a maximum of 12.1 percent in 1949 (post–World War II) to 5.7 percent in 1959–60 (4). This gradual decrease was a complex phenomenon and was the result of a combination of many factors: *(1)* pressure from society on women to marry, to have families, to forsake a career, and to pursue full-time homemaking duties; *(2)* concern on the part of medical school admissions personnel whether women, once trained, would be as productive over a lifetime as their male colleagues; *(3)* minimum support for women who did have a family and pursued a career, either from the institution (lack of day care, flexible residencies, etc.) and/or from their colleagues (faculty, coresidents, co-medical students); and *(4)* financial pressures on young families when both the female and male partner pursued long and expensive training, such as medicine.

There have been dramatic changes in the number and percentage of young women applying to, enrolling in, and graduating from the nation's medical colleges. Virtually all specialty training is now available to women graduates. These dramatic changes have resulted from several historical occurrences: (*1*) federal legislation prohibiting discrimination on the basis of sex; (*2*) private philanthropic support of women's medical education (particularly that of Dr. John Z. Bowers, while president of the Josiah Macy, Jr. Foundation); and (*3*) major changes in society regarding the definition of both female and male roles.

Women in the Academic Medical Centers

Medical Students. This discussion will focus on national data from the last twenty-two years (1960–1982). There was an 11-fold increase in the number of women applying for medical school between 1959–60 and 1981–82 (Table 1). There were 1,026 women applicants in 1959–60 and 11,673 women applicants in 1981–82, 6.9 percent and 31.8 percent of the entire pool of applicants, respectively. The number and percentage of women entering medical school parallel the increases in the number and percentage of women applicants. There were 494 women who entered

TABLE 1
Women Applicants and Women in Entering Classes, Selected Years, 1959–60 through 1981–82

Academic Year	Women Applicants		Women in Entering Classes	
	Number	%	Number	%
1959–60	1,026	(6.9)	494	(6.0)
1969–70	2,289	(9.4)	952	(9.2)
1975–76	9,575	(22.6)	3,656	(23.8)
1981–82	11,673	(31.8)	5,317	(30.8)

Data from references 5 and 6.

medical school in 1959–60 (6.0 percent) and 5,317 (30.8 percent) in 1981–82. Thus, approximately 32 percent of the applicants were women in 1981–82, and there were approximately 31 percent women actually entering medical school in this same year. In 1981–82, 27.9 percent of the medical students enrolled in the nation's medical schools were women; in 1980–81, the last year for which data are available, 24.8 percent of the graduates of the nation's medical schools were women (Table 2) (5, 6).

In 1976, as part of a study initiated and supported by the Josiah Macy, Jr. Foundation (7) I had the opportunity to interview 154 medical students (108 female and 46 male) in eleven medical centers throughout the United States. In general, both female and male medical students were enthusiastic about the presence of more women and the greater opportunities available for women in the medical centers. Some of the male students thought changes initially proposed for women medical students might also result in better conditions for them (recreational and on-call facilities, for example).

Female students reported they thought there had been equity in admissions procedures; in fact, most had actually enjoyed their medical school interviews. The minority of female students, who remembered an

TABLE 2
Women Enrolled in and Graduated from Medical School, Selected Years, 1959–60 through 1981–82

Academic Year	Women Enrolled		Women Graduated	
	Number	%	Number	%
1959–60	1,710	(5.7)	405	(5.7)
1969–70	3,390	(9.0)	700	(8.4)
1975–76	11,527	(20.5)	2,200	(16.2)
1980–81	17,248*	(26.5)	3,892	(24.8)
1981–82	18,505	(27.9)	—	

Data from references 5 and 6.
* Two schools not reporting.

isolated comment from a faculty member during an interview such as, "We get less mileage out of our women doctors," considered the remark as reflective of an individual interviewer's attitude, rather than reflective of an entire institution's attitude. Female students reported they liked having a variety of female colleagues with whom to associate. Male students commented on enjoying the camaraderie of their female colleagues. My more recent personal experience with medical students in my parent institution is that, in general, there is mutual sharing and concern among female and male medical students about each other's well-being, and mutual enjoyment of activities, particularly sports (track, basketball, etc.). Relationships between female and male medical students appear to be more informal than they once were.

Medical students meet more full-time and part-time faculty in the clinical years than during the preclinical years. They also become acquainted with residents from many specialties during the clinical years. In 1976, some medical students expressed concern that a number of attending physicians, particularly in some community hospitals on services where there were few women, were flippant in their remarks about women medical students. The students thought, in general, this was due to inexperience with women students rather than negative attitudes toward them as a group (7).

Overall, there have been marked changes for women medical students in the nation's medical schools, which have been reflected in equitable admissions policies for women and men (in fact, several institutions have accepted older women, a distinct change in admissions policies), a generally comfortable and supportive interchange among female and male students, and acceptance of women on the clinical services equally with their male colleagues, with the exception which has been noted.

Residents. This discussion will focus on data from 1968 and 1979 and, when available, data from 1980. There has been approximately a 4-fold increase in the number of women entering residency training in the United States during the last decade. In 1968, there were 3,239 women in residency training in the United States. Of the total number of residents in filled positions, 9 percent were women (8). Fifty-six percent of the women were graduates of foreign medical schools and 44 percent were graduates of American and Canadian medical schools (9). In 1979 there were 12,431 women in residency training—19 percent of all residents. Approximately 74 percent of the women were graduates of American and Canadian medical schools and 26 percent were graduates of foreign medical schools (10).

Virtually all specialties with accredited programs were open to women in 1980 (11). Flexible (shared) residencies were available to women and men in at least 198 programs (12).

Table 3 contains the number of women, by specialty, who graduated from American and Canadian medical schools in 1968 and in 1979. These data have eliminated information on graduates of foreign medical schools. The primary care specialties (family medicine, internal medicine, and pediatrics) all had major increases in the number of women graduates of American and Canadian medical schools. There was nearly a 200-fold increase for family medicine (5 in 1968 vs. 966 in 1979); a 10-fold increase for internal medicine (239 in 1968 vs. 2,408 in 1979); and nearly a 7-fold increase for pediatrics (246 in 1968 vs. 1,569 in 1979). Obstetrics and gynecology, sometimes included as a primary care specialty, had nearly a 12-fold increase (80 in 1968 vs. 947 in 1979), and general surgery had nearly a 9-fold increase (65 in 1968 vs. 571 in 1979) (9, 10).

Another comparison between the 1968 and 1979 data can be made by ordering the specialties according to the number of women who entered each specialty for residency training each year. As shown in Table 4, the order of specialties entered in 1968 by women graduates of American and

TABLE 3

Number of Women Residents, by Specialty (Graduates of American and Canadian Medical Schools) 1968 vs. 1979

Specialty	Number of Women Residents	
	1968	1979
Anesthesiology	99	247
Family medicine	5	966
Internal medicine	239	2,408
Obstetrics and gynecology	80	947
Pathology	120	411
Pediatrics	246	1,569
Psychiatry	326	877
Radiology	82	363
Surgery (general)	65	571

Data from references 9 and 10.

TABLE 4

Women (American and Canadian Medical Graduates) Entering Specialties for Residency Training, 1968 vs. 1979

1968			1979		
rank		*total*	*rank*		*total*
1	Psychiatry	326	1	Internal medicine	2,408
2	Pediatrics	246	2	Pediatrics	1,569
3	Internal medicine	239	3	Family medicine	966
4	Pathology	120	4	Obstetrics and gynecology	947
5	Anesthesiology	99	5	Psychiatry	877

Data from references 9 and 10

Canadian medical schools were, in descending order: (*1*) psychiatry (326); (*2*) pediatrics (246); (*3*) internal medicine (239); (*4*) pathology (120); and (*5*) anesthesiology (99). In 1979, the order was strikingly different. The specialties entered by women graduates of American and Canadian medical schools were, in descending order: (*1*) internal medicine (2,408); (*2*) pediatrics (1,569); (*3*) family medicine (966); (*4*) obstetrics and gynecology (947); and (*5*) psychiatry (877) (9, 10).

Thus, in 1979, a primary care specialty (internal medicine or family medicine or pediatrics) was the most popular choice of women graduates of American and Canadian medical schools for residency training. These numbers reflected not only the increase in the number of women in the residency training programs, but also the proliferation of residency training programs in these primary care specialties. National pressure for the training of more primary care physicians, also, has affected the numbers of graduates of the medical schools entering the primary care residency training programs.

Obstetrics and gynecology has become a popular option for today's young women. The dramatic increase in the popularity of this field for women residents is probably a reflection of the changes in obstetrics and gynecology; it now offers a wide diversity of career options from perinatal obstetrics to gynecologic oncology. In addition, women patients are requesting a wide range of obstetric and gynecologic services, including a choice of whether their physician is a woman or a man. General surgery has also become an attractive specialty for women. Medical students reported an increased interest in this field when they saw women residents in general surgery doing well.

Flexible (shared) residencies allow both female and male house officers to choose an extended, less intensive training program as opposed to the traditional training period for a given specialty. In 1974, there were 118 individuals in flexible residencies (13) compared to 1,388 individuals in 1980 (12).

There has been a great deal of discussion about the advantages and the disadvantages of the flexible residency. Individual women and men who have chosen the flexible program are positive about its merits, as it allows greater personal freedom for family, personal and professional interests, and relaxation. One pediatric resident at the University of Rochester pursued a number of activities (provided medical services at an adolescent/young adult clinic and took an advanced woodworking course, among other activities), while other residents in the same flexible (shared) program took subspecialty training during their less intensive periods of training. A married couple shared one position and alternated child-care responsibilities.

Colleagues of residents who have chosen the flexible residency provide

mixed reviews of its advantages and disadvantages. Their opinions reflect the specialty (surgery vs. psychiatry, as an example), the actual program (3-months-on/3-months-off vs. working one-half time throughout the week, month, etc.), and the amount of disruption and inconvenience the flexible program entails for their patients, their colleagues, and for themselves.

Faculty also give mixed reviews of the flexible residency program and state similar concerns as the residents who give mixed reviews. The major concerns that faculty raise are whether the flexible residency disrupts the rest of the residency program, places a hardship for coverage and responsibility for patient-care activities on the full-time residents, and possibly, negatively affects the continuity and quality of patient care. Whether the advantages of the flexible residency outweigh the disadvantages perhaps is best distilled to the question of whether the advantages accrued to the individual (the resident on the flexible program) are greater than the disruptions to their patients, colleague residents, and faculty.

Overall, dramatic changes have occurred within residency training for women in this country. There have been a major increase in the number of women in residencies, major changes in the choice of specialty training, and greater flexibility in training programs in 1979 than there were in 1968.

Faculty. In 1975, Jolly and Larson (14) reported that the participation of women physicians on 1975 medical school faculties was generally greater than the participation of male physicians relative to the numbers of each sex in the graduating classes since 1951. The results of a 1980 study by Jolly (15) indicated that the trend has continued with relatively higher participation for women on academic medical faculties than for men. For example, 2.3 percent of women in the class of 1969 were either assistant, associate, or full professors compared to 1.7 percent of the men. In 1980, 12.7 percent of the women and 9.8 percent of the men were either assistant, associate, or full professors.

In the aggregate, in 1979, approximately 10 percent of all medical faculty with M.D. degrees were women, compared to 15 percent in 1965 (16). There were relatively more women assistant professors (16 percent of all assistant professors) than full professors (4 percent of all professors) (15). In senior faculty, the highest percentage of women was in pediatrics (17).

In 1981, there were twenty-three women chairing basic science departments in the country's medical schools. Seven (30 percent) were chairing departments of anatomy; five (22 percent) were chairing microbiology departments. The remainder were: three (13 percent) in both biochemistry and pathology; two (8.7 percent) in both pharmacology and physiology; and one (4.3 percent) in biophysics. In 1981, there were thirty-two women

chairing clinical science departments in the nation's medical schools. The breakdown by department is as follows: seven (22 percent) in pediatrics; seven (22 percent) in rehabilitation medicine; four (12 percent) in preventive and/or community medicine; three (9.4 percent) each in anesthesiology, dermatology, and psychiatry; two (6.2 percent) in family medicine; and one (3.1 percent) each in internal medicine, neurology, and radiology (18). In 1981–82, there were no women full deans, fifty-five associate deans, and fifty-nine assistant deans. In comparison, in 1975–76, 3.4 percent of the associate deans were women, compared to 9.8 percent in 1981–82; in 1975–76, 11.7 percent of the assistant deans were women, compared to 17.2 percent in 1981–82 (19).

The question of whether women receive the same consideration for opportunities for academic achievement and advancement within the medical schools is still somewhat a matter of debate. Jolly reported that the modal graduation periods for both men and women on the 1980 faculty were similar: a 6 to 10 year period for assistant professors; 16 to 20, for associate professors; and 21 to 25, for full professors (15).

Wallis, Gilder, and Thaler (16*a*) studied academic promotion policies in the faculties of four medical colleges in the country: one medical college each from the Midwest and the South and two from the Northeast. The data from all clinical departments of a northeastern college revealed the median number of years of service before promotion: at the professorial level, 21 years for women (range, 15–26) and 12.8 years (range, 0–32) for men (P less than 0.02 by Student's t test); 7.5 years (range, 1–31) for women and 7.5 years (range, 0–35) for men at the associate professor level; and 3.0 (range, 0–16) years for women and 2.8 (range, 0–23) years for men at the assistant professor level. In reviewing the data for all four schools, the authors wrote, "The data assembled in this study, meager as they are, indicate that women physicians are promoted more slowly than men at all levels of the academic ladder and that an increase in the representation of women in colleges does not ensure equalization of promotion rates" (16*b*). This study, however, failed to consider whether all the women who were listed as full-time faculty had been full-time employees for their entire appointment or whether they were employed intermittently full time. Some women believe that rather than utilizing the same system of promotion for full-time and part-time women faculty, individual faculty should be able to move horizontally for a certain amount of time and not have those years counted against them in promotion considerations.

At the national level, research proposals have fared as well for women investigators as for men investigators in funding recommendations by the National Institutes of Health Advisory Councils. Seven percent of the research grant proposals of women investigators were approved for awards

in 1974 and 9 percent in 1978 (20). Data on the comparison of women's and men's salaries by rank were unavailable at the time this report was written.

Summary

Approximately one in three students entering the nation's medical schools are women. Virtually every specialty is open to women for residency training, and the majority of women are choosing the primary care specialties. An increasing number of residency training programs are flexible to accommodate both women's and men's needs for time to receive their training and accomplish other personal and professional goals. A higher percentage of women than men physicians from each graduating class enter academic medicine, but women are still underrepresented at the professorial level. The debate about whether women are promoted as quickly as men persists, as the issues related to promotion are complex and are not just a matter of comparing their respective numbers of years of service on academic faculties.

The majority of women physicians may prefer to enter the primary care specialties and practice medicine full time, rather than to enter medical academia. The full impact of the increasing number of women medical students on the medical schools administratively has yet to be felt. These changes may take generations to occur.

Gratitude is expressed to Drs. Davis G. Johnson and Kathleen S. Turner from the Association of American Medical Colleges for their assistance in obtaining the recent data.

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DISCUSSION

DR. JOHN BOWERS: We should first ask Dr. Avery for any comments or questions.

DR. MARY ELLEN AVERY: I would like to share an anecdote from the front lines. Last week on the wards of the Children's Hospital, Roberta Adams, an intern, was talking to a four-year-old, a little boy, and brought up the issue of "What do you want to do when you grow up?" He paused a moment and said, well, he thought he wanted to be a doctor, but they are all women.

DR. LUIGI MASTROIANNI: There has been a dramatic change in our own department. We take six residents a year. Last year five were women and we had one token male. Actually, it's a much more pleasant department in which to work these days. The tone has changed, perhaps because the attitudes of our residents have changed. I think women have brought a great deal to us which we didn't have in the past.

The problem at the faculty level is a complex one. We have looked at this very carefully in an effort to identify women who would continue in an academic career. For a variety of reasons, this has been difficult to arrange, at least in our institution. It is not that the opportunities haven't been made available. Somehow along the way the career choices of women are influenced by a number of other factors, perhaps more so at this point than career choices of men. I suppose this will change. For example, two women finished our program this year and elected to go elsewhere into a practice setting because they had associations with men who were moving to that area. At some point I am sure we will see—and I think we are beginning to see—situations in which the man will follow the woman. This should add gradually to our opportunities for appropriate balance at the faculty level.

DR. ROBERT JAFFE: It would seem to me that we now have, or should have, the time experience to lay to rest the old statement that there is a longer career for the man than for the woman finishing medicine. I haven't seen these data, but I would think since there are a number of 1969 graduates who have been followed, we should begin to find out.

Secondly, as is true with Dr. Mastroianni, we have experienced a dramatic increase in the number of female house officers in our program. We take seven residents each year. We have between three and five hundred applicants for those seven positions, and, over the last few years, four or five have been women. At the other end, three new faculty positions were filled this year, two by women. I think we are going to see more women coming into the field and more filling academic roles, at least in our discipline.

DR. JOSHUA LEDERBERG: I wanted to ask a question about statistics. I realize that I may be troubled by some of the issues that Dr. MacMahon mentioned about classifying, staging, and so on. But simply, what is there on the research productivity of women as compared to that of men in academic and research settings?

AVERY: I don't know.

DR. ROBERT PETERSDORF: I will bet there are no data on that.

DR. ALVIN TARLOV: I wanted to comment on a statistic from 1978 that is called, "Adjusted Lifetime Productivity," with which you are familiar. It was noted in a GMENAC work that women had a tendency over the course of their professional lifetime to work fewer years, fewer weeks per year, and fewer hours per week. The adjusted lifetime productivity of women was calculated to be 78 percent of that of men. We used that statistic in our manpower data on requirements for physicians. If that 78 percent figure is not going to obtain in the 1990s, that would make a very large difference in the number of physicians needed and would aggravate the surplus of physicians that some people think is around the corner.

We interviewed 100 women who were house officers in 1978 to get some indication of their plans for the future. That group of women indicated they were planning their lives in such a way that the 78 percent adjusted lifetime productivity seemed reasonable.

DR. BRIAN MACMAHON: The most recent data is the Marion Hines data, which appeared as a series of two or three papers in *Family* in the late 1970s. I believe her estimate was based on actually looking at women in practice and was quite similar to what you have noted. According to these data, the most recent I could find, women actually spend slightly less time in practice than do men.

BOWERS: Do you have any update on that GMENAC data?

TARLOV: No.

BOWERS: Just the big area?

TARLOV: Yes. We have updated the supply figures, and it looks like the total of 536,000 practicing physicians is accurate within approximately 1 percent. The requirement for physicians' services I will discuss later.

DR. SHELDON WOLFF: I have just two comments. Fifty percent of my applicant group are women. From the comments made around the table, there is a lot of camaraderie between the men and the women. The problem we are facing is that three of these applicants are currently pregnant. That is going to give, I believe, pause in the future in terms of their relationship with the men, if men have to pick up the slack because pregnancies obviously are unscheduled. Certain adjustments must be made, and men are the ones to make the adjustments,

The second point I would make concerns the male spouse following the female. In each of the last three years, we have had one resident who, after accepting an appointment for the next year, came in later in the year to say she would have to leave. In each case, the resident was female. In each case, she was going because of the spouse's commitment somewhere else. I have not seen the reverse, which I believe is a societal problem.

Last year, two-thirds of our interns were women. We had 850 complete applications for twelve positions. We found that two-thirds of our applicants were female, two-thirds of the people who were interviewed. Women come to the inverview, see that there are lots of other women, and realize that they are actually the ranking group.

JAFFE: The opposite is true in our department. We see many more male applicants than female, but the women whom we are seeing are better. The female applicants, at least to our discipline, are all from the very tops of their classes to a greater extent than the male applicants. It is not because of the proportion of

both types of applicants; it is because of the superiority of women applicants that most of our interns are women.

WOLFF: That is one of the reasons, Dr. McAnarney, that this specialty is relatively attractive to women.

DR. ALFRED HAYNES: I am thinking of all the presentations this morning, clinical as well as basic science, and it would seem to be even more important in the postgraduate level that there be radical changes in medical education itself. We seem rather fixed with the idea of having basic sciences taught first and then clinical sciences taught afterwards. If indeed we could restructure the whole situation so that the clinical departments would train in basic science and public health science, with these courses being taught throughout the entire period, it might significantly change medical education.

With respect to the women, I think that one possible solution might be for the men to shorten their lifetime career span to that of the women. This might be one way of dealing with the oversupply.

THE FUTURE OF PSYCHIATRY: FROM COUCH TO PET

H. KEITH H. BRODIE

The future of psychiatry will be determined principally by new developments in the neurosciences—clinical neurobiology, psychopharmacology, and biological psychiatry. Historically, this represents a return to the medical concepts of madness, which we know from the writings of Hippocrates existed in the fourth century B.C. Hippocrates delineated the four bodily humors—blood, black bile, yellow bile, and phlegm. It was Galen who emphasized that health was related to a proper proportion of the four humors, while melancholia—the name applied to mental illness—was due to an excess of black bile.

During the Middle Ages, the mentally ill were no longer treated by practitioners of medicine but were subjected to harsh treatment in the religious sector. Superstition prevailed, and large numbers of psychotic patients were classified as witches and burned at the stake. The Renaissance brought the mentally ill back into the mainstream of medicine. In 1756 the first group of psychiatric patients was admitted to the cellar of the new Pennsylvania Hospital—the first general hospital in the United States. The nineteenth century saw the construction of large numbers of psychiatric hospitals located far away from the large urban centers of our country.

H. KEITH H. BRODIE studied medicine at Columbia University, College of Physicians and Surgeons, where he was awarded the M.D. in 1965. He trained in psychiatry at Columbia and at the National Institute of Mental Health, 1966–70, after which he joined the Department of Psychiatry at Stanford University School of Medicine. In 1974 he was selected to be Chairman of the Department of Psychiatry at Duke University. Dr. Brodie is now James B. Duke Professor of Psychiatry at Duke, and on July 1, 1982, became Chancellor of the University. He is currently president of the American Psychiatric Association.

These hospitals increased in size during the first part of the twentieth century, during which psychoanalysis gained in respectability such that at the start of World War II, neuroses and personality disturbances were treated principally by psychoanalytic approaches. Psychotic patients, however, were sent off to state mental hospitals where they received a large number of relatively ineffective somatic therapies such as hot tubs, revolving chairs, lobotomies, and ultimately, insulin shock and electroshock therapy.

World War II brought an increased awareness with respect to the prevalence of mental disorders and the need for crisis intervention focusing on the acute psychotic episode treated under combat conditions with barbiturate sedation and intensive psychotherapy.

In the 1950s, major advances were made in the pharmacotherapy of mental illness. Lithium carbonate had been discovered in 1949 in Australia and was rapidly being employed in the treatment of mania. Tricyclic antidepressants were discovered as were monoamine oxidase inhibitors, and dopaminergic blocking compounds such as chlorpromazine were found to be extraordinarily effective in the treatment of schizophrenia. It is of note that all these compounds were developed serendipitously, monoamine oxidase inhibitors having been discovered in the quest for an antituberculosis drug, the phenothiazines having been discovered in an attempt to develop a potent antihistamine, and the tricyclic antidepressants having been developed in the quest for a better antischizophrenic agent. With the introduction of these compounds, the population of inpatients hospitalized in the state hospitals began to decrease. In 1957, there were more than a half million inpatients in these facilities. This number has decreased rapidly due principally to the introduction of effective chemotherapeutic agents such that now the number is less than two hundred thousand.

During the period 1955 to 1975, there was a large increase in outpatient care rendered to the mentally ill. Community mental health centers moved the psychiatric patient from the enormous state hospitals located some distance from the big urban areas back to the community. Seventy-seven percent of the treatment sessions provided to psychiatric patients in 1955 occurred in an inpatient setting, whereas in 1975, 27 percent of these sessions occurred in an inpatient setting and 70 percent transpired in an outpatient setting. The decrease in geographic separation between the loci for the delivery of mental health services and general health services now affords us an opportunity to strengthen linkages between the two health-care systems. This linkage will be facilitated by the increased number of psychiatric units in general hospitals and by the increase in the number of mental health clinics in health centers throughout the country.

Recent data indicate that 15 percent of the American population suffer some form of mental illness. This 15 percent figure was derived by Regier

and Taube (1) from a number of different epidemiological studies including the Midtown Manhattan study, which found 23 percent of the adult population aged twenty to fifty-nine affected by serious psychiatric impairment in 1954. A recent update of a 1967 study performed in New Haven, Connecticut, showed a point prevalence mental disorder rate of 16 percent in the adult population. Of greatest interest to psychiatrists was the finding that 58 percent of the mentally ill in treatment were receiving treatment by non-mental health practitioners in a primary care medical outpatient setting in contrast to 15 percent who received treatment by mental health professionals. Regier estimates that 21.5 percent of the mentally ill are not in treatment. These data indicate that three times as many patients with mental illness are being treated by primary caregivers as by mental health professionals. I will not dwell on the merits of this arrangement; however, some data suggest that the treatment of mental illness exacts a heavy toll from the primary caregiver. Several studies have surveyed these physicians about their attitudes towards experiences with the mentally ill. Those surveyed typically report that they have inadequate training for the most effective treatment of mental illness and that the mentally ill are more difficult to treat than other patients. They also report that, given the fact that the majority of the primary caregivers are operating on the fee-for-service system where time equals money, and given the fact that the mentally ill demand a lot of time, these patients are financially less rewarding. Further, there are some studies which show that the primary caregiver prescribes psychotropic drugs more often in the treatment of personality disorders and the neuroses than does the psychiatrist (1).

In the 1960s, clinical investigators began to develop working models of mental illness based on the action of the drugs used in treatment. The catecholamine hypothesis of affective disorders was introduced by Bunney, Davis, and Schildkraut (2). These investigators explained mania on the basis of an increased functional availability of the biogenic amine neurotransmitters dopamine, serotonin, and norepinephrine at the synaptic cleft. Further, they related depression to a functional decrease of these compounds using the observations that the drugs useful in the treatment of depression seemed to increase their availability at the synaptic cleft and that compounds useful in the treatment of mania decreased functional availability of these neurotransmitters. Several years later, Seymour Kety and others introduced the dopaminergic hypothesis of schizophrenia, relating this illness to an increase in dopaminergic activity in human brain. This hypothesis was based on the observation that the principal compounds used in the treatment of schizophrenia serve to block dopaminergic receptor sites.

The 1970s brought an explosion of knowledge in the neurosciences. The concept of a presynaptic receptor was introduced specific for opium

compounds and the benzodiazepines, and other receptors were discovered in human brain. With the discovery of these receptors, the quest for endogenous compounds synthesized in brain was successful in turning up endorphins and a whole host of polypeptide fragments of a large adrenocorticotropin (ACTH)-endorphin molecule referred to as pro-opiocortin (3). This compound is found in the pituitary gland where it is subjected to cleavage in anterior and intermediate lobes. The finding that β-endorphin and ACTH are secreted stoichiometrically is of great interest given the stress-induced secretion of ACTH.

With these discoveries, new hypotheses concerning the etiology of mental illness were introduced. The Yale group of Roth, Maas, Redman, and colleagues has suggested that a subgroup of depressed patients may exist, which is characterized by having hypersensitive α-2 adrenergic presynaptic receptors (4). This abnormality, the investigators claim, may result in decreased synaptic norepinephrine output from these nerves and thus decreased neurotransmission at the synaptic cleft. It is interesting to note that clinical improvement in this subgroup, treated with the drug desipramine, may be explained on the basis of this compound's reduction in the hypersensitivity of these presynaptic receptors, thereby reversing the hypothesized abnormality. The Yale group has been able to show that during desipramine treatment, α-2 adrenergic receptors become subsensitive and, in addition, plasma 3 methoxy-4 hydroxyphenylglycol (MHPG), the principal metabolite of norepinephrine, is reduced.

In addition to the investigation of biological factors responsible for the psychoses, several investigators are utilizing biological markers in the diagnosis of mental illness. These markers have included the use of dexamethasone suppression and the monitoring of rapid eye movement (REM) sleep latency.

It has been noted for years that many depressed patients have elevated levels of cortisol, particularly during the sleeping hours. Carroll at Michigan has noted that, in many depressed patients, one milligram of dexamethasone does not suppress the output of cortisol to the extent seen in normal control subjects. Dexamethasone suppression testing has been reported to be clinically useful by many investigators across the country today (5).

Kupfer at Pittsburgh has noted that the period of time between the onset of sleep and the onset of REM sleep is decreased in depressed patients. He has shown that prolongation of this shortened REM latency, occurring on the first or second night following the administration of tricyclic antidepressants, appears to be a very good predictor of response to tricyclic drug therapy (6).

Studies of schizophrenia reveal that platelet monoamine oxidase levels are decreased in the majority of schizophrenic patients. This seems unrelated to drug treatment and may be associated with a decreased

ability of the brain to metabolize endogenous biogenic amine hallucinogens which have been shown to be synthesized in humans (7).

I review this brief history of our field in order to focus attention on the relevance of neuroscience and neurobiology to the diagnosis and treatment of mental illness. Most of the biological studies which have been carried out to date focus on the psychoses—the depressions, manias, and schizophrenias which have been referred to in the past as functional illnesses—that is to say, illnesses without gross anatomical lesions of the brain as observed at autopsy. These functional illnesses are now associated with biological markers and, as I suspect Seymour Kety will shortly tell us, with genetic loading factors. One of Pauling's classic quotes, "for every crooked thought, there is a crooked molecule" is now enjoying growing respectability.

With the increasing medicalization of psychiatry has come an increased respectability and appeal for medical school graduates. In 1980 the number of postgraduate first-year positions in psychiatry filled by graduates of American medical schools was 446; in this year's match it was 603. This represents an increase of over 30 percent. This increase is important, for the burden of major mental disorders in our country is enormous. Three hundred thousand new cases of schizophrenia are diagnosed each year in addition to the 1.5 million people who are being treated for a depression annually. Given the increased effectiveness of biological treatments, we need physicians capable of handling this burden of illness.

Recently there has been increased interest in treatment outcome and therapeutic efficacy, coming not only from psychiatrists but also from third party payers and the federal government. The majority of studies indicate that psychotherapy is more effective in treating the neuroses than placing patients on waiting lists and that psychotherapy decreases the utilization of general health-care services by the mentally ill. This finding has sparked a new field of research referred to as "offset research," wherein investigators are now focusing their attention on the cost of providing psychotherapy as offset by the economies effected in decreased health services utilization (8). The therapeutic efficacy of drug treatments of the psychoses is well established.

In attempting to predict the future of our academic speciality, I would project a closer relationship between psychiatry, neurology, and the neurosciences underpinning both medical subspecialities. The development of positron emission tomography (PET) has allowed us for the first time to measure metabolic activity in brain visually, and has already shown that for some schizophrenics there is a decreased metabolism in frontal cortex as compared with normal subjects. I suspect that nuclear magnetic resonance will allow us further diagnostic capability in the study of the psychoses.

With respect to the future of the neuroses, biological variables will no doubt legitimize the medicalization of both diagnosis and treatment of these disorders. It is of note that clonidine, an α-2 adrenergic agonist, has been shown to be effective in reversing panic anxiety associated with opiate withdrawal. Clonidine acts on the nucleus locus coeruleus, a noradrenergic nucleus, the electrical or pharmacological stimulation of which produces fear-associated behaviors and increased norepinephrine turnover in animals. As studied in humans, clonidine's antianxiety effect was most potent in individuals who had the highest noradrenergic activity as measured by urinary MHPG excretion associated with high anxiety levels (9).

In 1981, Riley published a very elegant study in *Science* on the ability of stress to reduce immunocompetence and increase the vulnerability to neoplasia in animals (10). Thus, the study of stress and anxiety may well affect many of the other clinical disciplines in medicine, such as immunology and oncology.

In summary, over the past twenty-four centuries we have moved full circle, returning to our medical roots as established in the fourth century B.C. The future looks promising as we remedicalize and attract students to our speciality who have become excited by the revolutionary developments in the neurosciences. We will, no doubt, have to jettison some baggage. The recent decision of the American Psychoanalytic Association to review the possibility of training large numbers of clinical psychologists in the practice of psychoanalysis may move the Freudian couch from our cargo, to be replaced by psychiatric imaging techniques such as the PET scanner. The technologies of behavior change developed in several departments of psychiatry will endear us to our medical colleagues as they grapple with decreasing lifestyle risk factors such as smoking, excessive drinking, and sedentary existences. The interface between psychiatrists and primary caregivers will expand around such issues as disease prevention, compliance with medical regimens, and stress reduction. Indeed, the future of academic psychiatry now seems assured, mortgaged perhaps on a diminished emphasis on some of the psychotherapies, and nurtured by a medical respectability born out of the neurosciences and the serendipitous discoveries of drugs that work.

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PSYCHIATRIC RESEARCH: PRESENT DIMENSIONS AND FUTURE OPPORTUNITIES

SEYMOUR S. KETY

The great change that has been taking place in psychiatry over the past decade or two has been described by Keith Brodie. It is quite clear that this is a greater change than has occurred in any other branch of medicine, not only because research has entered the field in increasing strength, but also because the thrust of psychiatric effort and research has changed drastically. Psychiatry, which had wandered away from the biomedical field, is returning to it, but with very special characteristics.

Psychiatry played a very important role in the past twenty or thirty years in introducing into general medicine the importance of psychological processes and social influences, and the importance of life experience, in the determination and modification of medical illness. But while it was doing that, it may have been neglecting the role of the biomedical sciences in its own area of interest.

No other organ system has a function or an output which is so dependent on past experience as does the brain. This is not surprising, since it is the major function of the brain to evaluate and store experience and to use it adaptively in later behavior. We must recognize that in the

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SEYMOUR S. KETY graduated in medicine from the University of Pennsylvania in 1940 and was an NRC fellow at Harvard Medical School and Massachusetts General Hospital in 1942–43. He then returned to Pennsylvania to spend eight years in the Departments of Pharmacology and Physiology. In 1951 Dr. Kety was selected to be the first scientific director of the National Institutes of Mental Health and of Neurological Diseases and Blindness. In 1967 he was appointed Professor of Psychiatry at Harvard and director of the psychiatric research laboratories at the Massachusetts General Hospital and later at the Mailman Research Center of the McLean Hospital. He was elected in 1962 to the National Academy of Sciences for his research on cerebral circulation and metabolism.

human brain and in its output—human behavior—we have, as in the case of a modern computer, two very important interacting spheres. There is the hardware or the machinery of the brain, which is the province of biology, but there is also the stored information, which the sciences that deal with information and experience, such as the social, psychological, and the communication sciences, can grapple with more effectively than can biology.

Much of the variance in human behavior is more the result of the information than of the machinery. Biologists recognize this generally, and I do not know any biochemist who is studying the brains of Democrats and Republicans hoping to find the difference between them at the biochemical level. But what about the various mental illnesses? Can we also assume that schizophrenia and manic-depressive illness, like political affiliation, have no biological roots?

Early in this century, pellagrous dementia and general paresis, which accounted for a substantial segment of the patients confined in mental hospitals, were explained in biochemical and biological terms and have been practically eliminated as a result of this knowledge. But schizophrenia and manic-depressive illness remained with us, and an understanding of their biological as well as their psychosocial substrates still eludes us. Their treatment, although it has improved dramatically through the use of recently discovered drugs, still leaves much to be desired. Over the past two decades, however, substantial research has indicated that these serious mental illnesses do have biochemical substrates, and powerful new techniques and concepts have been developed which make the search for these causes more promising than it has ever been before.

Early Biological Approaches

The idea of a biological basis for insanity is not new. The Hippocratic physicians of ancient Greece argued against the then popular belief that insanity had supernatural causes: ". . . and by the same organ (the brain) we become mad and delirious and fears and terrors assail us . . . . All these things we endure from the brain, when it is not healthy but is more hot, more cold, more moist, or more dry than natural, or when it suffers any other preternatural and unusual affliction." (1)

The modern biochemical approach to mental illness can be traced to Thudichum, a physician and biochemist who hypothesized nearly a century ago that many forms of insanity were the result of toxic substances fermented within the body, just as the psychosis of alcohol was caused by a toxic substance fermented outside. He received a research grant from the Privy Council in England that enabled him to spend ten years examining this hypothesis. Significantly, Thudichum did not go to mental

hospitals to examine the urine and blood of patients; instead, he went to the slaughterhouse, obtained cattle brain, and began to study its normal chemical composition (2). It is very fortunate for us that he did, because in so doing he laid the foundations of modern neurochemistry, and therefore the essential basis for studying the abnormal chemistry of the brain. If Thudichum had been less wise and courageous, or if the parliament had been more insistent that he do "relevant" research, what contribution could he have made with the little knowledge that existed at that time? He would have frittered away the public funds and wasted ten years of his life in a premature and futile search. By following the course he did, Thudichum was able to identify a large number of substances in the normal brain which were later found to be abnormal in a variety of neurological disorders.

Fifty years ago, biochemistry began to trace the complex processes of metabolism by which foodstuffs and oxygen are utilized and energy is made available. This understanding was eventually applied to the brain, the brain's dependence on glucose was discovered, and the oxygen utilized in various mental functions was measured. Investigators found that many clinical states of mental abnormality were associated with diminished oxygen consumption in the brain; these included senile psychosis, diabetic and other forms of coma, and a large variety of conditions in which there are clear primary metabolic interferences with the energy utilization of the brain (3). Our studies in 1948 found no difference in oxygen consumption of the whole brain between schizophrenia and normal mental state (4). We concluded that if biochemical disturbances were fundamental in schizophrenia, they must involve particular regions of the brain and processes more complex and specific than simple energy supply. Oxygen levels were also found to be unaffected in normal sleep, LSD psychosis, and the performance of mental arithmetic. The study of these four states led to a very important insight: the brain is qualitatively different from most other organs in the body. While the heart, the muscles, and the kidney show a work output which has something to do with their energy utilization, the output of the brain cannot be measured in such simple terms. The brain as a whole uses the same amount of energy whether the individual is talking nonsense or speaking brilliant prose, thinking an irrational thought or a rational one. It soon became clear that what mattered in mental functioning was not so much the supply of power to the brain as the neuronal systems in which that energy was utilized.

When the major psychoses could not be explained as energy deficiencies, a number of other biochemical hypotheses were proposed. One hypothesis, developed twenty years ago, was that adrenaline was changed chemically in the blood of schizophrenics to a substance called adrenochrome, thought at one time to be hallucinogenic. This hypothesis en-

couraged Julius Axelrod to elucidate the normal pathways of catecholamine metabolism in the body and brain (5). His fundamental contributions in this area provided an important base for much of current research. When the metabolism of adrenaline in schizophrenics was examined, however, no evidence for adrenochrome formation could be found. Other chemical theories of schizophrenia abounded; the disease was ascribed to the presence of particular psychotogenic proteins in the blood, described by some as "taraxein," by others as "S-protein." These claims were not confirmed. In retrospect, the difficulty with the theories proposed at that time is quite obvious. These heroic efforts were simply premature. They were attempting to bridge the great gap between existing biochemical knowledge and mental illness in one span, before the foundations had been laid. The numerous "breakthroughs" that turned out to be illusory contributed to a disparagement of biology in the field of mental illness and a conviction that those disorders were primarily psychological and social problems.

In the absence of credible biochemical findings pertinent to schizophrenia and manic-depressive illness, observations suggesting their hereditary nature became crucial. Clear evidence that these illnesses had important genetic bases would justify a continued search for biochemical causes, since genetic factors can express themselves only through biochemical processes.

The Genetics of Schizophrenia and Manic-Depressive Illness

The evidence for the operation of genetic factors in the major mental illnesses was compelling but not conclusive, since other than genetic factors could account for the observations that were available. Psychiatrists had known for a long time that these illnesses run in families. There is a 5 to 10 percent risk for the occurrence of schizophrenia in the parents, siblings, and children of schizophrenic patients, depending on how broadly schizophrenia is defined; and manic-depressive illness shows a comparable familial tendency. Although this is compatible with genetic transmission, it is by no means proof. Wealth and poverty run in families but are not genetically transmitted, and the familial occurrence of pellagra once permitted a belief in the genetic nature of what we now know to be primarily a nutritional disorder. Members of a family share not only their genetic endowment but also their environment, and either or both of these factors may be responsible for familial disorders.

For many years, the best evidence for the importance of genetic factors in mental illness came from studies of the twins of schizophrenic and manic-depressive individuals. These studies have generally shown a high

incidence of schizophrenia among the identical twins of schizophrenics, and a considerably lower incidence among their fraternal twins, about the same incidence that occurred in their siblings (6). Similar results have been obtained for the manic-depressive psychoses. These findings are compatible with genetic theories because identical twins share all their genetic endowment, whereas fraternal twins are no closer genetically than are ordinary siblings. Recent studies of twins have been able to avoid ascertainment and subjective bias, and still find the same results. But because these studies could not control environmental factors, they did not provide conclusive evidence for genetic transmission. Identical twins share more of their environment than do fraternal twins. They usually live together and sleep together, their parents parade them in the same perambulator and dress them alike, and they have the same friends and experiences. Unless one could randomize their environment, one could not be sure to what extent the shared psychosis in identical twins was due to ego identification, mimicry, or the many other environmental factors they shared in addition to their genetics. There seem to have been some loopholes in the genetic evidence large enough for whole schools of psychiatry to march through them.

Over the past fifteen years, however, another approach has been used which appears capable of separating genetic from environmental factors in the transmission of schizophrenia and permitting the study of each in purer culture. This consists in the study of adopted individuals, who share their genetic endowment with their biological relatives, but share their environment with their adoptive relatives. In the several studies which have been completed to date, the results are quite consistent (7, 8). Schizophrenia continues to run in families, but now its high prevalence is restricted to the biological relatives of schizophrenic adoptees with whom they share genetic factors, while their environmental influences are randomized. The adoptive relatives of schizophrenics, who reared them and shared their environment, show no more tendency to schizophrenia than does the population at large. Schizophrenia, however, is not randomly distributed among all the biological relatives, but is clustered in certain families; about half of the schizophrenic adoptees have schizophrenia in their biological relatives, and the other half do not, supporting what the 50 percent concordance in monozygotic twins indicates—the importance of environmental as well as genetic factors.

These studies also emphasize the likelihood that schizophrenia is a heterogeneous collection of many disorders with a common pathological process producing the characteristic symptoms which schizophrenics share (9). There is at present suggestive evidence that birth injury may cause some kinds of schizophrenia, and evidence from studies of cerebrospinal fluid suggests that the cytomegalovirus may cause some forms of schizo-

phrenia. There may also be dietary factors and rearing factors that operate with or without a genetic predisposition to bring about a state of schizophrenia. But there is obviously a great deal of work to be done, to better define not only the genetic mode of transmission and form of genetic influence in schizophrenia, but also the types of environmental variables which appear to be important.

We have carried out a similar study of the relatives of depressed adoptees. Here we find an elevated prevalence of various types of depression in both the biological and adoptive relatives. One form, the so-called endogenous depression, which seems to come from within and is not precipitated by any known experiential event, is concentrated significantly in only the biological relatives.

Perhaps the most striking finding that has emerged from our study of depressed adoptees is the distribution of suicides in their biological and adoptive relatives as compared to that in the relatives of control adoptees. There are eighteen instances of suicides in all of these relatives, and fifteen occurred in the biological relatives of the depressed adoptees, the only group which was genetically related to them, even though in most instances they knew nothing about the whereabouts or fate of their adopted-away relative.

What this means, I think, is not that there is a gene for suicide or that some of us are wired in at birth to commit suicide. We know of many environmental factors that play an important role. The incidence of suicide varies markedly from one country to another, from one religion to another, and in the same country from one time to another. Practically every suicide is preceded by some drastic life situation. Perhaps the most reasonable interpretation is that among a large number of people who are subjected to some apparently hopeless or catastrophic life situation, only those will commit suicide who have some genetic predisposition to do so, or who lack the genetically derived hormones or neural processes that would favor an alternative response.

There is some interesting evidence that the biogenic amines may play a role in suicide; there is one report that in the cerebrospinal fluid of depressed patients who go on to commit suicide there is a significant decrease in serotonin metabolites. Another study involving normal college students found that those students who had the lowest levels of monoamine oxidase in their blood platelets had eight times more suicide in their family than did the students with the highest levels of that enzyme.

The studies of suicide, schizophrenia, and depression have demonstrated the importance of genetic factors in their occurrence or development. They have also suggested that the major mental illnesses are not simple or single diseases but are heterogeneous and multifactorial in nature. We must learn more about their genetic components and also

about the numerous environmental factors, biological as well as social and psychological, which are necessary for their development.

Chemical Synapses and Psychopharmacology

While the nature:nurture controversy was going on, those equipped to study the fundamental processes of the brain had not been idle. The past twenty-five years saw a dramatic growth in the neurosciences and an unprecedented development of knowledge regarding the brain and behavior. One of the breakthroughs that occurred, with special pertinence to psychiatry, was the recognition and demonstration of chemical transmission at the synapse, the highly specialized junction between nerve cells through which information is carried.

Previously, the brain had been thought of as a highly complex electrical computer. While the ultimate energy source for this computer was known to be biochemical and involved the utilization of oxygen and glucose, it was widely believed that the "wiring" of the computer itself was electrical rather than chemical in nature. The discovery of chemical synapses changed this picture radically. It now became evident that the brain was different from any machine which had ever been devised by man; it was a computer in which the billions of switches were not electrical but chemical switches which were turned on and off by biochemical processes. Since sensory processing, perception, the storage and retrieval of information, thought, feeling, and behavior all depended upon the operation of these chemical switches, this discovery suggested the important sites at which chemical substances, metabolic products, hormones, and drugs could modify these crucial aspects of mental state and behavior. If there are biochemical disturbances in mental illness, they could be expected to have effects at the synapses; and drugs which alleviate these illnesses should exert their influence there as well.

Although there may be hundreds of billions of synapses in the human brain, they are organized in a marvelously systematic way along certain pathways that are being mapped by neuroanatomists. Scientists have identified several types of neurotransmitters and have found these different substances to be associated with different pathways, functions, and behavioral states. The catecholamine transmitters adrenaline, noradrenaline, and dopamine were first identified in the adrenal gland and in the peripheral sympathetic nervous system; they are now known to be important neurotransmitters in the brain, where they appear to be involved in emotional states such as arousal, rage, fear, pleasure, motivation, and exhilaration. Serotonin, first discovered in the intestine, was also identified in the brain, where it seems to play a crucial role in sleep and wakefulness, in certain types of sexual activity, and perhaps in modulating, damping,

and balancing a wide range of synaptic activity that we are only beginning to understand. Acetylcholine, the transmitter between nerve and muscle and therefore a key to every voluntary movement, is also known to be involved in a significant proportion of brain synapses. There are amino acid transmitters such as aspartic, glutamic, and gamma-aminobutyric acid, and the exciting new repertoire of polypeptides; and, undoubtedly, many more remain to be found. Fundamental knowledge of the synapse and chemical neurotransmission has important implications for the understanding and treatment of nervous and mental disease and represents an area of unusual promise for the future.

While noradrenaline and serotonin were being identified in the brain, several drugs were discovered quite independently, and almost accidentally, to exert important effects on mood. The first of these was reserpine, which was known to be useful in the treatment of hypertension. In a small percentage of patients, reserpine produced a state of depression very much like that known to psychiatrists. At the same time, scientists at the National Heart Institute made the important discovery that reserpine caused a decrease in levels of serotonin and noradrenaline in the brain.

A few years later a new drug, iproniazid, was shown to be highly effective in the treatment of tuberculosis. When it was found to cause emotional excitement in some patients, it was supplanted by other drugs equally effective and without such side effects. But this strange side effect of iproniazid, while a hazard in the treatment of tuberculosis, became the basis for an effective treatment of depression. It was discovered that iproniazid blocked the enzyme monoamine oxidase, which is responsible for inactivating serotonin and the catecholamines. Thus, iproniazid enhanced the effect of these transmitters, an action opposite to that of reserpine. A number of other monoamine oxidase inhibitors were developed, which were also effective in the treatment of depression. Even more effective were the tricyclic antidepressants, including the drugs imipramine and amitriptyline, which enhance the synaptic actions of noradrenaline and serotonin by another mechanism than monoamine oxidase inhibition. Electroshock therapy is effective in the treatment of patients with some kinds of severe depression; and it is interesting that the administration of similar shocks to experimental animals also increases the levels of noradrenaline and serotonin in their brains, and changes the activity of some of their receptors.

In 1950 a drug was developed which was found to be more effective than any previous treatment in the relief of the major symptoms of schizophrenia. This action was discovered in an interesting and unexpected manner. Pharmacologists had been developing and studying drugs which blocked the action of histamine; one of these drugs also blocked the activity of the sympathetic nervous system. Laborit, a French anes-

thesiologist, had been looking for a drug which had such properties for use in the prevention of surgical shock, reasoning that both histamine and sympathetic overactivity might contribute to shock in surgical operations. He used this drug in preoperative medication and noted that it produced an unexpected sedation in his patients. This sedation was different from that which was known to occur with the barbiturates; Laborit described it as a "euphoric quietude." He felt that such an effect might be helpful in the treatment of disturbed patients, and suggested this to some psychiatrists. The drug used by Laborit was the immediate forerunner of chlorpromazine, which revolutionized the treatment of schizophrenia.

Chlorpromazine was immediately seized upon and used throughout the world because it was different from any previous treatment for schizophrenia. While this new drug quieted schizophrenics, it didn't act like a tranquilizer; its action was much more specific. Not only would it quiet a disturbed and agressive schizophrenic patient, it would also attenuate his hallucinations and delusions. In a normal individual this drug has a sedative effect but does not interfere with normal thought processes. It appears to be acting specifically upon the behavioral and cognitive features that characterize schizophrenia.

It was suggested first by Arvid Carlsson (10) that the antipsychotic drugs might act by blocking the effects of dopamine in the brain, since this would explain their tendency to produce the symptoms of Parkinson's disease. It is now clear that Carlsson's insight was correct. A common action of all of the antipsychotic drugs which have now been developed is their blockade of dopamine receptors within the brain.

These findings do not necessarily indicate that schizophrenia is caused by an overactivity of dopamine synapses. One hypothesis does hold that the disorder is due to an excess of dopamine, stemming perhaps from a deficiency in the enzyme responsible for converting dopamine to noradrenaline; but there are several other possibilities. Dopamine-containing neurons interact with many other neurotransmitters and neurohormones in the brain. For example, dopamine inhibits the release of the hormone prolactin from the pituitary gland; the phenothiazines, by blocking the effects of dopamine, have been shown to raise levels of prolactin throughout the bloodstream and in the cerebrospinal fluid. The activity of dopamine pathways is also affected by neural circuits that use acetylcholine, serotonin, gamma-aminobutyric acid, and the endorphins, and it could be that these substances are more directly related to schizophrenic symptoms. But whatever the reasons for the therapeutic effects of the antipsychotic drugs, it is clear that continued and expanded research in the field of neurotransmitters, their distribution and synaptic activity, and on the interrelationship of these neurotransmitters to behavior at very

basic as well as clinical levels, cannot help but contribute to our understanding of these illnesses.

Application of Brain-Imaging Techniques to Mental Disorders

Recently a convergence of sophisticated mathematical, physical, and biochemical concepts and techniques on the human brain has resulted in observations of considerable interest to those concerned with the nature of mental illness. These represent early glimpses into what appears destined to become a highly productive area of clinical research. By making a large number of measurements of radiographic density at various angles through the head and solving the series of resulting equations by means of a computer, it is possible to reconstruct the brain in a series of sections, each displaying the components in varying shades depending on their individual densities. Computerized tomograms, or CT scans, of the brains of schizophrenic patients have now been obtained by several groups and show rather consistently that abnormalities in ventricular volume, signifying subtle atrophic changes in various parts of the brain, occur in about 25 percent of such patients. Furthermore, the patients so affected differ from the others in showing more indications of dementia. Conversely, the schizophrenic patients without demonstrable brain abnormality are more apt to display hallucinations and delusions, to respond more favorably to antipsychotic drugs, and to show other signs of dopaminergic hyperactivity. It is reasonable to expect further progress in the differentiation of types of schizophrenic illness from this approach and some clues regarding the location in the brain of the pathological changes responsible for particular symptoms.

The early studies which found no change in the overall circulation and metabolism of the brain in this disorder left open the possibility that such changes might still be present in particular areas of the brain, and led to the study of these functions locally (11, 12). The new technique of positron emission tomography (PET) can demonstrate and measure the regional accumulation of certain isotopically labelled substances making it possible to visualize regional blood flow and glucose metabolism in the human brain. Because of the close linkage that exists between functional activity in the brain and the glucose metabolism and blood flow which support it, these procedures are capable of visualizing the functional activity throughout the entire brain, not simply the electrical activity at the surface which has been accessible to study by the electroencephalogram. In the limited number of schizophrenic patients thus studied to date there appears to be a reduction in both the circulation and glucose metabolism in the frontal lobe. This lobe, which has major connections with the limbic system and has been known to be associated with many of the higher mental

functions, may thus emerge as a prime site in which to search for the morbid processes responsible for the symptoms of schizophrenia.

It would be premature to suggest that at the present time any of these provocative morphological, physiological, or biochemical findings are capable of explaining or are even characteristic of the major mental illnesses or clearly defined subgroups. What has emerged are still hypotheses or preliminary findings, but for the first time these are plausible and heuristic. And, of equal importance, a generation of new investigators, well grounded in the fundamental biological disciplines, has entered the field of psychiatric research, equipped with powerful new techniques and concepts.

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DEPARTMENTS OF MEDICINE: EXAMPLES OF ACADEMIC HYPERTROPHY

ROBERT G. PETERSDORF

Departments of medicine are commonly described as the linchpins of medical schools. They are often the largest departments in the medical school and, indeed, in the entire university. They do the most teaching of medical students, have the largest house staff, train the greatest number of fellows and, in most institutions, do the most research. Most have major service responsibilities. Perhaps because of their size, they are also the most vulnerable to the perturbations that are engendered by the external environment of any teaching institution, such as changes in the level of funding by the National Institutes of Health, reimbursement formulae of third party carriers, and level of state appropriations. Moreover, because of their diverse functions, these departments are more vigorously buffeted by change than any other clinical departments. Today, I want to examine one aspect of departments of medicine—their extraordinary size—to analyze how they came to be so large, and to make some suggestions for their containment.

Probably the single largest factor in the growth of departments of medicine has been their organization into subspecialty divisions. This was

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an amorphous movement that began in many schools about 1950. Divisionalization of departments of medicine certainly has some definite advantages. It groups individuals with common research interests; it facilitates the care of patients whose disease is primarily in the organ-system subserved by the division, permitting the busy, and usually peripatetic, academician to be cross-covered for patient care; and it tends to improve teaching, if not of medical students, of advanced residents and fellows. It also makes large departments of medicine governable, to the extent that these departments are governable at all.

On the other hand, the inexorable trend to divisionalization has resulted in progressively narrower individuals in departments of medicine. Being narrow in a field of research is understandable; being a master in one field of pedagogy is defensible; but being excessively narrow in patient care may be to the advantage of some patients but to the detriment of others. Moreover, divisionalization brings with it a sense of professional isolation. Somehow, pretty soon, faculty will identify with a division of a department and not the department itself; and soon thereafter they are placed by students and some colleagues in "departments of cardiology" or "departments of endocrinology," rather than in departments of medicine. This is too bad, because whatever "clout" departments of medicine in medical schools have had, or still have, is based in part on their unity and size, and when both unity and size are sacrificed to divisional autonomy, the influence of the department of medicine in the medical school will inevitably diminish.

The degree to which subspecialization has flourished was not imagined by anyone in academe as recently as twenty years ago. In 1957, my distinguished predecessor as chairman of the Department of Medicine at the University of Washington, the late Dr. Robert H. Williams, conducted a survey among department chairmen of medicine in which he inquired about the size of their departments in 1957 and the size and distribution of faculty that they desired by 1970 (1). The average number of faculty in the departments surveyed in 1957 was 15, and the chairmen hoped that these numbers could increase to 32 by 1970! Among these 32, they wished for 4 general internists, 3 cardiologists, 2 endocrinologists, 2 neurologists, 2 hematologists, 2 gastroenterologists, 2 pulmonary disease specialists, 2 dermatologists, 2 nephrologists, 2 infectious disease physicians, 2 rheumatologists, and 1 allergist, 1 nuclear medicine specialist, 1 oncologist, 1 geneticist, 1 nutritionist, 1 clinical pharmacologist, and 1 gerontologist. A sizable plurality of chairmen considered the subspecialities of nuclear medicine, oncology, genetics, nutrition, pharmacology, and geriatrics superfluous and indicated that they did not need them in their departments at all.

As crystal ball gazers, the department chairmen in 1957 left something to be desired. If the Department of Medicine I chaired from 1964 to 1979

serves as an example, their estimates of optimum departmental size were exceeded twofold in 1964 (six years before the projected target date), fivefold by 1970, and tenfold by 1980 (Table 1) (2). Admittedly, our department of medicine was large to begin with and grew still larger, but I would venture to say that its rate of growth—fivefold between 1959 and 1964, and fivefold between 1964 and 1979—was no greater than that of many other departments of medicine.

While I admit that the rapid growth of knowledge in categorical specialities, the emergence of highly specialized technology applicable to patient care, and the revamping of curriculums along system-oriented lines made the organization of departments of medicine along divisional lines inevitable, could not the divisions have remained as the one- or two-person operations that were visualized by the chairmen in 1957 instead of growing to a size that now exceeds most surgical and basic science departments combined? Let me review briefly the reasons for the phenomenal growth of departments of medicine.

In 1964, when I became department chairman, both my predecessor, in his valedictory, and I, in my maiden speech, justified continued growth for a department of medicine that had already increased fivefold in the preceding five years. We did so primarily because we felt the need to

TABLE 1

Number of Faculty, by Specialty, in the University of Washington Department of Medicine

Specialty	No. of Faculty		
	1964	1970*	1979
Allergy	1	1	3
Infectious disease	3	8	16
Ambulatory (general) medicine	0	6	33
Cardiology	7	12	19
Clinical pharmacology	1	2	5
Dermatology	3	5	10
Gastroenterology	5	7	12
Hematology	9	13	20
Medical genetics	5	8	14
Metabolism and endocrinology	14	26	44
Gerontology	0	0	3
Nephrology	4	9	17
Neurology	5	10	18
Nuclear medicine	1	3	7
Oncology	1	8	26
Respiratory disease	1	6	15
Rheumatology	2	4	7
Other	7	20	53
Total	69	148	322

* Numbers for 1970 are estimates.

train more manpower for research, for subspecialty practice, and for the practice of general internal medicine; and we rationalized that we needed to enlarge the faculty to perform research, to teach, and to care for patients. Now, in 1982, these rationales no longer apply, if indeed they ever did. But how did we become victims to this numerical overkill in the first place?

One reason was the expansion in the number of medical students in almost every medical school. On the average, most medical schools doubled the size of their classes between 1964 and 1979. This sheer increase in numbers doubled the undergraduate teaching load of the department of medicine. Moreover, yet another factor was added by curricular revisions that, in many schools, mandated teaching by body systems. When anatomy, physiology, pathology, pharmacology, and clinical correlations are taught together for each system, the department of medicine is bound to absorb an increased teaching load. Indeed, when the curriculum at the University of Washington School of Medicine was altered along these lines, our department ended up with a significant amount of teaching in the cardiovascular, respiratory, renal, endocrine, neurological, dermatological, gastrointestinal, and musculoskeletal system courses. We also taught the major part of medical genetics and hematology, not to mention history-taking and physical diagnosis. Given the larger classes and the altered curriculum, it seems fair to assign a growth factor of at least 2.5 based on medical student teaching alone.

Although graduate medical education has not increased at the same rate as undergraduate education, in our department the graduate teaching load nearly doubled between 1964 and 1979. In 1964 we had 24 interns, 42 residents, and 82 fellows, a total of 148 graduate trainees. In 1979 the number had increased to 265—34 interns, 82 residents, and 149 fellows. Moreover, fellowship training had expanded to encompass several new specialities—general medicine, clinical pharmacology, gerontology, oncology, and respiratory disease. In 1964 we had no trainees in any of these subspecialties; in 1979 there were 32 fellows in training in these five disciplines, and a sizable number of residents on rotation.

Departments of medicine are also assuming a significant teaching load by taking under their wings a substantial number of residents from other departments. This phenomenon was nonexistent in 1964 except for rotating interns (among the 24 interns assigned to medicine at that time were 10 rotating interns). In 1979 we said grace over 14 full-time equivalent, house officers from programs in family medicine, surgery, rehabilitation medicine, psychiatry, ophthalmology, orthopedics, obstetrics, anesthesiology, and several others. While these additional house officers certainly help with the work, they also preempt more teaching time from the faculty.

Finally, there has been a sharp increase in the contributions that the

faculty is making to the field of continuing medical education. Unfortunately, there are few quantitative data to substantiate this point. It is clear, however, that at the University of Washington, continuing medical education progressed from participation in an occasional postgraduate course to monthly forays into each of our WAMI[1] units in Wenatchee, Washington, and Missoula and Billings, Montana, and to affiliated programs in Yakima and Spokane, Washington, and in Boise, Idaho. It is my conservative estimate that the participation in continuing medical education quadrupled in the course of fifteen years.

Next to teaching, a second major factor instrumental in the significant growth in the faculties of departments of medicine has been the availability of funds for research and research training. Although inflation has brought marked erosion of the research dollar, there has, nonetheless, been an absolute increase in research dollars in many departments of medicine. For example, in 1964 our department had 12 research faculty; in 1979 there were 67. In our system, research faculty consist primarily of individuals with advanced—either master's or Ph.D.—degrees who spend all of their time doing research and who are paid solely from research grants and contracts. In addition, there are now a large number of regular faculty, part of whose income comes from research grants or contracts, training grants, or research career development awards.

The temptations placed before talented and entrepreneurial clinical investigators by center grants, program projects, special career development opportunities, etc., are too good to pass up. Since the successful applicant necessarily has to commit himself to do more research, he obviously needs more people to help him fulfill his other obligations. In quantitative terms, our research enterprise quintupled between 1964 and 1979. It is not clear, of course, whether the faculty needed to compete for all the grants that it has managed to attract. But on the other hand, a good aggressive faculty that competes successfully for peer-reviewed grants is much more likely to assure academic excellence than one that fails to do so.

A third factor that has increased the demands on departments of medicine has been a marked increase in clinical responsibilities. In numerical terms, the number of in- and outpatients with whom we dealt at Washington approximately doubled. But several other influences conspired to increase the clinical load far above that. The first was a shift from house-staff care to care by attending physicians. Prior to the advent of Medicare and Medicaid, it was customary for full-time faculty in departments of medicine to make rounds for two hours a day, three times

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[1] WAMI is an off-site education program based in community clinical units and universities in Washington, Alaska, Montana, and Idaho, and is supervised by the University of Washington School of Medicine.

a week. Private patients were few, and clinical responsibilities were by no means demanding. Nowadays, however, Medicare and Medicaid regulations require that attending physicians see every patient every day, and document this care by carefully written notes. Put differently, in order to get paid for their services, which is an absolute necessity, faculty, rather than house staff, have now assumed the responsibility for patient care. It is not uncommon for an attending physician "on service" to spend twenty hours a week in patient care. Secondly, the development of technology has increased the time commitment of some subspecialists in internal medicine appreciably. This has been true most particularly in cardiology and gastroenterology, and to a lesser extent, in pulmonary disease and nephrology. Teaching and doing procedures are time-consuming and, in these specialties, they have added much patient-related activity to the day of each faculty member. Thirdly, in many institutions, a progressively greater portion of the faculty members' income is derived from patient care, and that requires devotion of more time and effort to the clinic and the bedside than was the case fifteen years ago. My estimate is that all of these influences have combined to increase the total faculty effort in patient care at least threefold during the past fifteen years.

In addition, there are the numerous other activities faculty members in the department of medicine are required to perform—activities that can best be termed bureaucratic. These range from such mundane tasks as time-and-effort reporting to the enormous amount of time expended in grant writing. Many departments have an elaborate internal committee structure that deals with all aspects of the curriculum, space, finances, program, etc. To this must be added the academic and nonacademic committees of the medical school, the university, and the hospital. Before the unsuspecting faculty member knows what has hit him or her, a substantial amount of time has gone into administration and faculty governance. I surmise that this activity has increased sixfold in the fifteen years during which I was chairman, despite my earnest efforts to run the department with a minimum number of committees and my well-known tendency to make most decisions unilaterally. I have always contended that benign despotism (I emphasize the word *benign*) is a more efficient form of faculty governance than democracy.

In Table 2, I have modeled the total activities of a department of medicine in 1964 and 1979. Given the expanded activities of the department, it should take three times as many faculty to accomplish the multiple tasks of a department of medicine now as it did fifteen years ago. Yet our department increased in size five times rather than three, implying that there were some major inefficiencies in departmental operation. One that I want to discuss briefly is geographic dispersion.

The two forms of academic tender that govern departments of medicine are space and money. Space, in turn, can be divided further into research

TABLE 2
Functions of a Department of Medicine in 1964 and 1979*

Function	Units	
	1964	1979
Teaching		
Medical student	2	5
Intern, resident, fellow	2	4
Continuing medical education	0.5	2
Research	2	10
Patient care	2	6
Other (administration)	0.5	3
Total	9	30

* Measured in arbitrary units.

space and clinical space, e.g, beds. Unless a department is fortunate enough to be part of an expansion program at its home site, the tendency has been to look for space outside the parent institution and to affiliate with other hospitals. For example, in Seattle, the University of Washington Department of Medicine affiliated with the U.S. Public Health Service Hospital in 1961, for the express purpose of acquiring more research space; a clinical affiliation did not follow until 1968. Likewise, the department affiliated with the Tacoma Veterans Administration Hospital in 1975 for the purpose of establishing a research program; plans for a clinical affiliation have not been consummated.

The degree to which space considerations influenced affiliations at the University of Washington was astounding. In 1964, the Department of Medicine had 53,000 total square feet of space, 40 percent of which was on the campus. In 1979, the department occupied approximately 160,000 square feet of space, only 25 percent of which was on campus. Put differently, in the fifteen-year period under discussion, campus space approximately doubled while off-campus space increased fourfold.

A second major reason for seeking affiliations is to obtain control of beds for medical student teaching or graduate education and, in a few instances, to enhance practice opportunities. In the competitive climate of practice in Seattle, with its large cadre of highly competent internists and subspecialists, the department would not and could not expand its base for private practice, but it needed to acquire more opportunities for teaching its medical students, house officers, and fellows. In order to attain this goal, the department affiliated with three large community hospitals, two in Seattle and one in Spokane, and also forged a strong alliance for purposes of teaching students and training residents with a previously non-deans committee Veterans Administration Hospital in Boise, Idaho. As part of the WAMI program, affiliations were created

with three group practices, two in central Washington and one in Montana. A consequence of these multiple affiliations has been that faculty has needed to be recruited for all of them. This geographic dispersion, therefore, required considerable expansion of faculty above the threefold increase projected on the basis of increased functions alone.

An inherent defect in carrying out teaching and research programs in multiple hospitals is that a number of facilities and services need to be duplicated. For example, in each of our major affiliated hospitals, we were required to have, at a minimum, a division of cardiology, gastroenterology, hematology, oncology, pulmonary disease, and a number of others. We had to operate four sets of clinics; we needed four chiefs of service. In short, we suffered from a dyseconomy of scale. Moreover, because some of our hospitals were federal institutions, others were state-owned, and still others private, bureaucratic roadblocks made sharing of facilities and services difficult. However, that was not the major reason for duplication; the geographic distance between institutions simply made it necessary to have similar services at each of the hospitals. Moreover, we did not duplicate all specialty services by any means. For example, we had cardiac catheterization laboratories at only two of the hospitals. However, the more necessary a service was to patient care, the more likely it was needed at each of the hospitals. The duplication engendered by this multiple hospital system accounted for at least an additional 20 percent increase in the size of the department.

Our department was made still larger by the need to have a critical mass at each of the teaching hospitals. We found that one-man divisions simply were not academically viable. When we assigned a single faculty member in a subspecialty to one of our hospitals, it soon became evident that he became the victim of his clinical duties, spent most of his time in teaching and seeing patients, and had no time for research. He became tired and disgruntled and, when promotion time rolled around, found that he had not been able to do enough research to meet the requirements of the Promotions Committee. It became necessary, therefore, to increase the divisions in each of the hospitals to a minimum of two persons and, in many instances, more. The necessity for adding faculty beyond what we had projected accounted for yet another increment in the size of the department.

I do not believe that this analysis of the size of the Department of Medicine is unique to the department at the University of Washington. On the contrary, I have observed similar developments in many other institutions. Moreover, as community hospitals have sought affiliations with academic departments of medicine, the pressure on the departments to expand has increased greatly. I believe, however, that for several reasons, the time has come to call a halt to this unbridled growth. In the

first place, in most institutions, the population explosion has not been paralleled by a growth in space. In our department, for example, while the number of faculty increased fivefold, the amount of space increased only threefold. Secondly, it is difficult to maintain quality in the face of rapid growth. It is patently impossible for the department chairman to monitor the quality of research, teaching, and patient care; and in many institutions even the division head is unable to do it. Thirdly, the financial resources to keep departments afloat are rapidly reaching saturation. And finally, the collegiality that is so much a part of the academic life, comes a cropper due to size.

While the multi-institutional system clearly has some of the disadvantages that I have mentioned, there are a number of positive features, not the least of which is the ability of the department to retain its best faculty members by giving them the opportunity to lead a smaller unit at an affiliated hospital. This permits more faculty to have more autonomy. Put in the vernacular, everybody can be a boss! It also allows for more diversification within a subspecialty. For example, in hematology, we had an iron laboratory in one institution, a clotting laboratory in the second, a red cell biochemistry laboratory in the third, and a laboratory dealing with platelets and cell kinetics in the fourth. This would not have been possible without the multihospital system.

I have made the assumption that the size our departments of medicine have reached is supraoptimal. Is this assumption correct? How do we know that big is not beautiful? I believe firmly that we have become too large and are suffering from an advanced case of academic hypertrophy, specifically:

—We have run out of space to accommodate the enlarging faculty.

—We are also running out of money. Certainly, the means to pay faculty from research grants is shrinking. At the same time, state appropriations (in the case of state schools) and endowment income (in the case of private schools) are at a plateau.

—Turning to practice to finance departments of medicine is a double-edged sword. It requires that more people be hired to do the practice or to substitute for the investigator who is called from the bench to the bedside or the clinic. Unless more patients are needed for teaching, to increase a department's involvement in patient care simply to put money into the departmental coffers is not a sufficiently strong reason to engage in this form of indoor sport. Moreover, it often costs more than it brings in.

If big is not beautiful or is even ugly, what can we do to contain size?

—First, we need to prevent academic accretion. Most departments of medicine grow from below. Division heads have a great tendency to keep the best of their fellows for a year or two at the instructor or

assistant professor rank, just to finish up some work, or to wait for a better job, or to see if that grant on which an additional faculty salary has been requested—but probably not funded—will come through. But pretty soon the year or two turns into three or four, and, believe it or not folks, it's tenure time. We have to stop this insidious growth from below, which over the years has placed such an enormous drain on the institution.

—We need to agree not to replace all faculty who retire, die, or leave. In fact, one of my decanal decrees is that all vacant state positions be returned to a pool to be reassigned to whatever departments need them, and that all replacement positions, even if funded by the hospitals, grants, or other sources, have the approval of the dean's office.

—We need to say no to the invitation to make more affiliations with community hospitals. By all means, let's help community hospitals start their own programs if we feel it appropriate, but let's not take the responsibility for them.

—Department chairs need to exert proper control over their division heads, and need to have a division head justify the need for filling open positions.

—Departments need to curtail unbridled growth of training programs, particularly in the subspecialties, because more trainees require more faculty.

—Departments of medicine need to learn to live within their means, paying in cash instead of with credit cards. The time when we could "bet on the come" is gone.

—And, finally, we need to learn to plan ahead—not only for growth but for phased deceleration. Hopefully, that will result in the proper balance between the teaching, research, and patient care missions of our departments of medicine.

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CONSEQUENCES OF THE RISING NUMBER OF PHYSICIANS AND OF THE GROWTH OF SUBSPECIALIZATION IN INTERNAL MEDICINE

ALVIN R. TARLOV

The connection, or disconnection, between the medical education/training system and the health care delivery system is the subject of this paper. Provision of an appropriate supply of physicians to meet the needs of the nation is one example of the requirement to coordinate the systems of education and delivery. I am going to consider the physician population both in the aggregate and in each specialty with emphasis on internal medicine. The information presented will be primarily from two sources, the Graduate Medical Education National Advisory Committee (GMENAC) and the National Study of Internal Medicine Manpower (NaSIMM) at the University of Chicago.

ALVIN R. TARLOV graduated from Dartmouth College in 1951 and from the University of Chicago School of Medicine in 1956. He held an internship at Philadelphia General Hospital, then returned to Chicago as resident in medicine, 1957–58 and 1962–63. He was appointed Chairman of the Department of Medicine at the University of Chicago in 1968, a post he held until 1981. Dr. Tarlov has participated in a number of national activities, filling the important post of Chairman, Graduate Medical Education National Advisory Committee (GMENAC), Health Resources Administration, Department of Health and Human Services, from 1978–1980. This committee attracted a great deal of national discussion when it predicted a surplus of physicians for 1980 and pointed out the need for a better balance in the various medical specialties. Dr. Tarlov is now Professor and Head of General Internal Medicine, Department of Medicine, University of Chicago.

Background

Accompanying the startling advances in the sciences in the twentieth century has been a rising public confidence in the usefulness of health services. Forceful action to improve the availability and quality of health care was taken by the industrialized countries after World War II. These nations now expend 5–10 percent of their gross national product on health. Much of the initiative in the Western European nations, where the modern welfare state was in development, was instigated by governments. Yet even in those nations where the education and health care systems are largely government controlled, there has been little coordination between medical education and the health services system. As a result, there are rising numbers of unemployed physicians in Europe, some of whom now appear on the unemployment welfare rolls (estimated to be 6,000 in Spain, 1,400 in France, and 600 in the Netherlands) (1).

Health services planning in the United States often is a joint undertaking between committees and commissions which make recommendations through reports, and the government which provides funds for implementation. Direct government intrusion into medical education or into the provision of health services has been opposed or cautiously accepted. One net effect of this joint private/government relationship in the past twenty years has been a sharp increase in medical school enrollment.

The Bane Report to the Surgeon General in 1959 advised that the physician-to-population ratio of 141 to 100,000, unchanged since 1940, could not be maintained for the future unless the medical school (M.D. plus D.O.) graduating class size were increased from 7,400 to 11,000 (2). The report advised enlargement of the eighty-five existing allopathic and six osteopathic schools and establishment of twenty to twenty-four new schools. Urgency was expressed (pp. 62–63, ref. 2):

> . . . probably the greatest immediate obstacle to expanding the nation's medical educational capacity in existing schools and in the development of new schools is the problem of financing the needed physical facilities. . . . the Consultant Group is convinced that the nation's physician supply will continue to lag behind the needs created by an increasing population unless the federal government makes an emergency financial contribution on a matching basis toward the construction of medical school facilities. . . .

Four years later, through the Health Professions Educational Assistance Act of 1963, Congress provided construction funds. The objective of helping expand the medical schools was accomplished, although federal support for their operating costs was avoided.

Added enthusiasm for increasing the supply of physicians was provided in 1964 by the Coggeshall Report to the Association of American Medical

Colleges (3). Coggeshall, quoting from the report of the President's Commission on Heart Disease, Cancer and Stroke, wrote, " '. . . The first hard fact to be faced is that there is not enough health manpower to meet the needs of the American people. There are not enough doctors and not enough supporting people.' " The Coggeshall Report acknowledged the increase in the capacity of the medical schools but noted that the increase in supply of physicians was not commensurate with the need. The Coggeshall Report conveyed urgency and concluded (p. 26, ref. 3), "In light of the growing need for physicians, despite the hopeful off-setting factors, it is clear that more physicians must be trained as quickly as possible. . . . It must be recognized, however, that it is not likely that America will ever be able to produce all the physicians that the nation would like to have." The tone of the report conveyed urgency.

The Brown vs. Board of Education Supreme Court decision in 1955 and the Voting Rights Act of 1965 bracketed a decade of debate on the concept of rights as specific entitlements. Evolving from that decade was the concept of the right to health care, for which the capstone was the Medicare and Medicaid legislation of 1965 and 1966, which committed equal access to high quality health care for the aged and the poor.

The Medicare-Medicaid legislation created concern about the physician manpower to fulfill the national promise. In 1966, the president of the United States established the National Advisory Commission on Health Manpower, chaired by J. Irwin Miller, "to develop appropriate recommendations for action by government or by private institutions, organizations, or individuals for improving the availability and utilization of health manpower." The blue-ribbon commission (1967) reported (p. 19, ref. 4):

> The production of physicians should be increased beyond presently planned levels by a substantial expansion in the capacity of existing medical schools, and by continued development of new schools. Federal funds in support of capital or operating costs of education should be provided to a medical school in such a way that they create economic incentives for the school to expand enrollment while improving its quality. Such incentives should be based on increases in the absolute numbers of medical students.

On March 5 and April 16, 1968, shortly after the Miller Report was published, joint statements were released by the American Medical Association and the Association of American Medical Colleges (5). The statements read (p. 101):

> To meet national expectations for health services, the enrollment of our nation's medical schools must be substantially increased. At a joint meeting held in Chicago on February 28, 1968, the representatives of the Board of Trustees of the American Medical Association and the Executive Council of the Association of American Medical Colleges

> emphasized the urgent and critical need for more physicians if national expectations for health services are to be realized. National policy which would best meet this need and would be consistent with the American ideal of equal educational opportunity for all would provide such resources that every young person interested in and qualified for entry to the study of medicine would have this opportunity. Both associations endorsed the position that all medical schools should now accept as a goal the expansion of their collective enrollments to a level that permits all qualified applicants to be admitted. As a nation, we should address the task of realizing this policy goal with a sense of great urgency.

These two associations recommended that increased funding be made available to support the educational component of academic medical centers and that the production of an increased number of physicians be assigned the highest priority. Their support was important to the passage of the Health Manpower Act of 1968.

The Health Manpower Act provided loans and scholarships for medical and other students in the allied health professions, and funds to medical schools for facility construction, operating costs, and educational innovation (shorter curriculum) linked to the requirement to increase their class size (capitation grants). Expansion of the physician supply received further impetus from this 1968 legislation.

More encouragement for expansion was provided by the Carnegie Commission on Higher Education, *Higher Education and the Nation's Health*, the Clark Kerr report of 1970 (6). The commission, again expressing urgency, recommended a 50 percent increase in medical student enrollment, enlargement of the medical school–teaching hospital role to the status of academic medical centers, and development of Area Health Education Centers (AHECs) to help improve services in sparsely populated areas. These recommendations were influential in the health manpower bills enacted by Congress in the first half of the 1970s.

Each of the four reports of the decade 1959-1970—Bane, Coggeshall, Miller, and Carnegie—expressed a sense of national urgency, recommended rapid and vigorous action to increase the supply of physicians, and resulted in federal authorizations and appropriations designed to implement their recommendations. A national consensus had developed relative to the need for corrective action to alleviate the shortage of physicians.

The critical question, how many physicians were needed, was not addressed by the four reports. Given the lengthy "pipeline" of training and the thirty-plus years of professional practice thereafter, how many students should be admitted to the medical schools each year to meet the nation's needs in an orderly fashion for the decades ahead? Should overproduction be avoided? These questions were not addressed. A shortage was agreed upon. Corrective measures without limits or targets were quickly activated.

Supply of Physicians—1990

The initiatives taken in the 1960s and 1970s to expand the capacity of medical education succeeded. Between 1959 and 1978 the number of allopathic schools increased from 85 to 126. The number of osteopathic schools increased to 16. The entering class size of the allopathic and osteopathic schools combined doubled from 9,000 in 1965 to 17,800 in 1978, and will reach approximately 19,000 in 1982. The lengthy period of training, however, concealed this expansion from the active practitioner pool through most of the 1970s. Sharp increases in the number of physicians will become apparent in the 1980s and 1990s (Fig. 1). In 1978, there were 375,000 actively practicing physicians in the United States. By 1990 this number will have risen to 536,000 (7). The twelve-year increase of 160,000 practicing physicians, a 43 percent rise, will be only partially offset by a 9 percent growth in the population (Table 1). This growth in nine specialties is illustrated in Table 2. Note the 79 percent increase in the number of actively practicing internists. Concurrently there will be sharp increases in the number of nurse practitioners, psychologists, ophthalmologists, podiatrists, and other health workers.

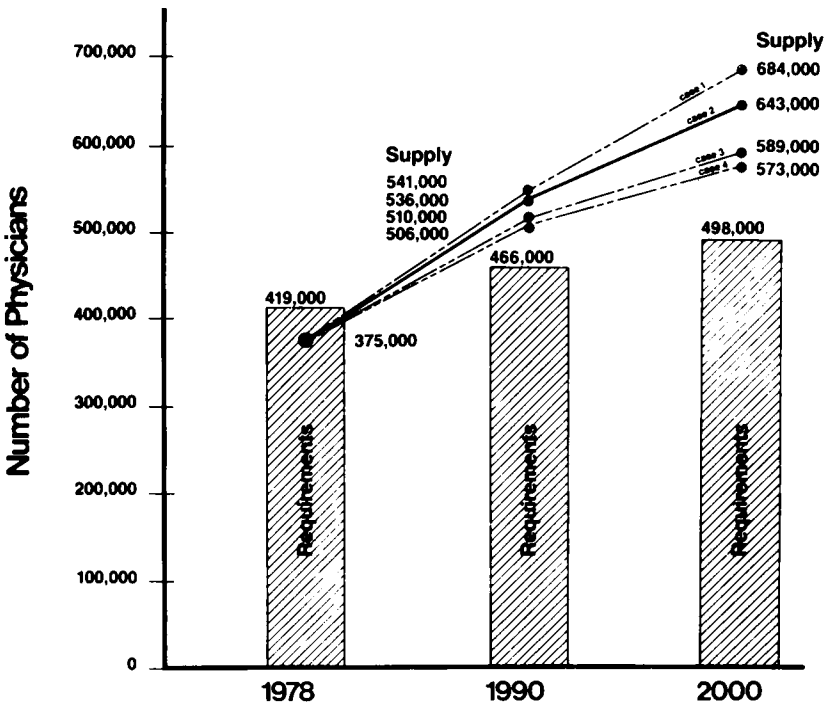

FIG. 1. Aggregate physician supply and requirements under four assumptions—1978, 1990, and 2000. (Data from reference 7, p. 8)

TABLE 1 (7)
*U.S. Population and Physician Supply**

Year	U.S. Population	Number of Students Entering Medical School	Number of Practicing Physicians	Population per One Physician	Physicians per 100,000 Population
	millions				
1965	181	9,000	278,000	651	145
1978	219	17,800	375,000	584	171
1990†	244	20,000	536,000	455	220

* Numbers of allopathic and osteopathic physicians combined.
† Projected figures.

TABLE 2 (7)
Physician Supply, 1978 and Projected for 1990

Specialty	Number of Physicians		Percent Increase
	1978	1990	
Osteopathic general practice	13,600	24,000	76
Family practice	54,000	64,000	18
Pediatrics	24,900	41,400	66
Internal medicine	72,200	129,000	79
Surgery	75,700	101,450	34
Neurology	4,850	8,650	78
Dermatology	5,000	7,350	47
Psychiatry	28,300	34,600	22
Obstetrics/gynecology	23,100	34,500	15
All physicians	375,000	536,000	43

At the beginning of this century, all internists were general in their training and practice. Special but not formalized interest in the diseases of one organ system was apparent among only a few internists. By the late 1920s, some departments of internal medicine established sections or divisions in a few subspecialty areas, notably cardiology, gastroenterology, pulmonary disease, respiratory disease, and nephrology. In the 1950s and 1960s, induced by the dramatic discoveries in the biological sciences, which were relevant to medical research and patient care, and encouraged by the advent of the National Institutes of Health extramural training grants in the subspecialties, the number of formal subspecialties in internal medicine increased to ten, and subspecialization of internists became the norm. By 1978 about one-third of all practicing internists were subspecialists (Table 3), and this rising trend continues. Presently, there are fourteen subspecialties. By 1990, over 40 percent of all internists will be subspecialists, and by the year 2000, more than 50 percent. At the end of this century, there will be more subspecialty internists than either general internists, family physicians, or pediatricians.

TABLE 3
Supply of Internists, 1978 and Projected for 1990

	Number of Internists		Percent Increase
	1978	1990	
General medicine	48,950	73,800	51
Allergy/immunology	2,100	3,050	45
Cardiology	7,700	14,900	94
Endocrinology	1,400	3,850	175
Gastroenterology	2,900	6,900	138
Hematology/oncology	3,000	8,300	177
Infectious disease	850	3,250	282
Nephrology	1,450	4,850	235
Pulmonary disease	2,800	6,950	148
Rheumatology	1,000	3,000	200
Total	72,150	128,850	79

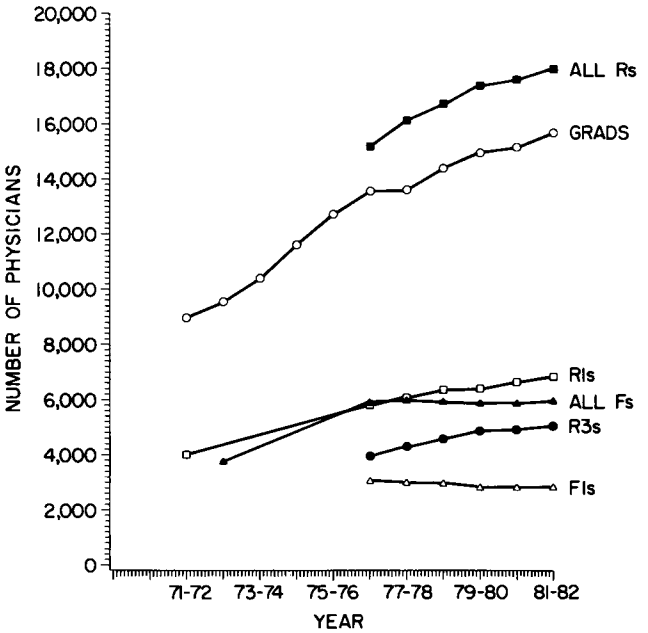

FIG. 2. Trends in internal medicine training.

Recent trends in the training of internists are summarized in Fig. 2 (8–11).[1] The number of M.D. graduates, currently at about 16,000, is continuing to rise. Approximately 35 percent of all graduates take their first postgraduate year as a resident in internal medicine (R1). The

[1] M. K. Schleiter, S. Blau, and A. R. Tarlov, unpublished data on 1981–82 residents and subspecialty fellows.

number of R1s continues to rise each year in proportion to the number of graduates. About one-fifth of the R1s plan and complete only one year of internal medicine and enter a training program in another specialty such as neurology, radiology, psychiatry, and others. The remaining four-fifths complete all three years of training. The number of "completers," R3s, continues to rise each year in proportion to the number of graduates three years before.

A high percentage of R3s elect to enter a two- or three-year fellowship training program in one of the subspecialties. In the first half of the 1970s, more than 75 percent of the resident "completers" went on to become subspecialists. Since 1977, the number of new subspecialty fellows (F1s) has remained constant. With the number of residents rising but the number of fellows remaining constant, the "subspecialization rate" has declined. A rough approximation of the subspecialization rate in any year can be obtained by dividing the number of F1s by the previous year's R3s. As illustrated in Fig. 2, the subspecialization rate has declined but continues to exceed 50 percent. In the 1990s, therefore, we can expect the number of subspecialty internists to exceed the number of general internists.

How many subspecialty internists are needed? Critics assert: (*1*) subspecialty internists establish practices in densely populated areas where physicians are least needed; (*2*) their orientation toward instruments and procedures leads to high application of technology; (*3*) their practices consist of a high proportion of general medical care where they approach problems outside of their specialty with less than ideal zeal; and (*4*) their fees are higher than generalists' fees. Conversely, advocates of subspecialty medicine assert: (*1*) the subspecialist, when dealing in his respective organ system, arrives more expeditiously at the correct diagnosis and therapy, thereby decreasing the length of illness and costs; and (*2*) subspecialists provide high quality general medical care because of having had full residency training in internal medicine prior to subspecialization. These rival views cannot be answered because of the lack of data comparing the outcome of care provided by different specialties. A National Outcome Study has been undertaken to address this problem. Outcomes will be measured in terms of the patients' functioning in their natural environment in neuromuscular, intellectual, emotional, social, and major role categories, as well as in terms of disease status, patient satisfaction, and cost-effectiveness. Meanwhile the debate continues at the level of assertive argument, with the author's preference for a subspecialization rate of about 30 percent.[2]

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[2] The requirements for academic internists, most of whom need subspecialty fellowship training, have not been specifically considered in this paper. Their numbers, however, are small relative to the total number of subspecialty fellowship positions.

Requirements for Physicians

Many methods have been used to estimate the number of physicians needed: physician-to-population ratios, the number of physicians employed in closed systems of care, a percentage of the gross national product, and various mathematical models of either the *demand* for medical services (current use rates projected to the future) or the *needs* (idealized) for services.

The most widely used method is the physician-to-population ratio, expressed as the number of physicians per 100,000 population. From 1940 to 1959, there were 141 physicians/100,000 population in the United States. Bane in 1959 recommended maintaining that ratio. (In 1978 the country reached 171/100,000 which will increase to 220/100,000 by 1990.)

Several "closed" systems for delivery of comprehensive health services to a fixed population provide experiences from which the needed number of physicians in each specialty can be estimated. The Kaiser-Permanente system, other large health maintenance organizations, the Veterans Administration, and the military services are a few examples.

Some of the European nations set annual limits on expenditures for health care as a percentage of the gross national product or of the national budget. They then target their health manpower requirements according to the fixed expenditure.

The Adjusted Needs-Based Model was developed by the Graduate Medical Education National Advisory Committee (12, 13). Large-scale national data bases collected continuously in our country over the past two decades provide an opportunity to estimate the requirements for physicians' services on an empiric basis. Data are available for both the incidence/prevalence of medical conditions and the norms of medical care for these conditions, including the number of visits to the doctor's office, hospitalization rates, and surgical rates. Measures of physician productivity have also been collected in each specialty, including numbers of patients seen per week, hours worked per week, weeks worked per year, and time spent in the office, in the hospital, in continuing education, and in teaching, research, and education. Thus, the incidence/prevalence of each medical condition multiplied by the norms of care yields the service requirement for that condition. A portion of the requirement is subtracted to account for the care delegated to nonphysician health care providers such as nurse practitioners, psychologists, and other health professionals. The service requirements for physicians are then divided by physician productivity to yield a "head count" of physicians required to treat that condition. Completing this exercise for each condition and summing the results yield an estimate of the aggregate number of physicians required. Complicating this methodology is the need to adjust 1978 data for incidence, norms, delegated care, and productivity to 1990 or some later

date when biological, technical, economic, and social changes may lead to modified figures. Panels of experts were used to make these adjustments. The Adjusted Needs-Based Model was used by GMENAC to estimate the 1990 requirements for physicians. A decade or more of experience will be required to assess the assumptions and validity of the model.

All of the methods for estimating requirements for physicians have some value, and all have shortcomings. Nonetheless, the expected 1990 supply of 536,000 actively practicing physicians in the United States surpasses the estimated requirements derived from these methods.

Potential Effects of a More Than Adequate Number of Physicians

There is no agreement on the optimal numbers of subspecialty internists, general internists, specialists in other fields, and the aggregate number of physicians. Even if agreement could be reached, there would remain disagreement as to the desirability of exceeding the optimum. Many economists, applying concepts of market and competition theory, propose that a surplus of physicians would have the beneficial effects of improving the geographic dispersion of physicians and decreasing the price of services. Others have cautioned against a surplus of physicians.

Henry S. Pritchett, the first president of the Carnegie Foundation, wrote in his introduction to the Abraham Flexner Report of 1910, p. xiv (14):

> It is evident that in a society constituted as are our modern states, the interests of the social order will be served best when the number of men entering a given profession reaches and does not exceed a certain ratio.... When, however, six or eight ill-trained physicians undertake to gain a living in a town which can support only two, the whole plane of professional conduct is lowered in the struggle which ensues, each man becomes intent upon his own practice, public health and sanitation are neglected, and the ideals and standards of the profession tend to demoralization.... It seems clear that as nations advance in civilization, they will be driven to throw around the admission to these great professions such safeguards as will limit the number of those who enter them to some reasonable estimate of the number who are actually needed ...

On April 20, 1976, the Secretary of the Department of Health, Education and Welfare established the Graduate Medical Education National Advisory Committee. The charter of GMENAC indicated specifically that a surplus, or a shortage, of physicians should be avoided and that a balance between supply and requirements for physicians should be achieved through modifications in the numbers of training positions in graduate medical education.

The European Economic Community, concerned about the rise in

unemployment of physicians and other health workers in their countries, convened the European Symposium on Health Manpower Planning in Maastricht, the Netherlands, April 14–17, 1982 (1). In her opening remarks, Mrs. M. H. M. F. Gardeniers, Minister of Health and Environmental Protection of the Netherlands, stated:

> With regard to the discrepancy between the supply of qualified health care staff and the demand for their services, it is equally serious whether there is a surplus or a shortage. A surplus of staff can easily lead to the performance of tasks, which are either unnecessary or unnecessarily complicated, and it is not impossible to imagine a situation where the best possible treatment is given but is then continued, when it might be better to terminate it. In addition, the possible loss of skills and routine resulting from a surplus will do equally little to improve quality. Shortages are no less of a problem. If there are not enough staff, the patient may not receive sufficient attention, and waiting lists may build up. Surpluses or shortages are not only undesirable as far as the quality of health care is concerned; they are also unwelcome from the point of view of those being trained. If too many people are trained, some of them will discover that although they have studied for years they have no opportunity to practice their skills, or at best that they have to wait before they can do so. If on the other hand, too few people are trained they will discover that the demand for their services is too great and that they are over worked, which may lead to illness, absenteeism and a high turnover of the staff or premature departure from the profession.

Despite disagreement on the desirability of a surplus, we can nevertheless predict some of the outcomes from an expansion of the number of physicians. The predictions can be based on discernible trends already visible nationwide and on information from small areas in the United States which are currently highly supplied. The likely effects are in five categories: access, use rates and costs, physicians' practices, community hospitals, and academic medical centers.

Access to Medical Services. Available evidence indicates that, coincident with their increasing numbers, physicians are selecting to practice in more sparsely settled areas. The survey by the American Academy of Family Practice of their recent graduates (15), and the recent paper by Newhouse, Williams, Bennett, and Schwartz (16) suggest that the problem of rural underservice is quickly being resolved. The problem of urban underservice for the poor minorities, however, appears to be recalcitrant and relatively less affected by an increase in the aggregate number of physicians. Overall access to medical services can be expected to increase in the decade ahead.

Use Rates and Costs. Available evidence indicates that, under the current system of reimbursement for health services, an increased density of physicians per population is associated with increased utilization of medical services and increased costs.

Wennberg and Gittelsohn have examined the rate of surgery and other

forms of treatment in 193 small areas (hospital service areas) in the six states of New England (17). Surgical rates per capita and the amount spent per capita on treatment in hospitals varied substantially among the areas and was strongly correlated with the number of surgeons and the number of hospital beds per capita. Although the overall rates varied more than twofold among the areas, the rates for hysterectomy, prostatectomy, and tonsillectomy, three of the most common procedures, varied sixfold.

Dr. Karen Davis, of Johns Hopkins University, predicted that an increased supply of physicians for 1990 would increase hospital admissions, length of hospital stay, cost per hospital day, and health expenditures per capita (18). In her econometric analysis, she used the 202 U.S. health service areas as the geographic areas for analysis, the Bureau of the Census population figures and demographic information, National Center for Health Statistics data on health status measures, the American Medical Association data on physician supply and density, and American Hospital Association and Health Care Financing Administration data on use rates and expenditures.

Some changes in the financing of health services are likely to be in place by 1990. These changes may modify the utilization rates, prices, and total costs. It is doubtful, however, that these will be of an order to reorient markedly the economic forces in health care within the next eight years. Therefore, utilization rates and costs can be expected to increase in the decade ahead as the supply of physicians expands.

Physicians' Practices. Salaried positions are becoming increasingly attractive to newly training physicians in an increasingly competitive environment as they demonstrate willingness to sacrifice income flexibility in favor of income security and fewer work hours. Salaried positions are available not only in anesthesiology, radiology, and pathology, but in all other specialties in municipal hospitals, mental hospitals, veterans hospitals, the military service, prisons, and in industry. Increasing numbers of paid positions are being developed by community hospitals in emergency medicine, ambulatory medicine, and specialized procedures.

Despite past lack of physician enthusiasm, health maintenance organizations (HMOs) will enjoy even sharper growth in the future. A report by Interstudy, Minneapolis, showed that on June 30, 1980, there were 9.1 million HMO enrollees, an increase of 10.9 percent over the previous year, and that on June 30, 1981, there were 10.3 million enrollees, up 13.2 percent (19). Twenty million enrollees can be expected by the end of this decade.

The increasing aggregation of physicians in institutional-type practice and in salaried positions will encourage them to sacrifice some professional autonomy for their collective interests. Collective bargaining by physicians will become common. Physicians are turning to health care

marketing firms for advice on where to practice, what the people in an area do and do not like about their medical care, strategies for attracting new patients, and how much to charge.

Physicians can be expected to become more entrepreneurial as competition intensifies. They will develop and own such freestanding facilities for para-hospital activities as sophisticated laboratory and treatment centers, primary care centers, emergency centers, birth centers, surgicenters, wellness clinics, nutrition centers, jogging clinics, and others. Some of these activities will be in direct competition with the hospitals. Generalist and specialist physicians will compete for patients. Physicians will compete more aggressively against optometrists, podiatrists, psychologists, and in some areas, nurse practitioners. The increasing use of mass-media advertising will modify the public's perception of physicians.

The pressure of these shifts will be felt on doctor-patient relationships. Physicians will try harder to accommodate their patients. Early morning hours, evening hours, weekend hours, house calls, and other actions to facilitate access to service will be undertaken. Health and wellness letters are being sent by some physicians to their patients. The trusting covenantal relationship between doctors and their patients, which has characterized medical practice for hundreds of years, will react to the contractual structures inherent in many forms of organized medical service plans. Patients may change doctors more often as physician services become more available. The effect of these changes in practice characteristics on quality of personal health services, patient satisfaction, outcome of health services, and professional satisfaction of physicians is unknown.

Community Hospitals. Hospitals will experience greater competition for patients, physicians, and capital (20). Neighboring hospitals will compete for patients and for staff physicians by making their facilities more attractive, by broadening services provided, especially in ambulatory care and in high technology, and by establishing satellite and ambulatory facilities. Tension will develop between hospitals and staff physicians as they compete against each other for services formerly provided exclusively within the hospital setting under hospital auspices. Funds available for hospital development will become even further restricted because of competing national priorities for income maintenance, education, housing, urban renewal, transportation, nutrition, national defense, and health. Great pressure to reduce hospital costs will be exerted by industry, employee groups, insurance companies, and physician-owned provider/underwriter groups which are increasing in number and power. To manage these competitive pressures more effectively, hospitals will abandon their isolated solo posture in favor of becoming part of regional or national umbrella multihospital corporations, with for-profit and not-for-profit corporations competing. Already one-third of all community hos-

pitals belong to multihospital corporations, and about 15 percent of all hospital beds are for profit.

Academic Medical Centers. Medical schools have already responded by holding constant the size of the entering class in September, 1981, compared to the previous year.[3] Decreases are anticipated in subsequent years. Federal and state governments, cognizant that there is no longer a need to increase the number of physicians, will decrease support for medical education. This decrease will inevitably lead to higher tuition, higher levels of student indebtedness, reductions in the number of applicants to medical school, and reductions in the number of blacks in the medical applicant pool. The number of blacks in medical school is currently less than half the level needed to achieve parity between the general and the physician populations.

The teaching hospitals will experience the same pressures as the community hospitals. Many teaching hospitals have large Medicaid populations which endanger their financial structure because of declining reimbursement rates. Similar restrictions on expenditures are expected to be applied to Medicare patients in the near future. Costs are generally higher in teaching hospitals due perhaps to a higher proportion of more complicated medical problems and the need to maintain a comprehensive high technology service capability. As the efforts of the 1960s and the 1970s to increase the supply of physicians attain full realization in the 1980s and 1990s, highly sophisticated specialized services will increasingly become available in community hospitals. The referral rate to the academic medical centers will decline. The net results of these pressures will be a declining patient population and diminished financial support for residency and fellowship training.

General Recommendations

In making some general recommendations, I should acknowledge that there is marked heterogeneity among the nation's hospitals and teaching institutions. There is contrasting diversity of purposes and needs at the state and regional levels. Institutional responses can be expected to vary.

The education and care systems now disjoined, must be joined. Both systems must be purposefully directed in operation and in philosophy by the goal of serving the health needs of the American people.

We should avoid making plans and taking action in a context of urgency.

The aggregate entering class size of the nation's medical schools should be decreased to attain a steady-state physician-to-population ratio of 200–220/100,000 by the year 2000.

[3] S. Blau and A. R. Tarlov, unpublished observations.

Some medical schools should be terminated.

Every school should adjust its class size to a level which would favor improved quality of education, and enhance teaching/learning opportunity and educational innovation, all within the context of national needs.

A broad national commitment should be undertaken to increase black and other minority enrollment in medical schools to 15 percent of the total by 1995. This will require initiatives which have not been attempted before.

American students should be discouraged from studying medicine in offshore and Mexican schools.

Medical schools should affirm and strengthen their dedication to medicine as a scientific discipline having a knowledge base dependent on advancements in biological science. The concept that science improves the potential for good health at the individual doctor-patient level should be reinforced. However, biological science itself leads only to improved potential for the attainment of good health. Other disciplines, notably those in the social sciences, must be integrated with biological sciences for effective medical practice. The outcome of medical services should be measured both in biological parameters and in terms which are relevant to the patients functioning in their natural environment. The need to integrate biological and social concepts has important ramifications for medical education and practice.

The academic medical center must reconceptualize its role, giving consideration to: maturation of the hospital market, aging physical plants, expanding physician supply, pressures to move from the hospital services which can be provided elsewhere, competition from newly developed diagnostic centers in the community, competition from multihospital systems with their own patterns of referral, pressures to reduce costs from health maintenance organizations and other risk-sharing systems, and evolution of an untenable system of different negotiated reimbursement rates for different classes of patients. Bold action is required to assure that the academic medical center becomes an even more integral part of its region's medical care system.

For data from the National Study of Internal Medicine Manpower at the University of Chicago, I am indebted to colleagues Mary Kay Schleiter, Ph.D., Sandra Blau, M.B.A., and Peter Weil, Ph.D.

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THE TRAINING OF ACADEMIC SURGEONS FOR THE FUTURE: THE CHALLENGE AND THE DILEMMA

DAVID C. SABISTON, JR.

In beginning this presentation on the future of academic surgery, I would like to quote one of the most outstanding and accomplished academicians of this century, Julius Comroe. He has had a tremendous influence both in the individual stimulation of young investigators and in science generally both nationally and internationally, and he states the challenge forthrightly: "I have always believed that a main responsibility of a faculty member is to be a talent scout—to determine the special abilities of medical students in clinical care, in teaching, or in research and then to encourage them to do the very best they can in their field of unusual competence. One field, of course, is *research*. I see no way for faculty to determine this special talent of their students unless students have contact with research while they are still in medical school." (1) That statement can be supported by the achievements that match this definition in the history of medical science.

To pursue Comroe's admonition that we should stimulate students to enter research while they are still in medical school, I will cite several specific examples from the past. Andreas Vesalius is an excellent example, since the day following his graduation in medicine at the University of

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DAVID C. SABISTON, JR., graduated in medicine from Johns Hopkins in 1947 after which he spent the next six years training in surgery. He fulfilled his military requirement by spending two years doing cardiovascular research at the Walter Reed Army Medical Center. On his return to Baltimore, Dr. Sabiston advanced to become professor of surgery at Hopkins in 1964. The same year he was selected to be James Buchanan Duke Professor and Chairman of the Department of Surgery at Duke University Medical School. In 1977 Dr. Sabiston was honored by election as president of the American Surgical Association.

Padua, he published his scholarly work on human anatomy and was made a full professor at the age of thirty-one, largely on the basis of this original work. Today, medical historians and anatomists alike agree that Vesalius was the first of the scientific anatomists to correct the many errors that had been handed down for a thousand years from Galen's texts.

The first investigator ever to observe the function of the capillary network was Jan Swammerdam. In 1665, as a medical student, he first noted the small cylindrical objects floating through the capillaries, namely, the red blood cells.

The entire story of the development of anesthesia is another example of basic observations by a bright medical student. In 1799, Humphry Davy was a nineteen-year-old medical student when he prepared and inhaled large quantities of nitrous oxide and discovered its marked analgesic effect. In connection with a very painful, inflamed wisdom tooth, he said, "One day when the inflammation was most troublesome, I breathed three large doses of nitrous oxide. The pain always diminished after the first four or five inspirations. As nitrous oxide in its extensive effect appears capable of destroying physical pain, it may probably be used with advantage during surgical operations." (2)

Moreover, William T. G. Morton was a medical student when he administered the first ether anesthetic at the Massachusetts General Hospital in Boston in 1846. Also, while a medical student, Poiseuille, the famous biophysicist, was the first to devise the mercury manometer for measuring arterial blood pressure. Later, he developed the equation for determination of blood flow, now termed "Poiseuille's law." As the thesis for his medical degree, Raynaud in 1862 wrote the classic description of his now famous syndrome.

The cells in the pancreas which secrete insulin were first described by Paul Langerhans, a student under the tutelage of the father of modern pathology, Rudolf Virchow. Langerhans was provided a laboratory and encouragement to pursue his work on the pancreas. These islets now bear his name. Similarly, in Sweden in 1888, a medical student at the University of Uppsala, Ivar Sandström, identified for the first time the parathyroid glands and wrote a monograph documenting his observations. The discovery of insulin is the product of two investigators, Banting and Best, the latter being a medical student at the time of their extraordinary work. For this monumental discovery, these workers were awarded the Nobel Prize.

America's greatest physiologist, the late Walter B. Cannon, entered the Harvard Medical School in 1896, the year following the discovery of Xrays by Röntgen. He at once went to work on the use of this technique in the study of gastrointestinal motility and presented his initial experiments as a first-year medical student before the prestigious American

Physiological Society in 1897. His classic paper on the influence of emotion on gastric motility was published when he was a third-year medical student, and with those landmark achievements, his career was well on its successful path.

Jay MacLean, while a second-year medical student in the laboratory of William H. Howell, who expressly directed him to identify a thromboplastic substance, actually found the opposite, namely, an anticoagulant which he later named heparin in recognition of its source in the liver. Today, there hangs in the Johns Hopkins Medical School a bronze plaque stating, "To Jay MacLean in recognition of his contribution in the discovery of heparin in 1916 as a second year medical student."

Finally, two surgeons received the Nobel Prize for achievements initiated in their medical school days. While a second year medical student at the University of Lyons, Alexis Carrel was greatly saddened by the fact that while visiting the city, the president of France was attacked and stabbed in the abdomen with a dagger, after giving a major address at the Palace of Commerce. The dagger was thrust deep into the right upper quadrant, causing massive intraperitoneal hemorrhage. He was operated upon as an emergency, and the surgeon found a large incised wound in the portal vein. At that time, all attempts to directly suture blood vessels had been unsuccessful and were followed either by massive infection and hemorrhage or by thrombosis. The operating surgeon feared ligation of the portal vein because of the high mortality associated with such a procedure and, therefore, chose simply to drain the abdomen. The president continued to hemorrhage and died a short time later.

The young medical student, Carrel, was stimulated by this event to begin his painstaking efforts at successful vascular anastomosis. Using exacting surgical technique, with fine bites of tissue, and using tiny, highly polished needles with small sutures, he was able to successfully reanastomose small vessels with a diameter as small as one millimeter. Because of jealousy and lack of support in his own medical school, he later came to the Rockefeller Institute where he was provided excellent facilities. Using his basic vascular techniques, he transplanted organs and tissues, and for this work he received the Nobel Prize in 1912.

Similarly, Werner Forssmann in 1929, while a first-year resident in surgery in Germany, captured the concept of passing a catheter through an arm vein into the heart. He first sought a volunteer for the procedure but was unsuccessful. Therefore, with great courage, he passed the catheter into his own arm and into the heart. Once the catheter was in the heart, he pondered whether or not he would later be believed unless he had some objective proof of this daring human experiment. Therefore, he arose from the operating table, walked upstairs, had a chest film taken, and then walked back down the stairs to remove the catheter. His painstaking honesty is reflected in the last sentence of his report, in which

he apologized to his readers since, a week later when he removed the bandage from his forearm, he had a superficial wound infection. He admitted he must have inadvertently broken surgical technique during this historic procedure.

Of course there are many other examples, and only a few have been selected to emphasize that recognition of such achievements underscores the significance of Comroe's admonition to all those who have an opportunity to stimulate medical students.

As a key part of preparing students for original investigation, continuing efforts must be directed toward improvement in medical education. Earlier this month, Dean Daniel Tosteson presented to the Harvard Medical Faculty a new proposal for a seven-year demonstration project to provide a new pathway to the M.D. degree. Twenty-five students are to be accepted each year, beginning in the fall of 1983, in an effort that this pathway would be the "beginning of a general transformation of the style of learning at the Harvard Medical School." Throughout the experience, the students will have a mix of electives and shared courses. The shared part of the curriculum will comprise about half the students' time and will stress problem-solving through the case-method approach, self-learning, and self-assessment using computer-assisted audiovisual devices. Acquiring the skills together with analysis of clinical data is to be an important goal.

The other half of the program is to be elective and will allow students to enroll in courses throughout Harvard University and the Massachusetts Institute of Technology. The program consists of two segments, the first four years devoted to the arts and sciences basic to medicine, and the second three years to clinical arts and sciences. Both basic and clinical materials will be interwoven throughout the curriculum, and a thesis describing an independent study will be required in both the basic and clinical segments of the program.

In approaching the future of medical education, we must face a number of dilemmas. The general features of these problems apply to all of academic medicine, and specific ones are of primary significance to the field of surgery and the surgical specialties.

The number of medical schools in this country rose from 79 in 1950 to 126 in 1981 (Fig. 1), a rapid increase requiring a number of additional faculty in all specialties including surgery. During this period, the number of medical students has climbed precipitously from 25,000 in 1950 to more than 65,000 in 1981 (Fig. 2). This increase has created what many believe to be a "glut" of physicians and is quite apt to be responsible for increasing economic problems in the entire health field of the future.

This problem is further reflected in the total numbers of approved residency positions in all specialties, rising from 17,000 in 1950 to nearly 62,000 in 1981 (Fig. 3). The total number of applicants for first-year

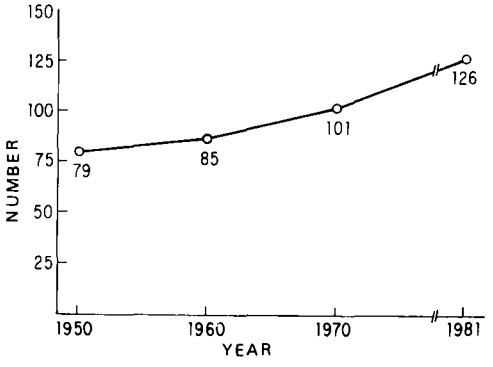

FIG. 1. Number of U.S. medical schools.

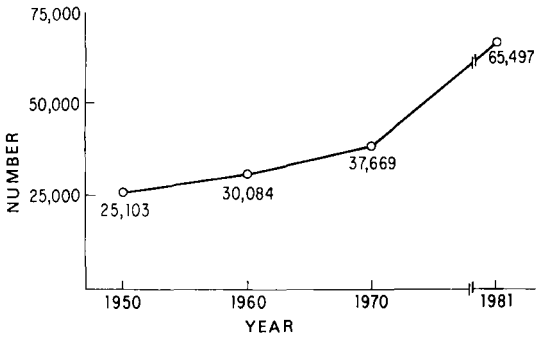

FIG. 2. Number of students in U.S. medical schools.

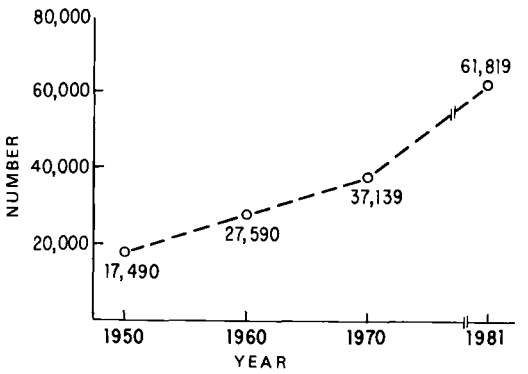

FIG. 3. Number of filled residency positions in the United States.

residency positions will soon exceed the number of approved residencies, thus creating a further dilemma. Although the number of graduates of foreign medical schools has been leveling off in the recent past, for the 1982 National Residency Matching Program, the percentage is again increasing, representing yet another serious problem.

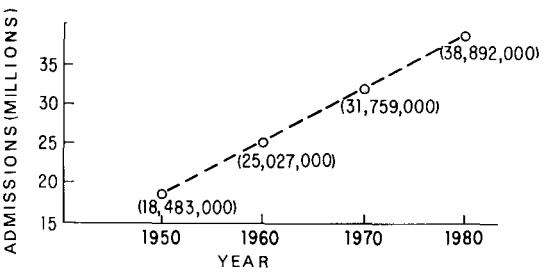

FIG. 4. Annual admissions to U.S. hospitals.

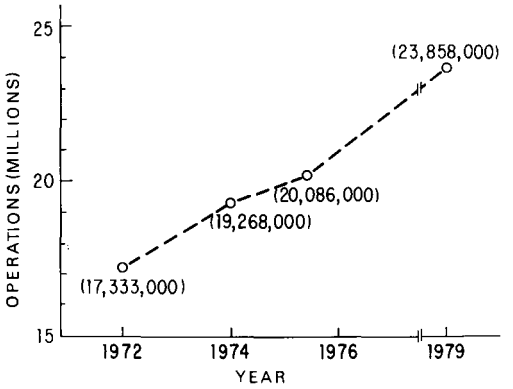

FIG. 5. Number of surgical operations in the United States.

For many reasons, including increased numbers of physicians, the annual admissions to hospitals in the United States have risen sharply, from 18 million in 1950 to nearly 39 million in 1980 (Fig. 4). Similarly, the number of surgical procedures has risen dramatically from 17 million in 1972 to almost 24 million in 1979 (Fig. 5).

The specific features that primarily affect surgery include the diminishing number of outstanding residency training programs as well as the most significant feature of these programs, that is, the number of patients who can be assigned primarily to the resident staff under the supervision of the faculty. In recent years, this group of patients has diminished sharply in all areas of the United States, and many believe this factor has had a serious effect on the quality of these training programs and on the competence of the surgical resident.

Another feature of considerable significance is the length of time necessary to meet the requirements of the various surgical boards. In surgery and the surgical specialties, this ranges from a minimum of four years to a maximum of seven years. The seven-year program is in cardiothoracic surgery and is the absolute minimum of required training

in order to meet the standards of the American Board of Thoracic Surgery. Moreover, in such programs in which young surgeons are being trained for academic posts with additional time devoted to research, the length of the training period is eight or even ten years.

Finally, in recent surveys of current medical students, considerable apprehension and concern are being expressed about the quality and numbers of medical student applicants in the immediate years ahead. Moreover, the ratio of applicants to available first-year openings in medical schools throughout the nation has begun to decline, thus emphasizing another significant factor.

In summary, while a number of challenges facing the future of academic surgery have been successfully met, there are clearly a series of problems that deserve our concerted immediate attention and thoughtful solution.

The illustrations in this paper were produced from data in the *Socio-Economic Factbook for Surgery 1981*, published by the American College of Surgeons, 1981.

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CAREERS IN ACADEMIC MEDICINE

JAMES B. WYNGAARDEN

I appreciate this opportunity to speak to you about careers in academic medicine. When I accepted the invitation last summer, before word of the NIH appointment had come along, I was to be addressing you as chairman of a department of medicine, and I will speak chiefly from that vantage point today. I should begin, though, by pointing out that in my new role I have a somewhat wider perspective.

The development of careers in academic medicine has long been a major function of departments of medicine, particularly those that have a strong research emphasis. The opportunities in such departments have depended heavily for the past two or three decades on the relationship between the Federal Government and the medical schools. Ideally, I suppose, the topic should be approached in a general fashion—academic medicine with a small "m." But my experience does not really extend to very many fields. What I say will apply chiefly to departments of medicine.

Most of us in this room are products of a medical school based on the Flexnerian model. We are dedicated to the bioscientific strategy of medicine, and that indeed has oriented most medical schools since World War I. Another powerful impetus toward that strategy has been the

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JAMES B. WYNGAARDEN was graduated from Western Michigan University in 1944 and the University of Michigan Medical School in 1948, after which he trained in internal medicine at Massachusetts General Hospital, the Public Health Research Institute of New York City, and the National Institutes of Health. He moved to Duke University Medical Center in 1956, and in 1961 was promoted to a full professorship in both medicine and biochemistry. His principal research interest was the metabolic basis of infectious disease. From 1965 to 1967 Dr. Wyngaarden was Professor and Head of the Department of Medicine at the University of Pennsylvania, but in 1967 he returned to Duke as Professor and Chairman of Medicine. After fifteen years in that post, in 1982 Dr. Wyngaarden was selected to be Director, National Institutes of Health.

impact of NIH on the structure of medical schools. All of us date from pre-World War II, and most of us go back to the days before the NIH influence. We have all lived through the period of tremendous change that brought us where we are today.

In many ways the most significant phase is what I like to refer to as the Shannon era. Dr. James A. Shannon served as director of NIH from 1955 to 1968.

I read recently some reflections by Dr. William H. Sebrell, Jr., director of NIH just before Shannon. Sebrell pointed out that when he became director in 1950, the budget was $52 million, and when he left NIH five years later, it was about $80 million. That, then, was the budget when Dr. Shannon took over. When Shannon left 13 years later, the NIH budget was around $1 billion and still growing rapidly.[1] During those years some incredible challenges were met with steady brilliance and good judgment, to benefit not only NIH but medical schools and American medical education as well.

With the increase in funds that came to NIH at that time, there was an opportunity to devise a strategy for the conduct of research that extended far beyond NIH itself. When Dr. Shannon became director, there was a grant mechanism in place, to be sure, but the intramural program budget was a very much larger fraction of the total than it is today. The bulk of new money went into biomedical research conducted outside NIH through its extramural program. The grant mechanism evolved to strengthen the new modalities that were developed, such as program project grants, center grants (on a relatively small scale then), and training, which averaged about 18 percent of annual obligations throughout the Shannon era.

The training grant and the direct fellowship were sharpened and expanded. Like the research grants, they operated under a peer review system, which was adapted to cover all types of awards as they were instituted.

All of this profoundly influenced the structure and function of the medical schools, and perhaps affected the department of medicine as much as any department.

Prior to the influence of NIH, research on medical problems was largely a part-time activity. By the end of the Shannon era, it had become a professional life for many people. And it exerted an influence in the department of medicine, where basic and clinical scientists were able to collaborate to their mutual benefit. NIH support sailed along nicely, creating a dependency that no one worried about then—at least, not

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[1] A strict comparison should take into account that the 1968 NIH appropriation of $1,179 million no longer included the National Institute of Mental Health, which had become a separate bureau of the Public Health Service in 1967.

enough to turn down NIH dollars. The dependency has had various effects. It has diverted the orientation and loyalties of faculty, for example. Many faculty members now feel more dependent on NIH for funding support than they do on their own department chairman or dean.

From the institutional point of view, there arose an intense dependency of another kind. This has been brought home to me—particularly in the last few months—as I talk with more and more university administrators on proposed cuts in indirect costs, a devastating prospect to many institutions.

I think back to the 1960s, when many of the established values were challenged—challenged by medical students whose interests changed remarkably. Before that time the typical applicant for a medical internship would express the intention of going into biomedical research at NIH and then into academic medicine. However, not nearly so many did that as said they would. They often stated the intention, I am sure, because they thought that was what we wanted to hear. Nevertheless, research did represent the major interest of a large number of medical students. Then their attitude changed dramatically during the Vietnam conflict, as studies have shown.

A challenge to the whole Flexnerian concept of medical education erupted. The critics proposed that the bioscientific strategy of medicine had been erroneous from the start, and that the great advances in health care had really resulted from improved sanitation and improved nutrition. To support their claim, they showed that death rates from tuberculosis and other infectious diseases had dropped substantially before the advent of antibiotics. They suggested that the money spent on biomedical research was unjustified and that the results were far too meager to warrant a continuation of the bioscientific strategy.

All those points, I think, can be effectively answered. But they were voiced, nonetheless, and an alternative plan—an "ecological strategy for health"— was advanced. In my view this is not really an alternative to the bioscientific strategy, but rather a coordinate, perhaps independently justifiable strategy. I think some of the changes in life style mentioned earlier today such as reduced smoking, proper diet, and proper exercise—behavioral changes of that sort—have played a role that is quantitatively uncertain in relation to the death rate from cardiovascular disease, but may have contributed to the decline from 522 (per 100,000 population) to 450 between 1968 and 1978.[2] Health progress is usually due to a mixture of influences. Control of hypertension, for example—a development based on the bioscientific strategy—certainly ranks with any advance

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[2] Includes four categories of diseases of the circulatory system—diseases of the heart, cerebrovascular disease, arteriosclerosis, and hypertension.

achieved through alternative approaches. Both strategies are probably valid. We have seen support for both around the table today.

The dependency on NIH mechanisms is a topic I would like to spend a little more time on, and also the change in attitude that developed among students and the house staff. I am referrring to the profound influence of changes in the philosophy of government support for training that took place during the Nixon administration.

You will be interested in some of the quantitative aspects of the utilization of NIH training devices by medical students and fellows over the past decade. We might start with Table 1, which tabulates the total number of NIH trainees and fellows from 1969–81 and projected through 1983 in terms of full-time equivalents. There is a gradual decline to an estimated low for 1983 of about one-half the 1969 level.

Figure 1 shifts to actual numbers for the years 1971–81. You can see that back in 1971 about 60 percent of all postdoctoral traineeships were held by M.D.s (or M.D.-Ph.D.s) and that this vehicle was used to a much lesser extent for the training of Ph.D.s. The subsequent years reflect a shift in these ratios, with a crossover around 1975. Specifically, the number of Ph.D.s utilizing the institutional and individual awards increased, while the number of M.D.s decreased from 4,634 in 1971 to 1,961 in 1980. In terms of funding, the turning point was in 1973, when the Nixon administration impounded funds and blocked new awards for fellowships and traineeships. Training awards came back the following year, but with remarkably different criteria and new legislative authority—the National Research Service Award (NRSA) Act.

TABLE 1

Numbers of Trainees and Fellows on NIH Research Training Awards 1969–81 and Projected through 1983

Full-Time Equivalents	
year	*number*
1969	16,138
1970	14,810
1971	14,288
1972	14,613
1973	12,675
1974	13,547
1975	12,272
1976	9,654
1977	10,198
1978	11,123
1979	11,197
1980	10,664
1981	10,695
1982 (est.)	9,702
1983 (est.)	8,915

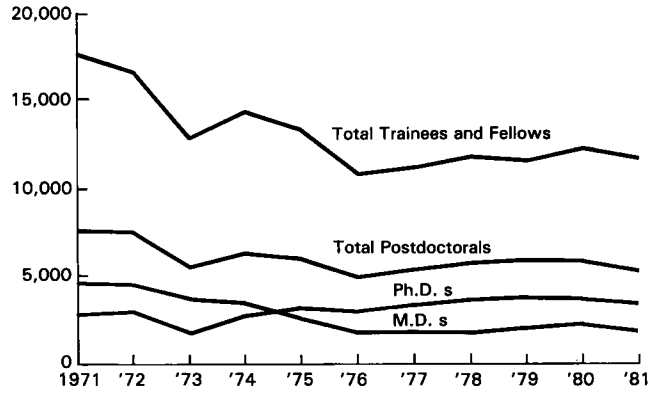

FIG. 1. Trainees and fellows on NIH research training awards 1971–81.

The traineeships in the 1950s, as they emerged during the growth of NIH, had a variety of purposes. These included production of skilled clinicians in areas where medical expertise was considered to be poorly represented. Diabetes training grants, for instance, were designed to train diabetes specialists to work in communities. Many of the people in the professional traineeship category were individuals who had predominantly clinical interests.

Under the NRSA Act of 1974, the National Academy of Sciences was asked to speak to the need for training and to advise Congress annually on the training areas and the numbers of trainees needed in each. I was privileged to serve on that committee. We clearly did not know how many of the 4,200 individuals in clinical training positions—3,200 trainees and 1,000 fellows—had academic interests at heart, but we estimated that perhaps two-thirds did and therefore recommended that 2,800 such positions be awarded annually. Well, as you can see, the number of M.D.s utilizing NIH traineeships dropped sharply. It leveled off around 1976. That probably represents to a large extent the disappearance of the purely clinical trainee. But also the award came with a pay-back requirement that may have acted as a disincentive for some.

Figure 2 focuses on postdoctoral trainees and fellows. You can see the dramatic drop in M.D.s as a percent of total postdoctorals. Meanwhile, however, there is an increase in total postdoctorals as a percent of total awardees. The downward trend in M.D. applicants probably reflects several factors, including the economic disadvantages of a biomedical science career. It may be noted that the trend is concurrent with increases in medical school enrollment and the production of physicians.

Turning to the research grant programs, some figures on the M.D. as principal investigator (P.I.) have received quite a lot of publicity and have reached the Congress through public testimony. Members of Congress

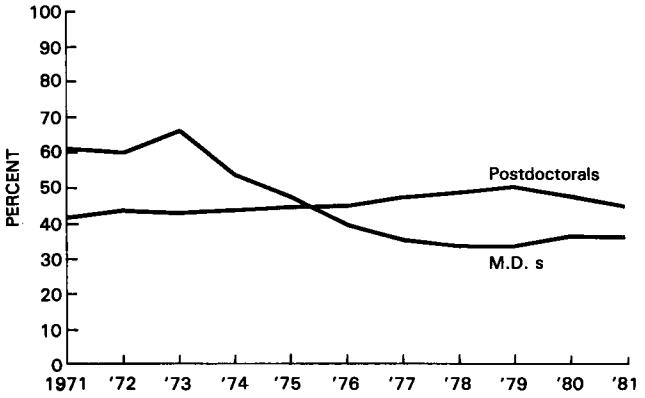

FIG. 2. Postdoctorals as percent of total NIH trainees and fellows, and M.D.s as percent of total postdoctorals 1971–81.

view the data as an alarming trend in biomedical science. They are concerned about the decline in the number of M.D.s receiving traditional investigator-initiated research (R01) grants. These dropped from 4,000 in 1966 to 2,943 in 1980. M.D.s as *new* P.I.s are leading the trend, dropping from 487 in 1966 to 252 in 1980. In relative terms, the M.D.s in 1966 were about 40 percent of all P.I.s on R01 grants and dropped to 23 percent in 1980. As new P.I.s, M.D.s dropped from about 40 to 20 percent over the same period. It should be pointed out that the number of R01 grants awarded to holders of professional degrees has really increased—from about 10,000 in 1966 to 12,600 in 1980. Thus the trend is upward for the Ph.D.s, who have just about doubled over the same period. Likewise, those with combined degrees—M.D.s with a Ph.D. or equivalent doctorate—have increased from about 650 in 1966 to 1,100 in 1980.

The decline in the number and proportion of M.D.s on R01 grants reflects two trends. The most significant is a relative drop in applications. Looking at all competing R01s, we see that M.D.s comprised about 30 percent (1,843) of the applicants in 1970 and only 24 percent (2,775) in 1980. The second trend is the declining success of M.D.s in obtaining grants, notably in the past six years. Among new M.D. applicants on new R01 projects, 50 percent (of 615 applicants) obtained awards in 1974, whereas only 30 percent (of 795) succeeded in 1980. By contrast, the Ph.D. success rate in the latter year was 38 percent. M.D.s have averaged about 6 percent below Ph.D.s in grant-winning success since 1975. The principal reason for failure of M.D. applications seems to be deficiencies in experimental design. I will also mention that the New Investigator Research Award, introduced in 1971 (as the Young Investigator Award), continues to attract M.D.s and Ph.D.s about equally. These

awards support junior faculty in specific disciplines. The program has grown steadily after a modest start.

But in the overall, it is clear that the M.D. as a research trainee or an independent investigator (in contrast to a P.I. on the larger grants—program projects and centers) has not kept pace with the growth of the system in general.

Disincentives have emerged that influence young physicians in the choice of academic medicine as a career. I think the perturbations of the Vietnam era have probably come and gone to a large extent, but we are now left with an economic situation that is drastically changed. The debt load of medical students has grown enormously. I do not know the average now, but it is frequently $30,000 or $40,000 upon graduation. Training stipends have not kept pace, though they have been increased from time to time. They average 26 percent less than the residency stipend. Clinical training has been gradually lengthened. In the research-intensive medical schools in particular, where most interns finish their general medicine and enter a specialty program, the usual minimum of training is now five years. All of this contrasts sharply with the rather extraordinary sums to be earned in practice, particularly in procedure-based subspecialties of medicine. We are seeing the rise of what one of my former chief residents called the resident-fellow-Porsche syndrome. Economic factors were always a counter-attraction to the academic life, but I believe this was much less the case when most of us made the decision to join.

The pay-back provision of the NRSA has been a disincentive, more for the M.D.s than for the Ph.D.s. A Ph.D. who accepts a training award has already made a career decision, but the M.D., about to take the first step into the research world and as yet uncommitted, may be deterred by the pay-back requirement. The Reconciliation Act of August 13, 1981, modified the pay-back obligation, and pending legislation would abolish it altogether.

In the field of internal medicine the American Board of Internal Medicine, in my judgment, has had a somewhat inhibitory influence through the rigidity of its clinical training requirements for certification. Recently they have been modified substantially. There was a time when short-tracking was permitted. One was allowed to take two years of general medicine, then start a subspecialty training program and apply the first year of that program toward both the general medicine and the subspecialty board requirements. In that manner one could finish in four years—five in some fields—rather than five or six years. Initially, only a small fraction of the residents in medicine, 10 or 15 percent, took the short track. But the trend increased. It was perceived that the short track was encouraging residents to choose a subspecialty career just at the time that general medicine was thought to need expansion, and so the short

track was discontinued. That decision forced residents into a standard pattern that did not allow much flexibility for research.

A third and very important influence is that so many students have no basis on which to choose a research career because of a lack of laboratory experience in the medical school. I have talked with many residents whose laboratory experience consisted exclusively of anatomical dissection demonstrations. The jettisoning of lab experience in biochemistry or microbiology or pharmacology has been a major loss. The Duke curriculum is an exception. It offers an alternative for acquiring laboratory experience in the third year. And the disappearance of the NIH postsophomore fellowship did not help. About a year ago NIH put back into the system a three-month research opportunity for medical students. This is available to any student, sometimes for three consecutive years. About a thousand medical students with such support got into the laboratory for a summer or an off-quarter. I would like to see that time extended. But not every student has a good experience the first three months and, if it turns out poorly, the experience may actually have a negative impact.

Another factor acting as a disincentive for the M.D. trainee is the growing sophistication of science and the professionalization of science in clinical departments. The finest medical education and the finest resident training in the world do not equip the young physician to function effectively in the laboratory. There is a large gap between the bedside and the bench, and one needs to spend a substantial amount of time acquiring new skills to be successful in research. Fellows realize that with the intense competition for grants, one has to decide whether to invest heavily in research training or not at all. This is not conducive to getting them just to try it. Nevertheless, there are splendid opportunities for those who make the necessary investment. In my opinion two years of full-time research training is a marginal minimum; three or four years are much better.

Now we might look briefly at the problems of size of departments and size of schools. The Association of American Medical Colleges (AAMC) figures indicate that clinical departments have about 1,000 new faculty positions available each year and about 2,000 additional positions from attrition and turnover. These may sound like large numbers, but given 125 medical schools, it is really about 8 new appointments annually per school and maybe 16 turnover positions, or a total of 24. That is only two or three per clinical department.

One of the interesting facts that came out of a recent AAMC study is that only 21 percent of those who received new appointments to clinical departments from 1975 to 1978 had had any postdoctoral research training. This is not difficult to understand because many are clinical appointments. In departments of medicine, for example, clinicians in the outpatient department or those who run the cardiac catheterization lab may

have had no research training. But it is rather alarming, from the standpoint of the tone set for the training of medical students, that more than three-quarters of the young faculty have never conducted research or had any research training.

On the research front, the prospects of support are still good, though not as generous as they used to be. Personally, I think the Hoechst and Monsanto types of award are anomalies and will not be widely replicated. I do not view such developments as a general solution for the support of medical science. Industrial competition may provide some new alternatives. There have been about 150 new biotechnology firms formed in the last couple of years, but I suspect that half of them will disappear shortly. Of course, there is still a substantial Federal budget. We are in a period of painful readjustment, but $3.6 billion still enables us to support a lot of very good science.

The competition will be greater, and we can expect the best-trained people to be the most successful. It is clear from our analyses that training at NIH or in NIH postdoctoral fellowships or traineeships greatly extends the survival time of the research grantee. For those who have been in the system since 1965, such experience has increased the median survival time by a factor of two. The median figure for Ph.D.s who had trained with NIH support was something like eleven years under NIH grants. Clearly, those who have obtained training and retraining stay in the system a good deal longer.

One of the stresses on the system, which is not always apparent from the numbers, is the extent to which physician investigators are being replaced by Ph.D.s. Even in departments of medicine, this tendency is growing. I am not saying that the trend is necessarily undesirable, but it is clearly discernible. Of the 2,800 traineeships earmarked for clinical departments each year, about 1,900 are filled by M.D.s and 900 by Ph.D.s. The Ph.D. fraction has been steadily mounting. It is 30 percent this year—up from 20 percent only three years ago.

One of the complex issues today is the Federal policy of stabilization. As a department chairman in a university, I thought it was splendid, because the policy of giving the highest priority to roughly 5,000 new grant starts per year (slated to be less this year) represents one of the most solid encouragements to the young investigator. The stabilization policy has had some major consequences. Placing the highest priority on the investigator-initiated award has resulted in certain readjustments. For example, there has been a decrease in the number and dollar amounts of research contracts and centers. The Institute directors are concerned about this because it has limited the flexibility of management. Obviously the system has become very tight. There is strong competition among the various kinds of support.

A magnificent partnership has evolved between universities and gov-

ernment, and I certainly would like to do everything I can to preserve that. We are collectively seeking ways to minimize the strains. One of the problems is to preserve the interest of a reasonable number of physicians in a scientifically oriented career. Fortunately, the supply of Ph.D.s in the biomedical sciences has held up well. But I think the balance between Ph.D. and M.D. scientists that has existed until just recently would be a good one to maintain. We need to encourage young physicians to enter the world of science-in-medicine. Indeed, there are stellar opportunities. One thinks of the implications of recombinant DNA, the explosion in the neural sciences, and other advances that should make the next decade unusually bright.

BLACKS IN MEDICINE

M. ALFRED HAYNES

The underrepresentation of blacks in medicine cannot be politically or socially justified in the context of American democracy. Some have interpreted this underrepresentation as the inevitable consequence of the genetic inferiority of blacks and support this position by referring to the consistently lower grade-point average (GPA) and Medical College Admissions Test (MCAT) scores. Others observe that significant progress was made from 1968 to 1974 but conclude that unless something is done now about the size of a qualified applicant pool, the admissions curve must remain flat, since preparation for medical school is the responsibility of high school and college, not the medical school.

Others seem to imply that affirmative action in medical education ended with the Bakke case and that "reverse racism" is now a more serious threat. They think that places can be justified for minority students if there are extra places but that minorities have no right to fair representation if seats are limited. Furthermore, it appears to them that the civil rights movement has long since ended, and concern about minorities is

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M. ALFRED HAYNES was born in British Guiana and educated at private and public schools in the British West Indies. He studied in the United States and earned a B.S. in mathematics from Columbia University in 1950. He graduated in medicine from the State University of New York, Downstate Medical Center, in 1954, and spent four years as the U. S. Public Health Service's Medical Officer at the Indian Hospital, Cheyenne Agency, South Dakota. From 1959 to 1964 Dr. Haynes was Assistant Professor of Preventive Medicine at the University of Vermont. This was followed by two years as a U. S. Agency for International Development (USAID) Visiting Professor at Trivandrum Medical College, Kerala, South India. During this period he was selected as Lecturer, Division of International Health, Johns Hopkins School of Hygiene and Public Health, and on his return was advanced to Associate Professor. In 1969 Dr. Haynes joined the faculty of the Charles R. Drew Postgraduate Medical School in Los Angeles as Chairman of Community Medicine and as Associate Dean. He is currently Dean at that school.

no longer in fashion. To complicate the matter further, most students are now in need of financial aid, and any assistance offered to minorities will only decrease the amount of funds available to others.

Despite these arguments, it is still true that the underrepresentation of blacks in medicine cannot be justified, and those responsible for the training of physicians cannot escape responsibility simply because the problem is complex. It is estimated that, based on representation in the population, there should be 2,000 additional black physicians in the state of California (1).

Black physicians play an important role in the provision of medical care. The Department of Health, Education and Welfare (2) has reported that in 1975, 87 percent of the patients of black physicians were black and that these patients had disease frequencies, cultural beliefs, and practices different from those treated by nonblack physicians. In a recent survey of Howard University alumni, Lloyd and Johnson (3) found that 77 percent of the patients of black physicians were expected to be black. This study showed that many of the black graduates of Howard University practice in a primary care specialty and that a large percentage of their patients are black and poor. A similar survey of graduates of Meharry and the King/Drew Medical Center will probably show the same kind of results, and one should not be surprised if, in the future, a similar profile is observed for graduates from Morehouse.

These findings indicate that the training of blacks in medicine is socially important and suggest that the problem must be seriously addressed. Those who are concerned about the problem must examine what happens in medical school and in the admissions process, and they must also consider the preparation for medical school, the process of postgraduate training, and the subsequent practice of medicine.

Preparation for Medical School

To admit students into medical school who are not academically well prepared is not fair either to the medical school or to the students. Increasing the number of black students involves some attention to the preparation for medical school and specifically to increasing both the quantity and the quality of the applicant pool. Some medical schools have reached out to potential students at the college level and others have gone to the high school level. There are indications that despite the generally lower level of educational opportunities afforded black students, the applicant pool can be significantly increased with some extra effort. McGinnis (4) discussed a number of special undergraduate programs for minority medical aspirants. The Harvard Health Careers Summer Program is one outstanding example of how talented minority students can

be identified and better prepared for medical school. The program, begun in 1969, specifically seeks students who are financially disadvantaged and have had inadequate secondary education. Ninety-one percent of these students have been accepted into medical and dental schools around the country. The Harvard program is cited not only because it is one of the oldest and best of such programs but also to show the progress that Harvard has made. Harvard did not always hold this enlightened view. In 1850, the celebrated Dean Oliver Wendell Holmes dismissed three blacks he had previously admitted to medical school because "the intermixing of the White and Black races in their lecture rooms is distasteful to a large portion of the class and injurious to the interest of the school" (5). It is clear that since that time Harvard has learned a great deal about the benefits of cultural diversity, but some medical schools today are still where Harvard was in 1850.

Medical schools cannot assume the responsibility for restructuring the basic education of high school and college, but they can identify young people with potential and give them a chance to succeed. Merely recognizing the potential of these young people adds a great deal to their sense of personal worth, and this recognition runs contrary to almost every other signal that a minority student receives living in a culture dominated by others.

A good source for such students is the predominantly black schools. It is possible that both blacks and whites tend to place too much weight on the disadvantage of having been brought up in a predominantly black culture. Dr. Charles Drew tried to use his Dunbar High School background as an excuse for his poor performance at Amherst College, even though Dunbar High School lists some of the most famous blacks among its graduates. Fortunately, the dean of Amherst at the time would not tolerate such an excuse (6). There are many potential medical students in black high schools and colleges, and other medical schools might do well to follow the Harvard example and provide opportunities for these students to achieve their potential. The Minority Biomedical Support Program at the Drew Postgraduate Medical School has attracted a number of these students, and special summer programs have significantly expanded the effort down to the high school level.

The present decline in the applicant pool is not peculiar to medicine and can be altered by additional effort.

The Admissions Process

The admissions process is one of the most critical functions of a medical school and, at the same time, one of the most difficult. If medical education were not so expensive, it would probably be easier to have open

admissions and allow those who can to survive. Instead, we conduct an elaborate selection process although we are really ignorant about how to select people who will ultimately become the best physicians. This area is in desperate need of research. In the absence of valid techniques for prediction, we use pseudoscientific methods combined with varying degrees of subjective appraisal, but, mostly, we bet on GPAs, MCATs, letters of recommendation, and interviews. All of these have large degrees of error.

A GPA of 3.5 from one institution is not comparable to a 3.5 from another institution, and the mathematical precision of the numbers is very misleading. A national test taken by all applicants could conceivably help, and this is supposedly one of the attractive features of the MCAT; however, this test may be the most pseudoscientific of all selection procedures. Minorities did not perform well on the MCAT, and the new MCAT is supposed to eliminate the cultural biases of the old; but neither test addresses the fundamental problem. Since there are no valid predictions of physician success, the tests are really a masterpiece of circular reasoning. Many feel comfortable with the use of the MCAT, but I suspect that future research will show that the MCAT is merely a way of confirming our biases and that, like the early crude approaches to the measurement of human intelligence discussed by Gould (7), the MCAT may prove to be simply a very popular "mismeasure of man." The test may be reliable but it is certainly not valid.

Letters of recommendation ought to add a great deal to our understanding of individuals. They are especially helpful if the medical school can identify specific, desirable criteria and if these criteria can be adequately addressed in the letters. Unfortunately, these criteria have not yet been unequivocally defined. Some letters provide well-documented, comprehensive reviews of a student's career in college, while others do not. Many black students from black colleges have been placed at a greater disadvantage than they deserve because letters were favorable but so devoid of content as to be practically meaningless. This was no fault of the student but merely a failure of the proponent to address those aspects of the student's career that could be most helpful. Some letters can make an average student look like a genius, and others make a genius look like a freak. My impression is that, in comparison with other students, minority students tend not to be helped as much by their letters as they could be.

Interviews as a basis for selection carry their own type of bias. What is effectively communicated in an interview depends on a number of variables and not merely on what is said. Interviews as a basis for selection of minority candidates are no worse a measure than the other measures used and may even be better if the members of the admissions committee are well trained (8). Workshops, based on the simulated minority admissions

exercise of the Association of American Medical Colleges, have proved to be very helpful in allowing admissions committees to make better choices of minority students. The process uses noncognitive variables such as positive self-concept, realistic self-appraisal, availability of strong support persons, demonstration of community service, and successful leadership experience.

Without specifically taking race into consideration, the admissions process is at best an effort to make rational decisions about complex human issues on the basis of a combination of crude, simple, and largely inadequate measures that give an undue measure of security because of our great faith in numbers and because we have no better tools currently available. Milstein et al. (9) have shown that there was no difference in the subsequent careers of a set of students who were accepted at Yale compared with those whom Yale rejected but who were accepted elsewhere.

When one takes race into consideration, the problem reaches higher levels of complexity. Recognizing the inadequacies of the process and wanting to create more opportunities for minorities, admissions committees have been stymied by charges of reverse racism and the declining popularity of affirmative action. Even "liberals" are opposed to providing opportunities for minorities if these might deprive them of a chance. They accept affirmative action in theory but not in practice. This is partly due to an unfortunate interpretation of affirmative action, which is often taken to mean giving a minority person what he does not deserve rather than giving what is fair and reasonable based on representation in society. The solution will not be easy, and it is unlikely that there will ever be a simple mathematical formula that will end the problem. Justice Blackmun's opinion in the Bakke case is most pertinent. He said, "I suspect that it would be impossible to arrange an affirmative action program in a racially neutral way and have it successful. In order to get beyond racism, we must first take account of race."

In Medical School

Despite the inadequacies of the selection process, most minority students admitted to medical school have the ability to complete medical training but may need additional support. Medical school presents a special kind of stress, and it is perhaps difficult for a person who is not a member of a minority group to understand this stress. A black student in a predominantly white school faces a difficult problem, especially if the number of black students is small and the student has not previously lived in that fishbowl experience. The same would be true for a white student in a

predominantly black institution. In this case, a minority student may not feel sufficiently comfortable even to talk about things that are stressful.

Under these circumstances, some black students have an unfortunate crash in their careers, and the theoretical basis for such a crash is not different from that of a highway accident. Accidents often occur not because the driver is incompetent, but because the demands of the situation are such as to make the performance inadequate (10). The black student's performance may not actually be below that of other students in the class, but the demands on the black student are greater because, in addition to the common scholastic demands, the black student carries a heavy burden of supposed inferiority, which is silently but daily communicated in many ways. For the black or Hispanic student, even if there are no financial burdens, the first year of medical school may be like walking a tightrope. Casualties can be prevented if there is a better understanding of the demands of the situation for the student and if the student can get the necessary support from a friend, a classmate, or a teacher. It may be difficult for one who has not experienced life as a black to understand that, under these circumstances, an observed difference in performance is not necessarily a difference in intellectual competence.

More problems arise from the failure to understand and diagnose the kind of support that is needed than from an unwillingness to provide that support. It does not really help to provide financial support when the need is for emotional support; tutoring is a poor remedy for a problem that is due to financial difficulties, often concealed because of personal pride. One of the most rewarding aspects of minority admissions is that medical educators are still learning a great deal about human nature, and whenever a serious attempt is made to help minority students, the lessons learned in the process invariably prove to be of greater benefit to students in general. If the attrition rate of minority students is higher than that of other students, the medical school should not merely take this for granted but should ask questions about the selection process and, equally important, about the support mechanisms in medical school. The school has a right to expect the same level of competence from minority students as from other students, and if this requires a greater level of support, the school must be prepared to give it.

In this context, a word must be said about the primarily black institutions. In view of the changes which have occurred in the United States since the passing of the civil rights law, one might wonder if there is still any reason for predominantly black medical schools. It is important to understand the history of these institutions, much of which has been documented by Montague Cobb (11). Following the Civil War, many blacks came to Washington, D.C. Hospital facilities were opened in former military barracks to take care of ill refugees, and these subsequently became The Freedman's Hospital. Blacks were not accepted in

regular hospitals in those days. It soon became clear that it was necessary to train black doctors. Howard University was chartered in 1867 and its medical department opened in 1868. In the postreconstruction era, eight black medical schools were established—four of them in Tennessee, of which the only surviving one is Meharry Medical School. This school was founded because "the difficulty of securing proper medical education for the colored people was very great and the mortality among them alarming." One hundred years after Howard University was chartered, the Drew Postgraduate Medical School was chartered in Los Angeles. This was the result not of civil war but of riots in Watts in 1965; the circumstances were different only in degree. The difficulty in securing medical attention in Watts was one of the problems leading to the riots. Drew started as a postgraduate medical school but is now offering undergraduate medical education in conjunction with the University of California, Los Angeles. More recently, Morehouse has developed its own medical school. These institutions are not segregated, but all have been especially responsive to the needs of minorities and will continue to respond to those needs in ways that other institutions are not likely ever to respond. As long as there continues to be a shortage of minority physicians, there will be a great need for these institutions; and even if the problem is finally solved, they should continue to exist as part of the cultural diversity of the United States.

Postgraduate Training

There has been a real change in the access of blacks to specialty training, although the numbers involved are still relatively small. The change is most likely due to a number of factors, including the attitudes of hospital administration, training program directors, and patients. Around the middle of the century, it was still difficult for black doctors to obtain specialty training in predominantly white institutions. This was especially true for clinical training as opposed to basic science training. Generations of white doctors had been trained using largely poor black patients as clinical material, but black doctors were not welcome in the treatment of white patients. When Dr. Charles Drew was sent by the Rockefeller Foundation to Columbia University to prepare for the chairmanship of the Department of Surgery at Howard University, it was clearly a break in tradition at Columbia, but it seems to have been a very cautious break. Most of Dr. Drew's time was spent not in surgery but in the laboratory. The records indicate that the foundation was concerned about when Dr. Drew would get to do surgery, but the university did not fail to inform the foundation of how important his research was. It was fortunate for mankind that the result of this research was that Dr. Drew became an

international expert in the preservation of blood and contributed to the saving of countless lives during World War II and afterwards, but we do not know how much the world has lost by depriving blacks of opportunities in medicine.

Some of the change that has occurred in postgraduate training is the result of increased opportunities in medical school. Having gone to a predominantly white medical school is often considered prima facie evidence of superior training, but there is more to it than that. There has been a general improvement in the racial environment. It was not so long ago that a black physician in an elevator at a white hospital would have automatically been assumed to be the elevator operator. This bias was not limited to uneducated lay people. On the first day of my internship training, I was ordered out of the dressing room by the anesthesiologist because it was "for doctors only." Decreasing opportunities for foreign medical graduates could mean increased opportunities for blacks. On the other hand, the conclusion that the United States is now producing too many physicians and the trend to decrease the number of training programs could result in decreased opportunities for black physicians.

Many blacks have opted to train in primary care specialties, and there is a definite need in these areas, but it is also important that blacks be well represented in all areas and that program directors keep the doors open for minorities as well as for others.

In the Practice of Medicine

Those who practice medicine tend to fall into four major categories: providers of patient care, teachers, research scientists, or some combination of the three. The providers of patient care are in greatest demand, and most physicians belong to this category. Black populations tend to be less well served medically because so many of them depend on black providers and because blacks are so greatly underrepresented among physicians. Many black physicians take a special pleasure in responding to this great social need, and this must be done; but over the long haul, it is important that black physicians also be well represented among teachers and research scientists.

At the present time, an investment in the development of black faculty is likely to yield a higher return than any other investment. At minority institutions, black faculty do what all faculty do. They not only teach, but also serve as role models, and black students are desperately in need of role models rather than critics. At white institutions, black faculty do even more. If at these institutions students see no minority faculty, the institution is effectively communicating a very powerful negative message to students. Black faculty at these institutions relieve a sense of isolation among minority students and they communicate a powerful, positive

message from the institution to all students and faculty. For the message to be the right one, these black faculty must have unquestioned credentials, no less than their white peers. The present problem is that black faculty are so few that there is great competition for their services. There will have to be the same aggressive, affirmative action directed towards identifying and developing black faculty that there once was and still should be for black students. Both processes should proceed simultaneously.

As research scientists, blacks are even more underrepresented. This may be due to a lack of interest among blacks. A more likely reason is the lack of opportunity. By and large, the doors remain relatively closed, and the chances for success are not great without opportunities for adequate training. Here there are few role models among blacks, but they are good ones. Dr. John Scudder (12), with whom Dr. Drew trained, described Dr. Drew's doctoral thesis at Columbia University as "one of the most distinguished essays ever submitted in both form and content." He described Drew as "a physician who insists on adequate controls in his experiments." Unfortunately, not enough is known about the contributions of blacks to medical science. In a paper written by Dr. Drew (13) and published shortly after his death, he discussed Negro scholars in scientific research and tried to explain the situation:

> Men of their type do not come to the public eye, but they represent the very essence of our scientific heritage. Men who carry on scientific research are, as a group, men who instinctively shun publicity and in most instances underrate their own accomplishments. From time to time, some unusual combination of the times and public interest will coincide with some particular piece of work of men such as these, and they are bathed in the flood-light of public acclaim for a day. These few become well-known. The vast majority spend lives of diligent searching, guided by rigid intellectual discipline, and led on much in the nature of the artist and the dreamer toward new creative goals. The true scholar, in science more than any field, has a tendency to create for himself a world largely made up of the problems he seeks to solve. Great need, or great crises, are necessary at times to advance his research and make his work known... The obvious conclusion one must reach is that our opportunities and our contributions as scientists have been meager.

The opportunities and the contributions still remain somewhat meager but, given the opportunities, blacks could make a more substantial contribution to medical research than they have made to date.

Summary

Despite the conclusions that the United States is approaching a period when the number of physicians will be considered excessive, there is a serious underrepresentation of blacks among American physicians. Some

progress was made during the late sixties and early seventies when there was a genuine attempt nationally to increase the enrollment of blacks. In recent years, there has been a deceleration of this effort. In order to make further progress, it will be necessary to increase the applicant pool by identifying and guiding potential students. It is desirable to improve the selection process by better understanding of how to select not only minority students, but medical students in general. The situation could be greatly improved by providing better support to minority students who are admitted to medical school and by developing minority teachers and research scientists who can serve as effective role models. Blacks could contribute much more if the opportunities were increased, and all Americans would benefit as a result.

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DISCUSSION

DR. JOHN BOWERS: Dr. Haynes, would you comment on the status of the Charles Drew facility. It is no longer just a postgraduate medical school. Would you please tell us briefly how it is put together now.

DR. ALFRED HAYNES: The Drew School began as a result of the effort on the part of some people, including Robert Marston, who was at that time Director of the Regional Medical Program. It was a direct outgrowth of the riots which occurred in Watts in 1965. It was felt at that time that health care was one of the reasons for the riots. A hospital was formed and then a postgraduate medical school, with a great concern for providing both training to specialists and continuing education to physicians in the area. Even though the school began as a postgraduate medical school, it has been interested in the training of health workers in general, including physicians' assistants and others. More recently, the school has undertaken a program of undergraduate medical education, in conjunction with UCLA. The students will spend their first two years at UCLA and their last two years at Drew. And so, in one sense, we are a part of the University of California system, and in another sense, we are a separate private institution.

DR. KENNETH WARREN: The crucial pathway to getting more minority people into research is that being followed by the Macy Foundation, which you mentioned very briefly, which is trying to involve people at a younger age, particularly high school age. Sheldon Segal at the Rockefeller Foundation has also developed a program for getting people, young blacks in particular, to research laboratories such as the Marine Biological Laboratories. It has been very successful.

We have had a proposal from a great medical school to do something at a much later stage, to get the black students who are in the school more interested in research. The cost per person of that proposal is absolutely astronomical, so I wonder about that.

I would like to add that I have just gotten a letter from Morehouse asking if I knew of anyone that they could take on to do research on diseases of the developing world. That brings up the issue of our having just given a grant jointly with another foundation to train minority people in working on the diseases of the developing world.

As someone who has worked in Brazil, the West Indies, and East Africa as a minority, it has always struck me that it is very difficult to get blacks in the United States interested in working on the diseases of the developing world. We are particularly interested in trying to do so, because if one looks at the whole black population of the world, the vast majority in the developing world, one wonders about how people feel about their responsibility for others outside of their own particular country and milieu. We are very concerned with this in the foundation generally, and are trying to help in this area.

HAYNES: I would like to respond by saying that I do not believe we should confine the training to the high school level. We have to do it at all levels. I could propose to you, if you would entertain a proposal, a more economical way of doing what needs to be done, because I think it has to be done at all levels.

We *are* interested in research problems of the developing countries. We *do* have international health programs at Drew, and there is a close relationship. Finally, I should say that Drew is itself a developing school. We are in the United States, but it is just as if we were in a developing country.

DR. FREDERICK ROBBINS: I wanted to ask Dr. Haynes his opinion of the effectiveness of the NIH program for stimulating research among minority groups. Under the Division of Research Resources, grants are given to colleges and institutions around the country. I was on that advisory council for a period of time, and I was rather concerned that the quality of some of those programs seemed not what I would like to support. I was worried that these programs might be working against the best interests of the minority investigator. Would you comment on that?

HAYNES: We are now having discussions with NIH on this very matter. I think that NIH is in a position to do a great deal more than has been done about stimulating research in these institutions on all these kinds of problems. There has to be the correct thrust, though. In one type of NIH program, they will pay for a visiting scientist from any institution to go to an institution such as ours. There has not been very much uptake on this program, because if the person moves, he then has the cost of maintaining two homes, one where he is going, plus the original home. NIH does not pay for that. We are willing to assist financially to make this program possible.

I think also we have to make sure that the kinds of research that NIH might be interested in are the kinds of research which ought to be the thrust of the institution accepting a visiting scientist. If there can be a marriage of those two interests, I think it can be successful.

DR. JAMES HIRSCH: Not all of you may know that John Bowers pioneered this area at the Macy Foundation. One of the first programs he started after he came to the Macy Foundation seventeen years ago was Minorities for Medicine. He did bring this problem and this inequity to the attention of the academic community. I think the foundation led the way in attempting to rectify the problem. The attempts of the Macy Foundation, other foundations, governmental agencies, and community organizations have been directed toward remedial work for minority students, generally blacks, in college or even postbaccalaureate, particularly for borderline students who otherwise might not get into medical school or might not survive medical school. Those efforts—and there are a great many of them now—have been modestly successful. The percentage of blacks in medical school now is two and a half times what it was when these efforts started, so we can all be proud that a lot has been accomplished.

However, we are only a little more than halfway to the goal—that black representation among physicians be concordant with the distribution in the population generally. I think the most discouraging aspect is the fact that in the last six or seven years there hasn't been any improvement at all. Things came to a peak and then, in fact, the percentage of blacks in American medical schools

last year was a little bit lower than it was six years ago. I agree with everything that Dr. Haynes has said, that we must continue efforts at all levels.

The Macy Foundation plans to redirect its efforts. Maxine Bleich, who was Dr. Bowers's colleague in this matter, and I set out to analyze why there has been so little progress in the last years, despite continuing remedial programs, affirmative action, and all the other programs. We came to the conclusion that the fundamental problem is the limited size of the pool of black applicants who have enough talent to compete and to survive. Of the applicants to medical school last year, only 10 percent were black, and their MCAT averages and GPAs (although limited in meaning) were lower than those of the whites. So probably less than half of these applicants were really competitive for medical school. The reason for this, I think, is the less than adequate educational experience at the lower levels of the educational system, grammar school and high school.

Blacks are graduating from high school at a rate concordant with the population—12.5 percent or so. At college, this rate drops off very drastically to 7 percent, which is exactly what it is in medical schools.

The deterioration in the public high school system throughout the country in the last ten to twenty years obviously has had greater impact on blacks and other minorities than it has had on nonminorities, because all of the school systems of our cities are predominantly black now. And so we decided that it was time to try a demonstration program at the high school level. We are now in the process of setting up demonstration programs in two New York City high schools and in a group of six high schools in rural Alabama. These take different forms, but they are all essentially magnet schools or model schools or centers of excellence in high schools. They will all be predominantly black. In these programs, we expect 300 students to be entering the ninth grade this fall. These programs will offer good teaching, extracurricular activities that are meaningful, good counseling, psychiatric and social assistance, and all the other things that can be done in terms of supplementing the public school offering. We hope that, four years down the road, we will turn out even from these modest demonstration programs 300 black students who are really good candidates, who will go on to college and into medical school without any need for special assistance, and who can compete on their own. We know the talent is there. We already know that as a result of the response to our recruiting.

This is not a quick fix. We are going back to the root of the problem and trying to do something about it. I think it is a very worthwhile activity, and I am optimistic that, in the long run, this program will be very beneficial. That doesn't mean we should drop or neglect in any way the other affirmative action and remedial programs that are in place.

DR. EUGENE KENNEDY: I would like to comment on your entering of the educational system. The key to any kind of career in science involves an intense preparation in mathematics which leads to a mastery of physics and chemistry. It is amazing how little awareness there is, not only among black students, but also among white students generally in the American population.

As an example, there was a proposal to develop a course at Harvard College on aspects of molecular genetics that would be of interest to the general citizen. This course would be offered to nonspecialists, nonbiology majors, and nonchemistry

majors. But in order to have any kind of adequate treatment of these topics, students would need to have had a preparation in high school of elementary chemistry. And so a survey was made of students entering their first year at Harvard College, which is a highly selective group. Of these, only one-third had sufficient chemistry in high school to take this course. Two-thirds of the class, probably unwittingly, had made a decision that they would have nothing to do with science for the rest of their lives, including medical school. Indeed, the course was dropped because the third that had had chemistry were too strong to get much benefit from a course at this level.

It seems to me that this problem must be more severe in the high schools of the inner city, in which students unwittingly give up their chance for a career in science because they haven't got what I call linguistic preparation. It is a common experience that the longer you delay that linguistic preparation, the more difficult it is to fill in. So that when one deals with a course in biochemistry in medical school, the preparation in physical chemistry and in mathematics is such that it is difficult to build up the skills at a much later stage. Getting into the system early seems to me to be the key to developing adequate tools.

HAYNES: I am very encouraged by what you said previously, that biochemistry is actually moving right down to the high school level, because that would help to give the kind of preparation that is necessary.

DR. ALVIN TARLOV: I wanted to comment about practice after medical school. In 1977, we administered a questionnaire to 2,000 residents in internal medicine at all levels of training and tried to correlate their demographic features, educational history, cultural history, and economic background to their career aspirations. We oversampled black residents in internal medicine; we had about 350 in that group.

Last fall, in 1981, we went back to those 2,000 individuals. They have now been out of their training two or more years. We wanted to find out what they were doing and how closely their actual career fulfillment at this stage matched their career intentions of four or five years ago. We did that both for the whites and for the blacks. For the blacks, there was a significant variation in career fulfillment. They didn't nearly approach the extent of career fulfillment expressed in 1976–77 as did the whites. A high proportion, compared to the whites, had dropped out of clinical practice and were engaging in other activities in the health field, but they were not taking care of patients. There were a number who were full-time employees in the insurance industry. Some had become hospital administrators or engaged in other such activities. Of those who entered practice, a high proportion were what I would term marginally professional. That is to say, many didn't have hospital privileges. Many did not belong to the local county or state medical society. Many did not have an avenue toward continuing medical education.

The cause of these things must be very complicated, and I don't have any ideas about that. Nonetheless, I think an eighteen-year-old black student, looking at the record of career opportunities in the medical profession, will find the record very unattractive. In order to shed more light on the subject, and to improve the image of and the opportunities for practicing, more studies need to be done.

ROLE OF MEDICAL GENETICS IN UNITED STATES ACADEMIC MEDICINE

A. G. MOTULSKY

Genetics occupies a somewhat anomalous position among the disciplines that are considered the content of the classical medical curriculum. While well established as a science since the beginning of this century, genetics clearly is not yet a traditional subject in medical schools. Although genetics has both basic science and clinical aspects, the field has only relatively recently been introduced into the structure and curriculum of many—but not yet all—medical schools.

Why Has Genetics Been Neglected by Academic Medicine?

The role of heredity in the etiology of disease had been known for a long time, but in the absence of knowledge of the mechanisms of inheritance there could be little meaningful research and teaching. While familial diatheses in the causation of disease were recognized and even overemphasized in the prescientific era of medicine, the familial transmission of disease could not be scientifically studied.

Microbiologic discoveries at the end of the last century altered medical thinking radically by focusing attention on discrete disease-producing microorganisms. Later came the metabolic approach to medicine that

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allowed the scientific study of disease by applying the methods of physiologic chemistry to medical problems. Scientific medicine largely dealt with those two paradigms.

The Mendelian revolution identified discrete genes of unknown composition as the units of heredity and established that such genes were carried in a definable order on chromosomes. However, human chromosomes could not be visualized in the laboratory, and the role of DNA was not elucidated until much later. Although some physicians applied Mendelian theory to explain a few odd and esoteric hereditary diseases, research in genetics proceeded outside medical schools in universities, colleges, and agricultural stations—just the opposite of biochemistry, which was started in the medical schools and then moved to universities and undergraduate colleges. Furthermore, the study of genetics in humans was not carried out at the laboratory bench until relatively recently. Earlier approaches were inferential and relied on statistical methods. Most biomedical scientists liked to deal with laboratory-based realities rather than with abstract formulae. Human genetics as a statistical science did not attract interest from most biomedical scientists and certainly not from medical students. Fundamental genetics was carried out with plants and fruit flies and did not seem of relevance to the medical scientists. Medical scientists were not alone in their neglect of genetics. Even many biologists did not recognize the central importance of genetic theory for all the biological disciplines. Genetics did not join the mainstream of biology until after the DNA revolution.

Development of Medical Genetics

The development of genetics was more of an American enterprise than that of most other biologic and medical sciences. Fruit-fly genetics at Columbia University under the leadership of Morgan and his students laid the foundation for gene mapping. Muller showed the effect of radiation on gene mutation, and Avery at the Rockefeller Institute demonstrated that DNA was the genetic material. Biomedical scientists in U.S. medical schools, however, were not influenced by these developments until much later. In the clinical sciences, the microbiological and metabolic tradition reigned supreme. It took several scientific "breakthroughs" to change the prevailing tradition. The first was the belated recognition of the "one gene–one enzyme" hypothesis enunciated by the British physician Garrod before World War I that explained diseases such as phenylketonuria and others. Another powerful force was the understanding of discrete mutations as the cause of molecular diseases such as sickle cell anemia. These insights came with various methodologic advances in biochemistry and allowed the laboratory detection of these

disorders. The effects of one type of genetic mutation in the etiology of hereditary diseases could now be studied directly and no longer needed to be inferred.

Another revolutionary development was the ability to visualize the human chromosome complement. Suddenly, disparate conditions such as Down's syndrome and Klinefelter and Turner syndromes were recognized as chromosomal aberrations. One-third to one-half of spontaneous abortions turned out to be embryos that were nonviable owing to various chromosomal mishaps. Soon thereafter the utility of chromosome studies in cancer research became apparent. The methodology that allowed examination of individual human chromosomes was quite simple and could have been discovered many decades before 1956. No new concepts or new technology were required for these innovations. However, the failure of medical scientists to follow developments in cytogenetics and the lack of contact of cytogeneticists with human diseases delayed these discoveries for many years. Cytogenetics "caught on" very fast—presumably because it was an extension of the time-honored histopathologic approach allowing ready visualization of abnormal cells and tissues. Seeing is believing! No statistical inferences were required to observe that three instead of two chromosomes 21 were invariably found in the cells of patients with Down's syndrome.

The recent flowering of immunology with its finding of genetically determined immune deficiency diseases and the role of genetics in the immune response and in autoimmune diseases demonstrated to another influential group of biomedical scientists the importance of genetic approaches—particularly when it became apparent that understanding of the immunoglobulin structure of antibody molecules required new genetic concepts (1).

The last few years have seen the rapid development of recombinant DNA research. Here, the human hemoglobins and the hemoglobinopathies have been at the forefront. We understand the structure and function of normal and abnormal human hemoglobin genes better than those of any other mammalian genes. The thalassemias are now comprehended as mutations often affecting processing of gene products (2). These findings are invaluable models for the role of mutation in other diseases. Somatic therapy using DNA is now on the horizon for the hemoglobinopathies and possibly for other single gene–mediated diseases.

The field of medical genetics now holds an interest for many faculty members oriented towards basic science, clinical, and public health areas in medical schools. Research on the biochemical genetics of DNA and proteins, work in immunogenetics with cells and immunoglobulins, and investigations in cytogenetics on structure and function of the human chromosomes in health and disease are only some examples of basic scientific implications. Genetics has become relevant for most basic

medical disciplines such as biological structure, biochemistry, reproductive biology, microbiology, immunology, cancer biology, pharmacology, and pathology. Only physiology has been left relatively untouched by genetic concepts and methodology. However, genetic approaches wait to be applied to the neurosciences.

Clinical genetics has become a fully developed field (3) that includes diagnosis of various genetic diseases, genetic counseling, family follow-up, intrauterine diagnosis, and management of certain genetic diseases. While Mendelian diseases and chromosomal errors comprise the essence of clinical genetics, the diagnosis and management of birth defects are now usually included in the repertory of clinical geneticists. Genetic counseling clinics exist in most large medical centers and are staffed by clinical geneticists and various ancillary personnel.

Genetically determined biochemical and immunologic individuality has become apparent. No two individuals are alike genetically except for identical twins. Most common diseases have underlying genetic susceptibility factors (4). While their laboratory study remains relatively new, progress is being made in understanding the genetic hyperlipidemias as risk factors in coronary heart disease (5), certain sodium transport abnormalities as risk factors in hypertension (6), and the hyperpepsinogenemias (7) as predisposing to peptic ulcer and HLA-D abnormalities in insulin-dependent diabetes and in many autoimmune diseases (8). Clinical genetics is likely to have its major impact on medicine by contributing further insights into the genetic basis of many common diseases, including the major psychiatric conditions and common birth defects.

Public health also has become concerned with medical genetics. Programs for screening newborns for phenylketonuria (9) and hypothyroidism (9,10) are practically universal in developed countries. Screening for carriers of Tay-Sachs disease in Jewish communities (11) and for sickle cell abnormalities among blacks (12) is widely practiced. Screening of pregnant women above the age of thirty-five years for chromosomal aberrations by amniocentesis is generally recommended (13). Other programs such as sonography or alphafetoprotein testing or both of pregnant women in the search for neural tube defects are being investigated (14).

Population testing—first sponsored by academic units in medical schools—has now moved out to health departments. Public health practitioners need to be aware of the practical logistics of such procedures. Genetic epidemiology (15) is a new approach in the study of chronic diseases with underlying genetic susceptibility factors and utilizes both genetic and epidemiologic methodology. Epidemiologists, as well as clinicians, increasingly need to be aware of these developments. An appreciation of the principles of population genetics is required to understand the distribution and spread of genes mediating susceptibility and resistance to disease. Furthermore, the need for two sets of laboratories, one

providing cytogenetic support for diagnosis and antenatal screening, and another for diagnosis of genetic biochemical disease, has spawned many units which provide such services. Thus, genetic expertise is required for trainees in clinical pathology, laboratory medicine, and related disciplines. Genetics thus touches on most basic sciences, clinical fields, and population-based sciences.

Institutional Response to Developments in Medical Genetics

What has been the institutional response to these sweeping developments that make genetics important for so many different biomedical disciplines? Medical schools have not had any clear models to develop medical genetics as a discipline. Among clinicians, some internists pointed out the etiologic importance of medical genetics and introduced the field into some departments of internal medicine. In view of the relatively high frequency of genetic diseases and birth defects among infants and children, it is noteworthy that pediatric interest in the field is relatively recent (16). The role models in academic pediatrics for many years chose microbiology, immunology, and metabolism as fields of their scientific interest. Medical school administrators saw a relatively diffuse field that was difficult to fit into the usual administrative structure in medical schools. Faculty members who professed genetic interests had widely divergent interests ranging from blood typing to clinical syndromology. The result often was failure to establish formal units dealing with genetics. A study showed that in the late 1970s, 24 of 106 medical schools lacked any formal genetics unit (17) (Table 1). However, of these 24, 15 claimed to have an informal genetics unit—usually (10 of the 15) in pediatrics departments (17). The majority of medical schools responded by establishing either subdivisions of genetics in clinical departments or departments of genetics. Formal divisions of genetics are now found in depart-

TABLE 1
*Genetics Administrative Units in U. S. Medical Schools (1976/77)**

Unit	No.
Departments	16
Divisions in both medicine and pediatrics	10
Divisions in pediatrics	39
Divisions in medicine	5
Divisions in other departments	12
None	24†
Total	106

* Data in this table from Childs et al., 1981 (17).
† Informal units in 15 of 24.

ments of pediatrics in about 50 percent of medical schools (17). About 15 medical schools have divisions of medical genetics in departments of medicine, and at least 10 schools have formal divisions in both departments of medicine and pediatrics (17). A few schools have divisions in departments of obstetrics and gynecology.

At the present time, 24 medical schools have independent departments of medical genetics or units with department-like status (18) (Tables 2 and 3). However, only 14 of the 24, or 12 percent of the total (14 of 118), have departments that are clearly labeled as departments of genetics without covering other responsibilities (18) (Table 2). In the remaining 10 (out of 24) departments, other areas such as biochemistry, biophysics, development, or microbiology are included in departmental responsibility (18) (Table 3). These medical schools have recognized the importance of genetics but have combined genetics with another basic medical science. Few schools of public health have genetic departments or divisions.

With a few exceptions, the 24 departments of genetics function as basic science departments. On the contrary, the activities in the pediatrics genetics units are largely clinically oriented. In fact, since the majority of faculty role models for genetics in medical schools currently are pediatricians, the image of medical genetics among medical students and medical school faculty members has often become that of a specialty largely concerned with cytogenetics, dysmorphology, inborn errors of metabolism, and other rare diseases. Clinical genetics has become "pediatricized"

TABLE 2

*U. S. Medical Schools (1980/81) with Departments of Genetics**, †*

Harvard University	University of Pennsylvania
University of Hawaii	University of Rochester
University of Illinois	Stanford University
University of Indiana	University of Virginia
Mayo University	Washington University
University of Michigan	University of Wisconsin
University of Oregon	Yale University

* Not shared with another basic science.

† Information from *AAMC Directory* (1980/81) (18).

TABLE 3

*U. S. Medical Schools (1980/81) with Basic Science Departments That Combine Genetics with Other Basic Sciences**

Brown University	Albert Einstein College of Medicine
University of Chicago	University of Massachusetts
University of Colorado	University of Mississippi
Columbia University	Southwestern University (Dallas)
Duke University	University of Texas (Galveston)

* Information from *AAMC Directory* (1980/81) (18).

to its detriment, in view of the considerable contribution genetics can make to *all* of clinical medicine (19). There are many genetic diseases in dermatology, neurology, and ophthalmology. The contribution of genetics to adult cardiology, endocrinology, hematology, rheumatology, clinical pharmacology, psychiatry, and other clinical fields has been clear, but research and teaching in many of these areas are neglected.

Teaching of Genetics to Medical Students

Childs et al. have reviewed this field recently (17). About 75 percent of medical schools provide obligatory courses of genetics. Slightly more than one-half (57 percent) of these courses are given in the first year, one-third in the second year, and one-tenth in more than one year. They range in length from 6 to 54 hours with a mean of 24 hours. As expected, schools with formal genetics departments or divisions are more likely to offer courses than those without. Courses are most frequently organized by pediatricians (in about 50 percent of cases).

Because of the orientation of medical geneticists towards families and populations and the increasing importance of genetics for primary care medicine, one would hope that departments or divisions of family medicine, community medicine, or preventive medicine might stress genetics as a significant approach to comprehensive primary care. In a study done in the early 1970s, it was shown that medical schools that stressed a community and family approach were less likely to have formal units in genetics or to teach genetics to medical students (20). Matters do not appear to have changed much since that time. Genetics in medical school still is considered either as a research-oriented basic science or as an esoteric pediatric subspecialty or both. Thus, the more research-oriented schools are more likely to have departments (Tables 2 and 3) and to some extent formal divisions of medical genetics. The result is that many medical graduates neither recognize the importance of genetic principles for the biomedical sciences nor have a feeling for the increasing importance of the field for general medicine and for practically all the medical specialties.

Effects of These Developments on Faculty

The field of medical genetics has become professionalized rapidly (21). Some basic scientists have obtained their Ph.D. training in human genetics and now work in medical schools. Competition for Ph.D. scientists in molecular genetics has become strong, with the opening of many biotechnology firms. An increasing number of physicians have also obtained training in the field, and clinically oriented fellowships in genetics can be

readily secured. Most clinical fellowships are under pediatric auspices, and because of the pediatric image of the field, most M.D. trainees currently are pediatricians. A newly established American Board of Medical Genetics has recently certified clinical geneticists as well as patient-oriented Ph.D. geneticists, M.S. genetic counselors, cytogeneticists, and biochemical geneticists. Two hundred ninety-two M.D. clinical geneticists (80 percent of those who took the tests) recently passed the board examination that was set up with aid of the National Board of Medical Examiners by an 11-member group elected by the American Society of Human Genetics.

What about the Future?

Genetics clearly is here to stay and its relevance for the basic medical sciences and clinical medicine has been established. Genetics can provide the conceptual framework for the basic biomedical sciences and for clinical medicine better than any other science. As disease prevention becomes increasingly emphasized, the importance of genetic factors interacting with specific environmental agents (22) and the ability to detect and treat genetic diseases both antenatally and postnatally emphasize the need for better knowledge of genetics by physicians and other health professionals. What do these trends mean for genetics as an academic discipline in medical schools? Ideally, more medical schools, regardless of basic orientation, need to establish formal genetics units that are not tied to a single clinical department. The creation of more departments of medical genetics would be the optimal solution, since interdepartmental centers and other informal arrangements lack the necessary "clout" in the power hierarchy of the medical school. Arrangements short of departmental status, therefore, are less likely to be as effective in securing and keeping faculty personnel, space, and teaching time. It is particularly difficult to keep outstanding Ph.D. scientists such as biochemical geneticists and statistical geneticists on "soft" funds in a clinical department. The absence of departmental status downgrades the field. Even medical students react to such nuances. Medical school departments of genetics should be different from genetics units in universities and colleges by strongly stressing human, medical, and mammalian genetics. Departments in schools that are less laboratory research–oriented could emphasize the many aspects of diagnosis, counseling, and screening posed by clinical genetics. Departments of medical genetics are ideal for bridging the basic and clinical sciences of the field. Faculty members can contribute most by exploring those basic approaches to human, medical, and clinical problems that are less likely to be tackled by researchers in institutions outside of medical schools. There is no dearth of research problems at the basic or at the clinical level. Multiple joint appointments of faculty

members with other basic and clinical departments are likely to be effective in bringing the many concepts of genetics to bear on problems in other fields.

Teaching of genetics to medical students ideally requires three steps. There should be a required course of *human* genetics in the first year that deals with the basic sciences underlying human variation, including molecular genetics, biochemical genetics, cytogenetics, and population genetics—an area that is often neglected currently. A required course of *medical* genetics should be taught in the second year. Here, modes of inheritance, complex inheritance, cytogenetic diseases, pharmacogenetics, birth defects, and approaches to genetic counseling should be covered. The clinical years should see the reinforcement of formal teaching by clinical conferences and bedside teaching. Clinical professors in their informal teaching need to pay more attention to genetic aspects of diseases.

The previous lack of exposure to modern medical genetics by most faculty members and administrators, the natural conservatism of the medical school establishment, and curricular overload will make it difficult to institute an ideal scheme. Nevertheless, the appearance of genetics as a late-comer on the medical academic scene should not relegate the field to secondary status as might happen under circumstances of financial stringency.

The potential impact of genetics on both research and practice in medicine is high. Medical schools need to pay increasing attention to this field by providing appropriate administrative support for its teaching, research, and service activities.

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BEYOND RECOMBINANT DNA

DANIEL L. HARTL

In the past thirty years, genetics has transformed our views of life. In the process, the field has transformed itself. Once concerned exclusively with understanding the transmission, function, and mutation of the genetic material, genetics can now be regarded equally as a collection of attitudes and approaches useful in prying apart almost any biological problem. A key element in the genetic approach is mutation. Mutations represent the ultimate in experimental microsurgery, and much can be learned about normal biological processes from the study of the effects of mutational lesions.

Genetics is a large subject to summarize in a few pages, so perhaps a brief overview of the organization of this discussion will be in order. For purposes of orientation, I wish first to discuss the place of human genetics in the broader context of genetic research, as this has changed markedly in recent years. This change has come about in part because of new techniques, such as recombinant DNA, but in larger part because of the success of genetics in revealing certain basic principles that govern life processes. Two of these principles, which may be called information flow and interlocking networks, seem to be of cardinal importance. From this broad perspective of general principles, I then plan to summarize briefly some of the principal discoveries made recently—particularly split genes,

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pseudogenes, and transposable elements. This leads naturally to a discussion of practical applications of genetic research and of future prospects for research in both the short term and the long term. Finally, a few words need to be said about the broader social context within which genetics and other sciences must exist.

One of the most significant changes in medical genetics is the relatively short time it now takes for basic discoveries to become translated into clinical practice. At one time human genetics was a rather specialized field—the human generation time is inconveniently long for genetic studies; pedigree and medical records were difficult to gather and collate; biochemical tests were relatively crude and required unacceptably much tissue mass to carry out; human chromosomes were difficult to study because of their relatively small size, large number, and similarity of appearance; human cells were all but impossible to maintain for sufficient periods in culture to permit their study and manipulation; few human genes were known, and these few were difficult to localize even as to chromosome, let alone as to position on the chromosome; and prenatal diagnosis and screening for carriers of genetic disease were unknown. In those days experimental organisms such as bacteria, yeast, fruit flies, and mice were the material of choice in genetic research. It seemed certain that virtually all important discoveries would be made first in these organisms and only later examined in humans. The transition of knowledge between the laboratory and the clinic was a slow, arduous process.

All this has changed. Human genetics is now solidly in the mainstream of genetics, and many important discoveries are made first in humans and later examined in experimental organisms. Pedigrees and medical records are now computerized, permitting easy access by authorized personnel and sophisticated analysis. Biochemical techniques have been miniaturized to the extent that many can be carried out with single cells or even parts of cells. Special methods and staining procedures have been devised that render human chromosomes not only amenable to study but favorable for study. Modern cell-culture methods not only permit the long-term maintenance of human cells but also permit their fusion with cells of other species to allow relatively precise mapping of human genes and to study their functions. Well over a thousand human genes are currently known, and the number continues to grow. Prenatal diagnosis and genetic screening are a routine part of clinical practice relative to many inherited disorders. Indeed, new techniques in cell culture, monoclonal antibodies, and recombinant DNA are accelerating the pace of change in an already fast-moving field. Experimental organisms are still an essential part of modern genetic research, but the transition of knowledge between experimental organisms and humans and between the laboratory and the clinic has never been so rapid.

Modern genetics includes an odd amalgamation of classical biochemistry, biophysics, cell biology, microbiology, and genetics. Part of this amalgam has come to be known as molecular biology, a felicitous term coined, incidentally, by Warren Weaver of the Rockefeller Foundation in 1938. Precise delineation of the boundaries between molecular biology and genetics is neither important nor informative, but it is worth looking briefly at the past because, as James Bryant Conant once remarked, the history of a subject *is* the subject, by which he means that the current attitudes and ideas in a field are an outgrowth of the past.

Genetics as a science goes back to Gregor Mendel and earlier, but the origins of the modern phase of molecular genetics are found in the "phage group" established by informal interactions between Max Delbrück, Salvador Luria, Alfred Hershey, and others, beginning in the early 1940s. Delbrück's view was that the best approach to understanding complex forms of life was first to understand the simplest forms of life—the bacteriophage viruses that infect bacterial cells. One of Luria's students—James Dewey Watson by name—sought the clue elsewhere, in the chemical structure of the genetic material itself. Watson and Francis Crick's discovery of DNA structure was fundamental in a way perhaps described best by Delbrück himself in a letter written on April 14, 1953, from the California Institute of Technology to his mentor and friend Niels Bohr in Copenhagen. As Delbrück saw it, "Very remarkable things are happening in biology. I think that Jim Watson has made a discovery which may rival that of Rutherford in 1911."[1] And so it was. As Rutherford's discovery of the atomic nucleus opened the way for a new understanding of the atom and for the development of quantum mechanics, so Watson and Crick's structure for DNA opened the way for a deeper understanding of the gene and how it works.

The success of modern genetics can be understood in terms of unraveling the mechanisms and implications of two central life processes. The first of these is information flow—the storage and transfer of genetic information—which involves the manner in which hereditary information is encoded in the sequence of nucleotides in DNA, of how this information can change spontaneously in the diverse processes of mutation, and of how this information is expressed anew in each individual by the processes that regulate gene expression and so guide embryonic development. The detailed mechanisms of DNA replication, repair, transcription, and translation were of course not revealed instantly with the unveiling of DNA structure, and much about these processes is still obscure. Nevertheless, the structure itself did imply that precise questions could at last be framed

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[1] For source of quotations, see last paragraph of paper.

and unambiguous experiments carried out. The promise of the structure was sufficiently clear, in fact, that a week before Watson and Crick had finished building their molecular model, Crick announced to all who would listen in his luncheon pub, The Eagle, "We have discovered the secret of life."

While the principle of information flow grew out of the structure of DNA, the second principle—that of interlocking networks—came from studies of proteins, particularly those that regulate genetic and metabolic activity. Jacques Monod and his colleagues realized that macromolecular transformations involve three-dimensional structural conformations that can become altered allosterically in response to the appropriate chemical signals in the cell. This principle implies that the regulation of any metabolic circuit can be integrated with the regulation of any other, because the appropriate small molecules can act as effectors of the regulation, and the metabolic networks can thus be interlocked. The preeminent example of the Monod sort of allostery is found in the lactose repressor protein, which has a DNA-binding conformation in the absence of lactose but which loses this conformation in the presence of lactose and so permits the lactose-degrading enzymes to be expressed only when they are needed by the cell. We are yet to appreciate the full implications of allostery, but Monod emphasized its place in the scheme of things by calling it the second secret of life.

The principles of information flow and interlocking networks have transformed biology in general and much of academic medicine in particular because they provide a sufficient preliminary understanding of life processes. They imply that all of life can ultimately be understood in the framework of the physics and chemistry of macromolecules. Ironically, this remarkable reductionist conclusion proved disappointing to physicists such as Delbrück, who entered the field of biology in hope of finding fundamentally new physical or chemical principles. From the standpoint of evolutionary biology, the reductionist conclusion is a testimonial to the extraordinary power of natural selection to use physical and chemical processes in opportunistic ways to decrease the entropy of living things on earth at the expense of the burning and disintegration of the sun. What is fundamentally new in biology in the last thirty years is that we can at last perceive the essential unity of all living things amidst the superficial diversity of adaptations to various environments.

The significance of general principles for academic medicine is that they allow a classification of human diseases into their appropriate categories as related entities. Once the diseases are so classified, the general principles guide the search for causes and for effective treatments, and, in the process, they not infrequently reveal genetic or physiological heterogeneity where none was suspected and so lead to more precise

diagnoses. Examples of this sort of strategy include such disease categories as the hemoglobinopathies, the mucopolysaccharidoses, and the immunodeficiencies. Because of the principles that exist and their usefulness in academic medicine, the distinction between "pure" and "applied" research that seemed so clear in the 1960s has completely broken down, as has the distinction between "medical" and "nonmedical" research. Because the general principles governing life processes are so important in medicine, it has become clear, once and for all, that organisms chosen for biological research need not always be relevant to medicine or agriculture. In the recent history of genetics, "relevant" research has often turned out to be irrelevant, and the most important discoveries have come from unexpected directions. In biological research, it is often best to use organisms such as bacteria, yeast, nematodes, fruit flies, or mice, simply because they are convenient and because we already know so much about them.

While the new principles have changed our way of thinking about genetic problems, new techniques have changed our way of doing the research. One of these techniques has even achieved celebrity status in the popular press. I refer of course to recombinant DNA, that marvelous group of techniques in which a piece of DNA from one organism can be spliced into another DNA molecule and introduced into a living organism, there to multiply and, in some cases, even function in its normal manner. Under the heading recombinant DNA should also be included such procedures as restriction mapping, Southern blots, and DNA sequencing, which routinely use cloned DNA fragments as probes or as material to be analyzed. A second group of new procedures is as important as recombinant DNA but less well known. These procedures involve monoclonal antibodies, which are homogeneous antibodies having a single antigen-binding specificity derived from a clone of a single antibody-producing cell. A third group of techniques important in genetics involves the manipulation of cells in culture, particularly cell fusion and DNA-mediated transformation, though transformation of experimental organisms such as bacteria and yeast is still the method of choice. These procedures are now rather routine and available for use in various combinations. The full potential of the procedures has hardly been tapped, and it is a safe bet that most of the major discoveries of the next twenty or so years will involve them or their offshoots. Indeed, modern molecular genetics has become so oriented toward techniques that a famous molecular biologist, one of the phage group, complained to me that contemporary graduate students are in danger of losing sight of why the techniques are important in the first place, which is to be able to learn new principles. Nevertheless, the techniques themselves are important because they are already being explored for their usefulness in diagnosis, for example in the use of

restriction digests and Southern blots in the prenatal diagnosis of sickle-cell anemia, and this serves to emphasize again the intimate connection between academic medicine and other areas of research.

In the interval of very few years, recombinant DNA has become the most widely used and most powerful set of techniques in molecular genetics, and new discoveries are being made almost more rapidly than their significance can be comprehended. A chief discovery involves the mosaic nature of many eukaryotic genes, the DNA of which is split into several or many protein-coding regions called exons interrupted by stretches of non-coding DNA called intervening sequences or introns. During gene expression after the DNA is transcribed into RNA, the introns are enzymatically cut out of the RNA and the exons spliced together in the nucleus to produce an intact protein-coding region in the mature RNA. The functions of intervening sequences are still unknown, though in some cases introns seem to be essential for normal gene expression. One remarkable observation is that exons often, though not invariably, correspond to functional domains of proteins, which Walter Gilbert has put into a broad evolutionary framework by suggesting that new protein functions can evolve by a sort of shuffling of exons to create new combinations of functional domains that have sufficient enzymatic activity that they can be improved upon by conventional processes of mutation and natural selection. The relevance of split genes in medicine is evident from the recent finding that certain thalassemias are associated with mutations that alter an exon-intron splice junction and so prevent normal RNA processing.

Recombinant DNA techniques have been instrumental in clarifying the genetic basis of antibody diversity, which until recently was a complete mystery. A principal mechanism involves combinatorial joining, in which new antibody genes are created piecemeal by DNA splicing of appropriate exons. Mammals have several or many exons corresponding to various parts of an intact antibody protein. During the differentiation of antibody-producing cells, these exons are spliced together in many different combinations, one per cell. Additional sources of antibody diversity include somatic mutations that occur during differentiation of the antibody-producing cells, as well as a sort of error-prone recombination of antibody genes. These processes together create the hundreds of thousands of different antibody proteins that every normal mammal is capable of producing in response to the appropriate antigenic stimulation.

Another major surprise resulting from the application of recombinant DNA techniques is the discovery of pseudogenes—genes having obvious homology with known genes but which are not expressed. Pseudogenes seem to be rather common. In the gene clusters that code for the human globin genes, there is an α-globin pseudogene and two β-globin pseudogenes, although some pseudogenes are known that are not even on the

same chromosome as their normal counterparts. Whether such unexpressed DNA sequences have any function is at present unknown, but the sequences are odd in any number of ways in addition to being unexpressed. The nucleotide sequences of pseudogenes evolve much more rapidly than those of conventional genes, and some pseudogenes, such as an α-globin pseudogene in the mouse, are missing their intervening sequences.

Our whole conception of the genome is being reassessed because of recent discoveries involving recombinant DNA. At one time not very long ago, we imagined the genetic material to be relatively stable. Mutations were known, of course, but these were thought to be relatively rare. In the absence of known mutagens such as radiation or certain chemicals, mutations were thought to occur at the rate of about one per hundred thousand or one per million genes per generation, and their molecular basis was thought to be well understood, involving mainly simple nucleotide substitutions or deletions or other simple chemical alterations. All this has changed with the discovery and analysis of transposable elements, the modern molecular study of which grew out of much earlier work in maize by Barbara McClintock. Transposable elements are certain types of DNA sequences found in prokaryotes and eukaryotes that have the capability of transposing from one position to another in the same or a different DNA molecule. In prokaryotes, most of these elements carry within their own nucleotide sequence the genetic information coding for an enzyme or enzymes that catalyze their own transposition. In addition, many prokaryotic transposable elements carry genes for toxin production or antibiotic resistance. These elements can transpose onto plasmids—infectious DNA elements that can be transmitted from one bacterial cell to another, sometimes between different species or even between genera. Once mobilized on a plasmid, an antibiotic-resistance gene can become widely disseminated. The plasmid can even pick up other antibiotic-resistance transposons as it goes along, and bacteria carrying plasmid-determined multiple drug resistance have become a significant public health hazard. Evidently, bacteria began to practice genetic engineering a very long time ago, and in much the way it is carried out by modern geneticists.

Much less is known about eukaryotic transposable elements, although such elements are widespread in species such as *Drosophila*, in which several dozen distinct families of transposable elements have been identified. These elements exist in multiple copies dispersed throughout the genome, and they are capable of transposing within and between chromosomes. They can insert in or near known genes and cause recognizable phenotypic effects that are superficially indistinguishable from conventional mutations, except that many transposable-element–associated mutations seem to have exceptionally high rates of back mutation to the

normal form of the gene. Humans have DNA sequences that strikingly resemble transposable elements from other organisms. Whether these sequences contribute significantly to human mutations we still do not know, but preliminary data in fruit flies suggest that transposable elements might be a very important source of spontaneous mutation.

The normal functions of transposable elements, if any, are unknown, and their evolutionary origins and the mechanisms of their maintenance are still mysterious. Nowadays it has become fashionable to refer to transposable elements as "selfish DNA" or even as "junk DNA." This is very unfortunate terminology. When one does not know the function or evolution of a large class of DNA sequences, it seems inadvisable to prejudice the issues by naming the sequences according to the precepts of some pet hypothesis. For the record, it is worth pointing out that recent evidence from my own laboratory has shown that prokaryotic transposable elements are neither selfish nor junky.

Related to transposable elements—or I should say *apparently* related—are certain eukaryotic RNA viruses called retroviruses, which are of immediate clinical importance inasmuch as they are associated with certain animal cancers. These RNA viruses are reverse-transcribed into DNA inside the cell and can become incorporated into various sites in the chromosome. These viruses tend to be very simple, having few genes, but in some cases the gene associated with the cancer transformation is astonishingly similar to a gene normally present in the host, as if the virus had pirated the host gene sometime in the past. Indeed, recent evidence from Philip Leder's laboratory suggests that the intron-less mouse α-globin pseudogene may have originated by the interaction between a spliced α-globin RNA and a retrovirus in a reverse-transcription and integration process gone awry.

All of these transposable DNA sequences have prompted a new view of the genome as being in a relatively rapid state of flux. "Relatively rapid" in this context means rapid in terms of evolutionary time. Unfortunately, we know little yet about the rules governing transposition or of the phenotypic effects of transposable elements, so this change of view has not yet become incorporated into evolutionary thinking. Evolutionary biology must constantly remold and transfigure itself in the light of new information, and much of the new knowledge has yet to be assimilated. In addition to transposable elements, evolutionary thinking has yet to digest and accommodate the information in the nearly one million nucleotides of DNA sequence that have accumulated.

The sort of discoveries I have discussed above, which are just a sampler, indicate the excitement and the rapid change occurring in modern genetics at all levels from molecular genetics to evolutionary genetics. There is a whole other area that has created excitement, and this is the application

of recombinant DNA and other techniques to problems in medicine and agriculture. These procedures evoked public concern and debate early on, when there were some potential dangers that were largely unassessed, although the potential dangers that could realistically be perceived were far less than the fanciful dangers reported in the press. Experience of the last few years has indicated that the concern was, for the most part, unwarranted, and accordingly, the once elaborate federal DNA research restrictions have been progressively relaxed though by no means eliminated. These recombinant DNA techniques have already given us human insulin and growth hormone for clinical trials, and human interferon for further research into what may prove to be for viral infections what antibiotics have become to bacterial infections. Recombinant DNA procedures have spawned a number of small specialized companies and have elicited major commitments in biological research from some large ones. Industries and universities are striving to establish new relationships in research and development without compromising their own unique goals and values.

So far, I have emphasized molecular genetics, recombinant DNA, and related matters because progress in these areas has been most dramatic in recent years, but it is important to emphasize here that not all of modern genetics is molecularly oriented. One obvious example is quantitative genetics, which confronts traits controlled simultaneously by several or many genes and by environmental factors and which has traditionally relied on statistical techniques for analysis. Originally developed in order to understand the statistical characteristics of the inheritance of complex traits in domesticated animals and crop plants for purposes of predicting response to artificial selection and designing optimal breeding programs, the techniques are being refined and extended for application to human traits, though, of course, with entirely different goals. The application of such techniques in academic medicine has come to be called genetic epidemiology, and the research is highly interdisciplinary, involving the joint efforts of clinical medicine, psychiatry, genetics, statistics, mathematics, and computer science. The objectives of the research include correct diagnosis and data acquisition, along with segregation analysis to detect major genetic factors, linkage analysis to detect associations between the trait of interest and known marker genes, analysis of genetic and environmental contributions to the traits, improved genetic counseling, and ultimately, disease prevention, treatment, or cure.

Classical genetic analysis also plays a continuing and important role in modern genetics. The first approach in the genetic analysis of complex traits such as are found in development, neurobiology, and immunology is still in the study of phenotypes produced by mutations and by combinations of mutations. The more complex the phenomenon of interest, the

more important is this level of analysis to establish a framework within which detailed molecular studies can be carried out. Without the accompanying genetic analysis, molecular biology is usually flying blind.

One of my tasks in this paper is to project the future of genetics in its relationships to academic medicine. Unlike the weather service, scientists have no radar with which to see clear or cloudy weather moving in, so any forecast in science, particularly in a fast-moving field like genetics, is always speculative, often wrong, and usually to be avoided by the prudent. Genetics has a long and distinguished history of wrong forecasts. Herman Kalckar tells a story from "the old days" when Max Delbrück "sailed up to old [Oswald] Avery" and said, "You know, I believe you're wasting your time." Those were the days when Avery and his colleagues were trying to show that the transforming substance in pneumococcus was DNA and that therefore DNA was the genetic material. Kalckar recalls that old Avery just smiled and that "Max looked very worried."

It seems safe to predict that important advances in genetics in the next several decades will emerge from those broad areas of study that currently command much attention. One of these is regulation, the manner in which cells coordinate their genetic activities. We still know relatively little about the rules governing transcription of eukaryotic genes, which recent data from Alexander Rich's laboratory suggest may involve DNA thrown into a left-handed helical configuration, and the rules governing RNA processing, translation of proteins, and post-translational modification of proteins. It seems to be becoming clear that regulatory control can be exerted at many levels in the course of gene expression, and perhaps there will be no general, universal patterns, though some mechanisms of control will surely be more important than others. In considering such a complex problem as regulation, it is perhaps worth bearing in mind that populations do not evolve in such a way that their regulatory processes will be elegant, clever, or simple, though many such processes are. Populations evolve to survive, and they are opportunistic. If a cumbersome system of regulation should arise by chance and work tolerably well, there will be evolution for further refinement and effectiveness, but not necessarily for simplicity. From the standpoint of what we know today, regulation seems to encompass a hodgepodge of diverse *ad hoc* processes, each of which is retained because it happens to do the job. Some of these processes are beautiful in their simplicity, others complex and poorly understood.

Another major area of emphasis is in understanding embryonic development. Earlier I mentioned two fundamental principles that have transformed our way of thinking about living things—information flow and interlocking networks. Embryonic development involves cell-to-cell interactions on a grand scale, and I expect that we will see a third major principle pertaining to such interactions emerge from this research. Of

course, regulation of the immune system also involves cellular interactions, and a major thrust of research in immunogenetics is in revealing the panoply of functions associated with the immune system and in understanding their interrelationships and controls. In discussing areas of current interest, one must also mention the present emphasis on understanding the molecular basis of animal viruses, particularly tumor viruses. Several of these viruses have been completely sequenced, so their genetic structure is understood; their interactions with the host cell are much more complex, but remarkable progress has been made. Somewhat more distantly, we will begin to comprehend the molecular basis of the workings of the central nervous system, and the genetic analysis of behavior in several experimental systems is making steady progress. Finally, I should mention the recent interest in the molecular biology of plants; this long-neglected field has finally come to the forefront because of opportunities made possible by recombinant DNA and because of its importance in agriculture and other areas.

So, I think we can expect steady progress in furthering our understanding of life processes, with hopefully some interesting surprises along the way. In the process, we can expect new and important practical applications of the knowledge and techniques. These applications seem to emerge from "pure" science more rapidly than biologists have become accustomed to, perhaps partly because the procedures have become technically rather easy and the applications well defined by the requirements of diagnosis and treatment. We are in the midst of a revolution in pharmacology. In the future we will be seeing an increasing use of natural products in treatment, particularly human proteins synthesized by bacteria. We will have batteries of monoclonal antibodies tailored for precise diagnosis of viral and bacterial diseases as well as various types of cancer. We will rely on bacterial production of antigens for immunization rather than on dead or attenuated disease organisms. All of this will transform academic medicine and clinical practice in multitudinous ways.

Beyond recombinant DNA there looms a whole series of important and difficult problems related to traits encountered in genetic epidemiology, whose expression involves the interactions of several or many genes in concert with environmental factors. Indeed, the most common diseases encountered in clinical practice fall into this category, traits such as diabetes, schizophrenia, multiple sclerosis, epilepsy, pyloric stenosis, spina bifida, congenital heart disease, anencephaly, and hydrocephaly—to mention only a few. The immediate needs regarding such diseases are for improved methods of diagnosis, treatment, and genetic counseling. The long-term needs are for understanding their genetic, molecular, cellular, and developmental basis in order to prevent the diseases, find more effective treatments, and offer more accurate counseling. Those traits with a strong environmental component, such as hypertension or alcohol

dependence, are particularly in need of study in order to learn which environmental factors produce the greatest risk and how to control or eliminate these factors. At present we have only rather indirect statistical tools with which to approach these traits. Further creative research in these areas is badly needed, but the field suffers somewhat by not being as flashy as recombinant DNA.

I chose the title "Beyond Recombinant DNA" for this essay because I wanted to emphasize that recombinant DNA is no panacea for solving biological problems. Difficult problems lie ahead that are beyond the power of molecular techniques as we presently know them, problems such as those studied in genetic epidemiology, having to do with the causation of complex traits such as schizophrenia or diabetes. But I also wish to use the word *beyond* in another sense in order briefly to address academic medicine, particularly genetics, in its wider social context, a context extending beyond what is circumscribed by genetics or by any other academic discipline. This wider context includes the resources allocated to research, the continuity of public support of research, and the commitment to appropriate scientific education at all levels. Along with many scientists and other citizens, I share an apprehension that science in general and academic medicine in particular may be in for a rough time in the years immediately ahead, not because the enterprise has been unproductive or unpromising—it has been quite the contrary—but because of the wider social context in which the enterprise must be carried out.

Academic medicine has obligations in public education that are not sufficiently emphasized. The United States finds itself in the paradoxical situation of being utterly dependent on technology both for maintenance of its standard of living and for its long-term global economic well-being, yet its citizens tend to be misinformed, skeptical, resentful, and often fearful of technology. Its citizens are unaware not only of what has been achieved in science, but also of what science is and what its implications mean to them. In genetic screening programs involving phenylketonuria or Tay-Sachs disease, for example, substantial sums are spent on the programs, but most of these resources go toward the screening itself, a negligible amount being spent on educating the public on such issues as the nature of genetic disorders and the meaning of carrier status, and on attempting to dispel parental guilt and social stigmata related to inherited disorders. Indeed, public misunderstanding of human genetics is said to be a principal impediment to effective genetic counseling because the average person fails to perceive the connection between heredity and health or disease. Equally serious is the observation that training in genetics in U.S. medical schools is at best spotty. Improved public scientific education is essential for the future of all sciences.

Lack of public understanding of science is in part a reflection of lack

of appropriate scientific education in schools at all levels, from kindergarten through college. We have brought upon ourselves a serious shortage of trained teachers in science and mathematics, and school systems throughout the country are under continuing pressure to relax their standards for teachers so as to be able to teach science and mathematics at all. Even so, science education in elementary schools is virtually nonexistent. Continuing education programs for science teachers have been drastically cut back, as have college student grants and loans. The attitude toward education seems to be that education benefits only the one educated, though in fact it benefits us all.

The future of science needs future scientists, yet we find ourselves backsliding into the pre-Sputnik era of unconcern for training in virtually all areas of science and technology. There is a growing national indifference, even a hostility, toward natural science and science education. Signs of the attitude are rife; witness this item from the May 5, 1982, issue of *Health Planning and Manpower Report*:

> The National Conservative Political Action Committee [NCPAC] has called for abolishing health professions education and science programs and sharply reducing others as a means of cutting the federal budget. Among those that would get NCPAC's ax would be the Education Department, the National Science Foundation, the arts and humanities endowments, basic energy and agricultural research programs and health professions' education aid. Biomedical research funded by the National Institutes of Health would be cut in half under NCPAC's "alternative budget" for fiscal 1983. "We don't need to increase taxes or to cut our vital defense programs, as big spending liberals have proposed," NCPAC head John T. Dolan told a news briefing last month. "We simply need to get rid of costly, ineffective and often counterproductive programs which are in the budget because of some special interest group."

The drift from natural science has been gathering momentum for more than a decade, and something deeper than balancing the federal budget is fueling it, although budget balancing provides a handy rationalization for those wielding the ax. The deeper reasons for the drift from natural science were touched upon by Sydney Brenner one night at King's College, Cambridge, in 1971. Brenner predicted:

> I think there is going to be much less pure science practiced [in the future]. Everyone, the man in the street, government, business, students—all distrust pure science. Legislators are suspicious of pure science. They don't think scientists can produce the effects fast enough; many of them don't think they can produce the effects at all. They are suspicious of universities. It's a very complicated business; but they want mission-oriented science. I mean, that's the squeeze from the top. It seems to me there's a big squeeze from below. Which is that the young aren't interested in nature anymore. They're much more interested in not how nature works but how society works and how people work.

> They don't believe that knowledge is power. This is very strong. The drift from natural science is the modern philistinism.

In short, C. P. Snow's Two Culture problem is still very much with us, and it behooves everyone in academic and clinical medicine to confront the diagnosis and to heal the rift.

I am grateful to Drs. Christine Blazynski, Daniel Dykhuizen, George Johnson, and Donald Shreffler for their advice and criticism in the preparation of this manuscript. The historical quotations in the text are all taken with permission from Horace Freeland Judson's magnificent history of the rise of molecular biology, *The Eighth Day of Creation* (New York: Simon and Schuster, 1979). Delbrück's letter to Bohr is cited on page 230, Crick's "secret of life" comment on page 175, the Kalckar reminiscence on page 93, and the Brenner quotation on page 218. The quotation from *Health Planning and Manpower Report* is taken with permission from Capitol Publications, Inc., Arlington, Virginia.

DOES BIOMEDICAL RESEARCH HAVE A FUTURE?

ROBERT W. BERLINER

These are worrisome times for those who are concerned with medical research. Despite its relatively healthy current state, one must look to its future, both in the short term and in the long run, with a certain amount of foreboding. In the last twenty-five years, the growth and productivity of the American medical research community have been remarkable. And the momentum gained in those years is still carrying that enterprise to new heights of achievement. Those who were responsible for providing the impetus for that expansion, among whom James Shannon at the National Institutes of Health (NIH) and John Fogarty and Lister Hill in the Congress were the key figures, can hardly have imagined the insights that would be achieved and the enormous potentialities of the techniques that have been developed. Things that only twenty-five years ago seemed forever beyond our hope of comprehension are now being explicated at an amazing speed. A Rip Van Winkle, after having slept those twenty-five years, would be certain he still was dreaming when he saw what was going on. Those who only a few years ago saw a monster springing from every clone must feel rather sheepish when they see the opportunities for

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progress established through the exploitation of recombinant DNA techniques and indeed the very practical and useful applications that are the immediate promise of cloning and which the doubters believed were only advertising puffery to hide the personal scientific ambitions of the molecular geneticists.

Nevertheless, at a time when so many roads are open, we are seriously in danger of running out of gas. None of us needs to be reminded that the national economy is in serious trouble and that many federally supported programs are going by the board. These being the current circumstances, we would seem, relatively speaking, to have little to complain about. After all, research has fared better than most items in the federal budget. But to do well on only a relative basis is a small consolation. And I think we can justifiably claim that the support of medical research has been one of the government's most successful ventures. In view of the changing circumstances, it behooves us to take stock of where we are and where we are likely to be going. If in that process we should find reason for concern about the future of medical research, it is probably understandable.

For some years now the funds that support medical research and training have been eroded by inflation. The increases built into multiyear grants have been kept at a level well below that which would have supplied constant purchasing power to the investigator. At the same time, the costs incurred by the institutions in which most of the work is done, in maintaining their facilities, providing utilities, and meeting the requirements of (mostly appropriate) government regulations, have continued to increase at least at the level of general inflation. The latter costs, which make up most of the indirect costs that have lately received so much critical attention, have perforce increased relative to the more arbitrarily stabilized direct costs.

Meanwhile, the percentage of approved grants that can be funded by NIH has dropped, and the priority score required to achieve funding has increased. The latter two statistics, the percentage of approved grants funded and the priority score at cutoff, can be deceptive, because they depend heavily on the behavior of initial review groups. Study sections frequently find it easier on their consciences and on the sensitivities of the applicants to approve weak proposals and assign them low priorities, knowing they will not be funded, than to give them an outright disapproval. And as funding becomes tighter, the priority scores awarded to proposals given wholehearted approval are likely to become higher and higher in the hope of assuring funding of a reasonable proportion. Attempts to compensate for this tendency, by normalizing the scores from all initial review groups so as to make the mean score the same for all, carry their own fallacy, since this requires the assumption that the average scientific merit and importance of the proposals are the same in each of

the fields for which the separate review groups are responsible. And that is a most dubious assumption.

These technical issues aside, the peer review system deals well with identifying the clearly excellent and the patently poor proposals. In the middle ground, where a few priority points means the difference between funding or not, it is a rather blunt and inexact instrument. One would hate to have to certify that the last 10 percent of projects that beat the cutoff are stronger than the first 10 percent of those that do not. While these decisions may be critically important to the individuals whose proposals do or do not make the grade, they are probably not very important to the progress of medicine and medical science when the funding is sufficient to reach well down among those proposals recommended for funding. But when the break point is high, some very valuable opportunities will inevitably be missed.

In recognizing and pointing out the weaknesses of the peer review system, I by no means intend to condemn it. As has been said of democracy: it is a very poor system of government but much to be preferred to any other that has been devised. So it is with the peer review system as practiced at NIH. I know of no other way of making choices that would come closer to making the right choices efficiently and equitably. Just now, however, neither our democracy nor our peer review system is in its best of phases.

For the reasons I have pointed out, neither the fraction of approved proposals funded nor the priority level at which the funding cutoff occurs is the best indicator of how well research is being supported. Perhaps the number of competing proposals being funded is a better barometer. While there is really nothing magical about the number 5,000 that seemed to have been agreed upon a few years ago, the changes that have since occurred certainly are an indication of the trend, and it is not encouraging. The decrease this year of 4 or 5 percent was compounded by an additional 4 percent cut in virtually all awards, both new and continuing. The budget for the coming year would have found the level falling some 30 percent below the goal of 5,000 except for the decision to attempt to raise the number from 3,500 to 4,100 by withholding 10 percent of the indirect costs due to the institutions in which the research is done. Setting aside for the moment the consequences of the latter highly controversial proposal and considering only the number of projects to be supported, one can see that at best the situation is not good. Furthermore, with the total budget still unsettled—to say nothing of the actual appropriation—there is no certainty that matters will not get worse by the time these issues are settled. Although the research enterprise has more often than not been treated by Congress more favorably than by administration proposals, the compromises that are going to be necessary to try to keep the budget

deficit within bounds make it unlikely that this favorable treatment will survive. It seems inevitable, therefore, that medical research is in for a bad year; just how bad remains to be seen. It may well be a long time before the final score is in.

Had the administration sought to find an issue that would divide the individual research investigators from those responsible for administering their institutions, they could not have chosen a more effective one than the proposal that the number of projects to be funded be somewhat maintained with funds withheld from the indirect cost reimbursement. No subject is more poorly understood by faculty than the matter of indirect costs. Most investigators believe that the indirect costs recovered are some kind of profit that they generate for their institutions, in effect a tax levied upon the investigators's grant. It is very difficult to get across the idea that the costs met through the reimbursement of indirect costs are those of the research and are just as real as salaries and costs of supplies and equipment which are charged directly to the grant. In any case, it is clear that many investigators believe that in the matter of indirect costs they are being "ripped off" by their institutions; for examples of this, one need only read recent articles in *Science* (1) and in *Federation Proceedings* (2).

The fact is that the proposed cut in indirect cost reimbursement is a method of transferring the support of medical research from the Federal government to the institutions in which research is done. It is in effect a tax on the institutions and one that falls most heavily on those that have most heavily committed their resources to medical research. When the funds available for direct costs are reduced, there are several possible outcomes. If the project is not funded, the work does not get done. If it is funded for less than the full amount, the work is correspondingly reduced, or one can try to make do with less. But the opportunities for reducing indirect costs, the overhead expenses, are much more limited; most will go on just the same. And furthermore, the institutions will gain little by finding ways to bring down the indirect costs of their research. They will benefit by only 10 percent of any reduction they are able to effect; the other 90 percent of the savings will accrue to the government. Thus the proposal offers little incentive to find ways to reduce overhead expenses. Its most important effect will be to destabilize the institutions, and this effect will be greatest upon those that do the most NIH-supported research. It is not clear where the funds will be found to cover the losses.

Although the cutbacks in the support of research that seem in prospect can be expected to produce serious disruption in the academic medical community, I believe there is even more reason for concern about the longer range consequences. The best of the currently supported work will certainly continue to garner the necessary resources, and the best is many times more important than the merely good. In a few fields, notably

biochemical genetics, in which the perceived potential for commercial exploitation is high, liberal funding from private sources seems fairly well assured. Much less certain is the support for that yet unidentified area of basic research that will one day open some other field of similar promise.

But I believe there is even more reason for concern about another of the likely longer range consequences of the current situation—the effect on the attractiveness of medical research careers for the next generation. Widespread concern has been expressed in the academic medical community about the serious decline that has occurred in recent years in the participation of those with M.D. degrees in the medical research enterprise. Several symposia devoted to this problem have not, in my view, clearly identified the reasons for this trend, but the current situation contains several elements that seem certain to accelerate the decline. Among these the constriction of research funding is surely one, but the financial pressures on many of those completing their medical education will weigh heavily against election of an academic medical career.

The costs of medical education have increased markedly in recent years. Most of the privately supported schools have managed to keep their tuitions substantially lower than the $19,000 per year that currently marks the upper bound, but the median for the coming year will certainly be over $10,000. To those figures must be added the currently inflated cost of living. Although Yale has managed to keep its tuition among the lowest in the privately supported medical schools, more than two-thirds of our students need some financial aid, and most of this must be in the form of loans. Because scholarship funds are limited, we are forced to require that students take in loans an amount approximately equal to the tuition before the remaining need is made up in outright gifts. The result is that it can be expected that students without personal resources will have borrowed more than $30,000 by the time of graduation. That amount of principal to be repaid is daunting enough. Under the conditions that have been available, the interest on much of this debt has been kept low by various subsidies, and both interest and repayment of principal have been deferred until the individual has completed training. The proposal that the Guaranteed Student Loan (GSL) no longer be available to graduate and professional students would put an end to that mitigating circumstance. The Auxiliary Loans to Assist Students appropriately named ALAS, would replace the GSL and would carry interest rates very close to the current market rates; the interest would be payable from the time the loan is made or accumulated to add to the indebtedness.

Some forty years ago when I was pondering my future, I was advised by my most respected mentor that since I had had neither the luck to inherit nor the good judgment to marry money, I should forget about academic medicine as a career. Fortunately for the satisfaction that I have derived from life, I disregarded that advice. But I am afraid that we may

be rapidly approaching a time when I will have to offer the same advice to a young physician. Academic salaries do now, as they did not then, provide for a quite comfortable standard of living. But they do not, in general, compare favorably with the incomes otherwise available to physicians so that, if one is required for a substantial period to share this lower income with one's creditors, it is less attractive. And if to this disincentive to an academic career is added considerable uncertainty about one of the most positive values in an academic career, the opportunity to engage productively in research, how many will consider it worth the financial sacrifice?

It is widely held that such substantial incomes are available to the medical graduate that the acquisition of substantial debts to achieve that status is no problem. This view neglects consideration of the wide range of career options open to physicians, at one financial end of which is academic medicine with a heavy commitment to research. But even within the sphere of medical practice the spectrum is a broad one. The general internist or pediatrician has an income quite different from that of a radiologist or cardiovascular surgeon. Perhaps some thought needs to be given to whether large debts acquired in the course of medical education will have an undesirable effect also on the specialty distribution of medical practitioners.

Obviously medical research is not an activity limited to those with an M.D. degree, although there are some kinds of necessary research that do require physicians. And I believe that in many areas of research in which the M.D. is by no means a requirement, a medical background does provide a very valuable orientation. But many of the most important contributions to medical research are made by individuals with other educational backgrounds. What are the prospects that holders of Ph.D. degrees in the biomedical sciences will be available in the future, in adequate numbers and quality? Recent graduates have already been finding the opportunities open to them to be limited. The time spent in postdoctoral fellowships has been lengthening, and there are stories about some of those postdoctoral positions being offered without salary (3). The rate at which tenured faculty can be expected to retire is low, and even in a period when institutions are more or less in a steady state, the number of new appointments to tenure must be correspondingly low. Should retrenchment be necessary as a consequence of reduced availability of funds, the prospects for faculty positions would be further narrowed. And the situation has been exacerbated by the changes in retirement age imposed by law, which essentially introduced into the retirement process a moratorium of two to five years.

Given this situation, the perspicacious individual, the one we would want and have been getting in medical research, will think carefully before embarking on the graduate education that will prepare him or her

to compete for what appear to be very limited opportunities. A decade ago, the Office of Management and Budget decided that the number of approved grant applications, the so-called application pressure, was leading to excessive growth in appropriations for medical research and determined that the way to avoid this trend was to reduce the number of candidates for support by cutting them off at the source. Accordingly, it was proposed by the administration that the training funds that support graduate education and training in the biomedical sciences be drastically reduced. That proposition was not accepted by the Congress, and the NIH training program remained largely intact. The situation is now reversed. There is no longer a need to reduce graduate education in the medical sciences in order to reduce appropriations for medical research. The aim is directly at the funds for research, and although the number of individuals to be supported by training funds will also decrease by some 17 percent over a two-year period, it may be a disguised blessing if the prospects for future employment were not to improve sharply in the next few years.

The potential of recombinant DNA technology for commercial exploitation as well as for unraveling many of the knotty problems of biology has created one striking exception to the tightness of the job market in biomedical research more generally. At the same time, it has created problems for academic institutions that have not previously been an issue in the biomedical area of endeavor. The hasty creation of the new biotechnology industry has placed this activity in competition with academic institutions for scientists to pursue work with recombinant DNA. Although only a few senior academic scientists have actually transferred their major focus of activity from the universities to the new biotechnology companies, many have assumed consulting relationships and major equity positions in such enterprises. A few striking instances of the overnight acquisition of substantial wealth provide an example that could introduce a new motivation into the efforts of biomedical scientists.

A concern for practical application of the results of research is, of course, highly appropriate in a field that has received generous public support specifically because of its promise of improving the public welfare. One would hope that the opportunities for application for the public good would not be overlooked even by those most oriented toward basic science. But the diversion of the efforts of the academic scientist from the most fundamentally important and intellectually challenging problems to those that appear to have the potential for quick economic payoff and personal gain must be carefully guarded against. Those scientists who are active in the fields relevant to biotechnology should be aware of the possibility that their motivation may be misunderstood. This has already occurred, graduate students and trainees becoming convinced (generally incorrectly) that the problems to which they have been assigned are more

relevant to the commercial interests of their mentors than to the progress of science.

A certain amount of competitiveness, a desire to receive credit for one's ideas and accomplishments, has always been an element in the motivation of scientists. To an extent that varies with the personality of the individual investigator, this may have provided a motivation for less than full sharing of ideas with colleagues and associates. When the possibility of significant economic return on the exploitation of such ideas is added, there is a serious hazard of excessive secretiveness. Open sharing of information may be the best prophylactic against misunderstood motivation.

There has been much discussion recently concerning the necessity for academic institutions to seek closer associations with industry in order to replace the anticipated losses of financial support by the federal government. And a few agreements between industry and academic institutions involving substantial amounts of money have drawn public attention. While I strongly favor appropriate working agreements between universities and industry and only wish that my own institution was on the receiving end of one of those large agreements, I believe it would be a serious mistake to think that a major cutback in federal support for medical research might be balanced by an increase in support from industry. The segments of biomedical research that are of major interest to industry are quite limited. Those areas related to pharmaceutical agents and to biotechnology are the principal ones. The remainder of medical research is quite likely to be out in the cold. But more important is that basic research more generally, the sort of research that seeks new knowledge without concern for its application and that in fact may never find application, is not likely to elicit the interest of industry. Biochemical genetics is now a prime target for industrial support but only because its applicability has become apparent. It is difficult to believe that industry would have supported the work of Watson and Crick, Kornberg and Ochoa, or Nirenberg and Khorana.

Not only is there the problem of limited fields likely to gain industry support, there is also an important quantitative matter. For all the attention it receives, industrial support of academic medical research is unlikely to constitute more than a very small percentage of the funds made available for academic research by the NIH. Although industrial support to work in universities may increase, it is very unlikely that it could make up for more than a small fraction of what could easily be lost in a reduction of the appropriation for NIH.

In conclusion, these are indeed worrisome times for those who are concerned with medical research. The optimist will see the situation as a glass half full. Medical research is, in any case, making great strides. And the tap is there to fill the remainder of the glass. The pessimist, fearing the worst, sees the glass half empty, the opportunities for progress that are

being missed, and the undermining of institutional stability. And he knows that the barrel to which the tap is attached is being rapidly emptied into other more capacious containers. All can hope for the best but should prepare for the worst.

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GEOGRAPHIC MEDICINE: THE GENESIS OF A NEW DISCIPLINE IN ACADEMIC MEDICINE

KENNETH S. WARREN

"Tropical medicine is a pejorative term!" answered Charles C. J. Carpenter, newly appointed chairman of the Department of Medicine at Case Western Reserve University. His prior question concerned the name of the division recently created with the material aid of the Rockefeller Foundation. Although I failed on my first reply, my second, "Division of Geographic Medicine," was acceptable. This name stemmed from three sources, the established field of geographic pathology, the use of the term geographic medicine in an administrative branch of the National Institute of Allergy and Infectious Diseases, and the Dutch journal, *Tropical and Geographical Medicine.*

Why did Carpenter say that "tropical medicine" was a pejorative term when the field has had such a glorious history? When tropical medicine was founded by Europeans at the end of the nineteenth century, life expectancy in the tropics was thirty or forty years, and for expatriates, the tropics were widely called "the white man's grave." In the latter nineteenth

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KENNETH S. WARREN graduated from Harvard College in 1951 and from the Harvard Medical School in 1955. He then launched a career in tropical medicine with emphasis on schistosomiasis at the Laboratory of Tropical Diseases, National Institutes of Health, from 1956 to 1963. During that period he earned the D.T.M. & H. degree from the London School of Hygiene and Tropical Medicine, and served as Visiting Professor of Medicine at the Hospital das Clinicas, University of Bahia, Brazil. Dr. Warren joined the faculty of Case Western Reserve University School of Medicine as Assistant Professor of Preventive Medicine and of Medicine in 1963, and ten years later became director of a new division of Geographic Medicine in the Department of Medicine. In 1975 he was named Professor of Medicine. He remained in that post for two years and then moved to the Rockefeller Foundation as Director for Health Sciences.

and early twentieth centuries, tropical medicine was a great adventure, with Manson's discovery of the mosquito transmission of filariasis in China, Laveran's finding of the malaria parasite in Algeria, and Ross's elucidation of its life cycle in India and Sierra Leone; the latter two were separate recipients of the Nobel Prize. Bruce worked out the transmission of African sleeping sickness, and Chagas in Brazil not only described American trypanosomiasis but discovered the parasite and its mode of transmission as well. Those were the days of glory when scientists worked in the bush with that incomparable, portable instrument, the light microscope (1).

One of the fruits of these great discoveries, largely by the colonial governments, was the establishment of schools of tropical medicine—in England (two), Holland, Belgium, and Germany. With the founding of schools of public health in the United States, tropical medicine became ensconced in those institutions. There it remained, devoted largely to the study of the morphology, taxonomy, and life cycles of parasitic diseases, and their control via public health measures. The favored instrument continued to be the light microscope. It remained a matter of faith that as much of one's career as possible would be spent in the bush studying the clinical problems *in situ*, usually with a microscope. Even today, one major foundation has provided long-term tropical medicine fellowships for young physicians as long as they remain in the tropics for ten initial years.

In the meanwhile, in the medical schools and research institutes, the study of the infectious diseases of the developed world—largely bacterial and viral—was proceeding apace. This study unleashed the power of the developed world with respect to full-time faculty appointments, excellent supply logistics, and the use of new and ever more complex instruments, including the electron microscope, a variety of spectrometers (from visible light to ultraviolet to infrared to nuclear magnetic resonance), and radioisotope counters (gamma and scintillation). The outcome of all of this activity was a spate of vaccines against viral and some bacterial diseases and potent antibiotics against most bacterial diseases. Furthermore, infectious disease research was the underpinning of the development of those modern and exceedingly powerful sciences, immunology and molecular biology.

In contrast, the control of tropical diseases has had to rely largely on insecticides, molluscicides, and public health measures. No vaccine exists for any of the major human parasite diseases, only one disease can be controlled by prophylactic drugs to which resistance has now developed, and therapeutic drugs are often inadequate and highly toxic.

The application of modern physiology, biochemistry, immunology, and latterly, molecular biology to clinical investigation led to a virtual explosion of knowledge. The annual meetings of the American Federation for

Clinical Research, the American Society for Clinical Investigation, and the Association of American Physicians were and are an exciting forum in which clinical investigators use all of the tools of modern biochemical research. Until recently, tropical diseases were virtually unknown in this forum, while the tropical medicine meetings continued their emphasis on morphology, ecology, and public health. Charles C. J. Carpenter did not want that image perpetuated in his department of medicine.

Case Western, oddly enough, was in a unique position to develop a division of geographic medicine. A small group of physicians specializing in infectious disease within the Department of Medicine were already involved in research on schistosomiasis, with collaborative arrangements in St. Lucia and Kenya. The new chairman of the Department of Medicine had spent two years as director of the Johns Hopkins research program on cholera in Calcutta. The dean of the medical school was a pediatrician whose primary work, for which he shared a Nobel Prize, was on polio. A proposal was made to the Rockefeller Foundation for support for a division within the Department of Medicine to work on the great diseases of the developing world. A letter to John Knowles, president of the Rockefeller Foundation, stated that, "We will attack the neglected problems of infectious disease and malnutrition with all the vigor and sophistication accorded to the rare and degenerative diseases which form the major interests of most Departments of Medicine. We plan to use a system combining work in the laboratory with that in the field on a feedback basis."

The proposal requested support largely for personnel and overseas travel. It was planned that each individual in the division would spend a significant period of each year (usually three months) doing clinical and field investigation in the tropics. Working relationships would be established with medical schools or research groups, and the projects would be carried on for at least several years. The period in the tropics would be counted as clinical time, and while division personnel were in the United States, only two months would be required on the wards, one month in general medicine, and one month in a subspecialty area such as infectious diseases, gastroenterology, or hematology. The rest of the time would be spent in the laboratory doing research on the diseases of the developing world. A major question was, could young investigators be found with an interest in the great diseases of the less developed countries, who would combine the ability to do both clinical and basic laboratory investigation?

The answer came surprisingly rapidly: a young internist and a young pediatrician from Case Western had already been working on sickle cell anemia in India and nutrition in Guatemala and were delighted to have a stable source of support. A young Australian allergist wrote from Papua/New Guinea, where he had been studying the relationship between

atopy and resistance to hookworm infection. Carpenter brought in a young American who had been working on typhoid and plague in Vietnam, and we were on our way. A young gastroenterologist with an interest in gut immunity also joined the group and began working on an animal model of giardiasis. Also joining us was an M.D.–Ph.D. (microbiology) who was an excellent immunologist and immunochemist. These, plus the two internists already working on schistosomiasis, formed the core of the group. Fellows, residents, and medical students joined the unit, and collaborative arrangements were continued and developed further within the Department of Medicine, with other departments in the medical school, and with outside institutions, both in the developed and the developing world.

In the first full year of its operation, the division produced 33 papers (13 reviews and 20 original studies). The most frequent publications were in the *Journal of Immunology*, *Journal of Infectious Diseases*, *American Journal of Pathology*, and *Journal of Experimental Medicine*. Over the first six years—through 1980—209 papers, including 75 reviews, were produced, for a mean of 35 papers per year. The journal distribution is shown in Table 1. Each year, from a few to as many as 8 papers were presented at both the clinical investigation and tropical medicine meetings. All investigators of the division were members of the American Federation for Clinical Research and the American Society of Tropical Medicine and Hygiene, and two were members of the American Society of Clinical Investigation. Collaborations within Case Western Reserve involved the Department of Medicine (divisions of Infectious Diseases, Endocrinology, Respiratory Diseases, Hematology, and Gastroenterology), Pediatrics, Surgery, Pathology, Pharmacology, Microbiology, and Anatomy. Outside institutions included the National Institutes of Health (NIH), Cleveland Clinic, Naval Medical Research Laboratories, Albert Einstein College of Medicine, schools of medicine at Harvard, New York University, Virginia, California, Johns Hopkins, and Bowman Gray. On the international level, papers were published with investigators from Great Britain, France, the Netherlands, Sweden, Israel, Canada, and Australia, and in the developing world from Kenya, Ethiopia, Egypt, India, Indonesia, the Philippines, and Vietnam.

Collaborative projects of several years' duration were established with Kenya, Egypt, Ethiopia, India, Vietnam, the Philippines, Brazil, and Guatemala. The organizations involved included government agencies, medical schools, schools of public health, the Wellcome Trust, the World Health Organization (WHO), and the U.S. Naval Medical Research Laboratories.

The Division of Geographic Medicine received grants from many sources in addition to the Rockefeller Foundation. These included: NIH,

TABLE 1

Papers Published in Leading Journals, 1975–1980, by Members of the Division of Geographic Medicine, Department of Medicine, Case Western Reserve University

Journal	Number of Original Papers
Journal of Immunology	22
Journal of Infectious Diseases	16
American Journal of Tropical Medicine and Hygiene	16
Infection and Immunity	8
Journal of Experimental Medicine	5
Journal of Clinical Investigation	4
Lancet	4
Gastroenterology	4
Nature	4
Bulletin of the World Health Organization	4
Transactions of the Association of American Physicians	4
American Journal of Pathology	3
Archives of Internal Medicine	3
Annals of the New York Academy of Sciences	2
Transactions of the Royal Society of Tropical Medicine and Hygiene	2
Antimicrobial Agents and Chemotherapy	2
Other journals*	31

Total (including 75 review articles) = 209

NOTE. Papers per year: range, 26–38.

* One paper each, published in such journals as the *New England Journal of Medicine, Annals of Internal Medicine, Journal of Pediatrics, American Journal of Medicine, Pediatrics, Gut, American Journal of Hematology,* and *Blood.*

the Edna McConnell Clark Foundation, the Fannie Rippel Foundation, the Cleveland Foundation, and the WHO Tropical Disease Research Programme. In addition to regular NIH research grants, both a tropical medicine training grant and a program project grant in parasitic disease research (the first ever given) were received by the division.

The division has produced a book entitled *Geographic Medicine for the Practitioner: Algorithms in the Diagnosis and Management of Exotic Diseases*, published by the University of Chicago Press. It also runs a travelers clinic for those departing for or returning from the tropics.

In 1976 the division began a series of annual lectures in geographic medicine, the first speaker being Dr. John Knowles. This encounter with tropical medicine as a discipline that could hold its own with other subspecialty areas of clinical investigation so bemused Knowles that he vaguely mentioned a position with the foundation to the then director of the division. Soon, thereafter, the director attended the last of the clinical investigation meetings in Atlantic City where he was able to obtain the proceedings of a recent Ciba symposium, *The Future of Philanthropic*

Foundations. Knowles's exciting chapter in that book demonstrated that foundation work could be a creative venture. Knowles wrote:

> No essay on administrative means can convey adequately what we hope is an environment within The Rockefeller Foundation that will foster the creative impulse and allow its work to be done with style. We enjoy the privilege of relative independence from the disadvantages that beset universities and governments. We cannot complain about rigid political or tenure controls. We can change rapidly and our funds and staff are relatively free of long-term commitments. We can develop the organizational skill needed for undertaking large-scale and long-range experiments.

The director, thinking about this over the next four months spent in Kenya, Europe, and St. Lucia, developed the idea for a global network of research laboratories in medical school departments of medicine, pharmacology, and immunology, and in great research institutes to study "The Great Neglected Diseases of Mankind."

Soon after the director returned to the United States, Knowles phoned him, the idea was discussed, and the director was rapidly transplanted to the Health Sciences Division of the Rockefeller Foundation. A year later the program, the Great Neglected Diseases of Mankind, was initiated, and fourteen units working in medicine, biochemical pharmacology, and immunology were established throughout the world. The medical units included four divisions of Geographic Medicine in the United States and one Tropical Medicine Unit at Oxford (the British were obdurate). The basic tenets of the program were:

1. That research would range from the basic level in highly sophisticated laboratories to clinical investigation and field epidemiology.
2. That research would be investigator-initiated in terms of the problem addressed, which could be any of the Great Neglected Diseases, including for example the diarrheas and pneumonias, dengue hemorrhagic fever, measles, and all of the parasitic diseases.
3. That support would be long term (probably for at least eight years) and would be flexible, although emphasis would be on the development of young investigators and on overseas collaborative research.
4. That each unit would contain a critical mass of investigators within a compact and identifiable group.
5. That the units would be gathered into a global network for communication and collaboration fostered by an annual meeting.

Today there are four divisions of Geographic Medicine in four major regions of the United States—the Northeast, South, Midwest, and Far

West. Developing each of the units posed particular problems illustrative of the process. The unit at Case Western Reserve was already established, and its new director, Dr. Adel A. F. Mahmoud, had been deputy director of the original unit. He brought new skills in clinical medicine to the unit and established a unique rapport with the house officers of the Department of Medicine, attracting outstanding young clinical scientists from each succeeding group of trainees. The quality and quantity of the work continues unabated, if not enhanced.

Negotiations in the South involved two excellent institutions. The University of Virginia, with Dr. Richard Guerrant, won out, principally because that institution fully backed the venture at every level, from the chairman of the Department of Medicine through the dean of the medical school.

The problem in the West at the University of Washington was a tendency to spread the funding among all groups working on any aspect of the Great Neglected Diseases at all institutions of the medical school—the University Hospital, City Hospital, and Veterans Administration Hospital. When Dr. Seymour Klebanoff decided to develop a compact unit within the Department of Medicine, an agreement was rapidly reached.

The last experience was unique in that Dr. Sheldon Wolff, chairman of the Department of Medicine at Tufts, suggested developing such a division. His understanding of our approach was so intuitive and deep that he was given carte blanche to proceed. I am delighted that he is here today to present his experience in developing a division of Geographic Medicine.

With respect to all four of these units, all of the directors are members of the American Society for Clinical Investigation. All of the units are highly productive, but the quality of their work is particularly worthy of emphasis. They are all publishing substantive work in outstanding journals including *Lancet*, the *New England Journal of Medicine*, *Journal of Immunology*, *Journal of Experimental Medicine*, and *Journal of Clinical Investigation*. They present papers each year at the clinical investigation meetings and are attracting outstanding young researchers into the field.

In conclusion, this is the way a new discipline has been established in academic medicine in the United States. What was particularly difficult in this case was to transform a discipline with a poor image into a highly dynamic and attractive career area. I doubt that Charles C. J. Carpenter would consider "geographic medicine" to be a pejorative term.

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THE DEVELOPMENT OF A GEOGRAPHIC MEDICINE PROGRAM IN A DEPARTMENT OF MEDICINE

GERALD T. KEUSCH and SHELDON M. WOLFF

The Department of Medicine of Tufts University School of Medicine and the New England Medical Center is similar in most ways to those at other quality academic institutions. We have divisions of General Medicine, Cardiology, Endocrinology, Gastroenterology, Hematology, Infectious Disease, and so forth. However, in some ways we are unique; for example, we have three new divisions, Experimental Medicine, Geographic Medicine, and Clinical Decision Making, with as many staff positions and equal administrative status as the more traditional clinical units. These recent additions to our department, however, have a somewhat distinctive mandate and method of operation. For example, the majority (generally 75 percent or more) of their members' time is spent doing research. For this discussion, we will focus our attention on the Division of Geographic Medicine (DGM). We will take a cue from Gaugin, who traveled to the South Pacific, observed carefully and recorded his insights on canvas, and in one painting asked, "D'où venons-nous; que sommes-nous; où allons-nous?" (Where do we come from, what are we, where are we going?) This

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SHELDON M. WOLFF's career in infectious diseases began in 1960 when he joined the Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases (NIAID) as a Clinical Associate. He had graduated in medicine from Vanderbilt University in 1957, after which he trained in internal medicine at Vanderbilt and at Albert Einstein College of Medicine, Bronx Municipal Hospital Center. At NIAID Dr. Wolff served as Head, Clinical Physiology Section, 1964; Clinical Director, 1968; and Chief of the Laboratory of Clinical Investigation, 1968. In 1977 he accepted appointment as Endicott Professor and Chairman, Department of Medicine, Tufts University School of Medicine, and Physician-in-Chief, New England Medical Center Hospital.

discussion will address several aspects of these queries: why was the Division of Geographic Medicine created? how is it supported? who is involved? what was its background? what impact has the DGM exerted on the hospital, the medical school? where is it going in the future?

Why Establish a Division of Geographic Medicine

Our institutions of academic medicine are very hard pressed these days. The financial pressure is being exerted from all sides—federal funding for research and teaching has been reduced, cost containment policies for the health-care dollar conflict with rising costs and expectations, and larger faculties are required because of advances in basic and clinical science, and the specialization that has occurred. To provide a well-rounded education and clinical experience now requires many more bits to complete the larger circle of knowledge. Why then add to the resulting fiscal, logistical, and administrative problems in a department of medicine by developing a group focusing upon tropical medicine and international health, in particular on the "great neglected diseases of mankind"?

You might ask, "Why Tufts?" When one of us (Sheldon Wolff) was being recruited by Tufts, he made as a condition for acceptance of the job that both Tufts and the New England Medical Center support the establishment of a program in geographic medicine. Although both institutions had a long history of involvement in innovative community health projects, the medical school had almost no prior activities in the area of tropical diseases. However, in 1976 an eminent nutritionist (Jean Mayer) with long-standing interests in world hunger problems became president of the university. Furthermore, the Fletcher School of International Law and Diplomacy is a part of Tufts, and Dr. Wolff was appointed Adjunct Professor of International Health on its faculty. Thus, the possibility for interaction with a distinguished group of scholars dealing in part with public policy issues in developing countries seemed to present a unique opportunity for meaningful work. One of President Mayer's major accomplishments at Tufts has been the creation of the School of Veterinary Medicine. Again, the latter seemed to be an ideal resource for potential scientific collaboration for investigators interested in health problems in the developing world. Finally, a large nutrition research center sponsored by the U.S. Department of Agriculture has been built and will soon open on our health sciences campus. Needless to say, the relationship between nutrition and infectious diseases is an important and exciting area for investigation. Therefore, in 1977 we felt that Tufts University provided a unique setting for the development of a multidisciplinary approach to the great neglected diseases.

In addition, other considerations prompted our decision to invest in the

DGM. First, the parasitic and protozoan disease agents are biologically so distinctive that to provide quality education to medical students and house officers and to give proper care for patients require an academic physician with both scientific interests and clinical experience. To have the necessary intellectual environment requires a critical mass of interested faculty. Second, we regularly see patients with a diverse array of tropical diseases, from visceral larval migrans to leprosy, from malaria to schistosomiasis (*Schistosoma mansoni*). Such patients are either U. S. citizens who have traveled abroad, or recent immigrants from regions in which these diseases are endemic. There is no doubt that our ability to diagnose and treat these patients is much better now. Third, it was apparent that tropical diseases were largely ignored in our preclinical curriculum, with only three hours devoted to parasitology in the general microbiology course. A physician coming from an institution with so little teaching of tropical medicine to a clinical training program devoid of expertise in these areas cannot be other than ignorant of the major diseases of the rest of the world. Fourth, the biology of the agents and host-parasite relationships is fascinating and in many instances represents model systems for other complex biological interactions that are less amenable to study. For example, diverse mechanisms of immunoregulation in parasitic diseases allow the investigator to probe self-recognition signals, effector functions of various cell types, immunosuppression, and functions of the phagolysosome that are applicable to many other diseases of nonparasitic or noninfectious origin. A fifth compelling reason is a sense of obligation to those developing nations whose populations suffer from these illnesses and generally lack the material and human resources to address the scientific questions that may lead to improved and practical solutions. By working in our own laboratories and engaging in collaborative studies with investigators in the field, we believed that our faculty could make a significant contribution. Thus, at the intellectual, clinical, and social levels, there were cogent reasons to invest in a tropical disease group within our department of medicine. The next question was the economic one, how to fund such a group.

How to Support a Division of Geographic Medicine

When medical school funds are limited, when student tuition is high, when clinical income is limited, how does one allocate resources? At about the time we were deciding to start a DGM at Tufts, Dr. Kenneth Warren moved to the Rockefeller Foundation to organize the foundation's initiative in tropical medicine; there he developed the "Great Neglected Diseases" program. The congruance of our goals with those of Dr. Warren and the Health Sciences Division of the Rockefeller Foundation led to

the awarding of a relatively long-term grant to Tufts as a part of the worldwide Biomedical Research Network being established by the foundation. Was it simply fortuitous for us to find external financing so quickly? We believe this was not just happenstance but rather an expression of the more widespread recognition of the five principles elaborated above being put into action by Dr. Warren and the Rockefeller Foundation.

Although generous, the award was insufficient for the developmental needs. Where was the space to come from? How was the equipment to be purchased? Who were the faculty to be and how could Tufts recruit them? One of us (Wolff) had recently moved from the National Institutes of Health (NIH) to the chairmanship of the Department of Medicine at Tufts with the commitment of the university and medical center to renovate 13,000 gross square feet of laboratory, support, and office space. The university invested $1.3 million in this construction, and one-quarter of the space was assigned to the DGM, the remainder being used for two other new divisions, Experimental Medicine and Allergy. The New England Medical Center and the Department of Medicine invested in equipping common instrument and special facility rooms for these three new groups.

The Rockefeller Foundation support has been instrumental in recruiting new faculty who were without grant support at the time. The reasons were different, such as moving from the NIH (Dr. David Wyler), or from foreign institutions such as the Federal University of Rio de Janeiro, Brazil (Dr. Miercio Pereira), or from an NIH-supported overseas base such as the Johns Hopkins International Center for Medical Research (ICMR) in Panama (Dr. Robert Ryder), but the requirements for seed money for laboratory personnel, supplies, and special equipment were the same. Each of these individuals in turn has obtained new grants, permitting us to use the Rockefeller Foundation grant in a flexible way to support new laboratory projects (e.g., studies on the insect vector of *Trypanosoma cruzi* or the attachment mechanisms of *Giardia lamblia* for mammalian cells) and new field ventures (a case-control study of hepatitis virus, hepatitis vaccine, and primary hepatic cell carcinoma in The Gambia). As a result, within three years the budget of the division has increased from $250,000 to approximately $1.5 million per year, and the percentage contribution of the Rockefeller Foundation has decreased from 60 to 10 percent.

Who Is Involved in the Division of Geographic Medicine

One of us (Gerald Keusch) arrived in early 1979 to become the head of the DGM. His background included internal medicine training, board certification in both internal medicine and infectious disease, one year of

overseas research experience between the second and third year of medical school, a two-year stint as an NIH Research Associate at the Southeast Asia Treaty Organization (SEATO) Medical Research Laboratory in Bangkok, and eight years of clinical and investigative work at Mt. Sinai School of Medicine in New York, with continuing field work in Guatemala, supported by the NIH.

Dr. David Wyler is also board certified in internal medicine and infectious diseases and came to Tufts from the Laboratory of Parasitic Diseases at the National Institute of Allergy and Infectious Disease (NIAID). He had extensive field investigative experience in Africa and Central America.

Dr. Miercio Pereira, a Brazilian physician who completed a Ph.D. in immunochemistry under the tutelage of Dr. Elvin Kabat at Columbia University, had returned to Brazil to initiate basic investigations on *T. cruzi* infection and leishmaniasis. He was excited about the opportunity in the DGM to advance his work and to maintain and expand his collaborative laboratory and field studies in Brazil. This expectation has been realized in a most gratifying and productive fashion.

Dr. Keith McAdam was raised in East Africa and worked in New Guinea for several years on the problem of amyloidosis in leprosy. He pursued this interest at the NIH and moved to Tufts with Dr. Wolff in 1977, and affiliated with the DGM when it was created. He is board certified in internal medicine and also in allergy. Since the creation of the DGM, he has conducted investigations in the field.

Dr. Robert Ryder, also board certified in internal medicine and infectious disease, and a graduate of the Epidemic Intelligence Service program of the Center for Disease Control (CDC), had worked at the cholera research laboratory in Dacca, Bangladesh, and headed the field unit for the Johns Hopkins ICMR in Panama for a year and a half before joining our DGM. Presently, he is a Milbank Fund Scholar.

Thus, the individuals we recruited into the DGM not only had already developed relevant areas of research and clinical experience but also had spent considerable time in the field and were committed to continuing these efforts. The creation of the DGM provided a central focus for their work and established a scientific milieu in which to carry out and extend it. We were not recruiting neophytes to the concept of basic and field tropical research. I must emphasize that such committed, already established young investigators were, and continue to be, in short supply.

The Impact of the Division of Geographic Medicine on the Department of Medicine and the Medical School

The arrival of several new, experienced physicians has markedly improved the diagnosis and care of patients with parasitic infections. The DGM

consults on cases on both adult and pediatric inpatient services, at the same time providing educational input to the house staff involved.

A major change has occurred in undergraduate medical teaching. The number of hours of teaching has increased elevenfold, from three to thirty-five hours. This year, the course has been designed to integrate tropical medicine and parasitology with the rest of medical microbiology in order to minimize distinctions that students often make between information important for their practice of medicine here in the United States and information they perceive to be of less direct relevance. The students' schedule is so packed that in practice they do make such distinctions in allotting study time. As a direct result of the increased teaching and emphasis, a number of students have taken electives in various developing countries in which we were able to place them under the supervision of close colleagues. Even without available financial support, a half dozen or so students per year have set up rotations in Guatemala, Costa Rica, Brazil, Haiti, or Jamaica, and we are currently making arrangements for two students to go to Africa next year.

The present course provides for more conference and case presentation hours to lighten the didactic session load and to reemphasize the clinical relevance of the material being presented. Some lectures previously included in Medical Microbiology, for example the bacterial enteric pathogens, are being presented in the tropical medicine course which is named Medical Microbiology II. General lectures on health care in developing countries, public health epidemiology, and malnutrition are included as well. We are greatly interested in the students' response to this program.

At the level of research, multiple collaborations have been formed with investigators from other divisions of the Department of Medicine, and from other departments as well. This activity has been especially gratifying. The collaborations include studies of macrophage membrane interactions with leishmania, the identification of an interleukin I type of molecule secreted by the granuloma of *S. mansoni*-infected liver which appears to be a mediator of fibroblast responses, the metabolism of complement in children with protein-energy malnutrition (with collaborators at the Institute of Nutrition of Central America and Panama, in Guatemala), the effects of zinc deficiency on T lymphocyte development and thymic function in a mouse model, the role of the eosinophil in killing of schistosomula, and the effect of *T. cruzi* on myocardial muscle cell metabolism in vitro. As a result, several of our colleagues with no prior interest in the great neglected diseases of mankind have become actively involved in research on these pernicious and highly prevalent problems. Thus, the Division of Geographic Medicine is having a major impact on our whole department.

Future Expectations for the Division of Geographic Medicine

The rapid growth of our DGM, its success in competitive grant applications, and its impact within the medical center have fulfilled the goals originally set. From this vantage point we should feel optimistic about the future and set future goals accordingly. Is the star really so bright or are there problems ahead? What should we anticipate for the future?

The first important area to look at is research and training funding. The major source of support for our DGM is the NIH, and many signs point to trouble ahead. The type of training our own faculty received, which nurtured their development into laboratory-based, clinically oriented research clinicians, is increasingly more difficult to obtain. Faced with the risks of funding, young physicians increasingly will opt for clinical careers and, if research oriented, may look for a specialty with a more secure economic base in the medical center. It is clear that early exposure to the challenge and needs of tropical medicine can be decisive in shaping career choices. What is there to fill the void when the NIH reduces its support? One option is the military, which maintains active research programs in tropical diseases. Their focus and priority, however, are clearly on problems of concern to the military itself and not necessarily those of greatest global concern or local interest. It is unreasonable to expect the military research operation to do otherwise. It is also obvious that major foundation support will not fill the gap either, and our experience in Boston is that local resources (such as the Medical Foundation of Boston) are stretched too thin and are unlikely to support field research experience. There remain a few university programs supported by the NIH, but these are geared to support already committed or established investigators and will not bring in new investigators to the field. Sadly, it has been our experience that it is far easier to obtain support for foreign trainees than for U.S. citizens.

The financial problems become apparent early in medical training when a medical school such as ours introduces a significant block of teaching of tropical medicine and international health. Since the introduction of these programs, the number of students requesting clinical rotations in a developing country has dramatically increased. However, the lack of resources to help students meet the costs of travel has limited the number who actually can take such a rotation, and they have had to largely finance their own trips. Among these students are several who intend to follow a career in tropical medicine. Their early experience in pursuit of training without financial support should stand them in good stead in the future.

What, then, are the prospects for field investigation? Somewhat brighter, we believe, but far from good. A considerable amount of money

is currently spent on field work, largely applied research or implementation of programs. The Agency for International Development (AID) of the U.S. State Department currently administers many millions of dollars for these programs. However, very little is for research on mechanisms of disease, much of it is awarded by contract to profit-making private consulting firms with no academic accountability, and some of it is awarded for political expediency, geographic distribution, or similar reasons. These activities certainly offer experience, and many are excellent in design and execution, but they do not provide training for researchers, and these are the endangered species.

Field work in developing countries is also fraught with uncertainty. Our work in Guatemala in now compromised by the political instability and violence in that country. Shortly before we began to work in The Gambia, there was an attempted coup d'etat, and to this day, our people there live in a Medical Research Council (MRC) compound with Senagalese soldiers patrolling the streets. A recent meeting sponsored by the NIH and the Indian Council for Medical Research, to which one of us (Keusch) was invited to discuss and develop joint Indo-U.S. projects in the diarrheal diseases, was canceled a few days before the opening by the Indian Government, amidst widespread publicity of alleged CIA involvement and surreptitious biological warfare research. To work where the great neglected diseases are prevalent requires one eye on the political scene, precluding complete attention to the health problems and scientific questions.

Faced with these realities, we have good reason to express concern and to monitor the growth of the program carefully to avoid outstripping our resources. Because of our success thus far, we recently were assigned an additional 6,000 square feet of space for new laboratories for the DGM. However, the space requires extensive renovation, and funding must be obtained for that purpose. Additional space is essential, for new faculty are needed to enlarge the scientific base of the group, for example, in the areas of molecular genetics and molecular biology. Our funding from the Rockefeller Foundation for the four remaining years gives us the resources and opportunity to recruit such individuals who must be highly competitive for grant support.

We believe it is important to recognize that a strong institutional commitment to a program such as ours is crucial for success. At the present time there is no doubt about the status of the DGM at our institution. Would this continue to be the case if there were a change in leadership? Under such a circumstance, a change in priorities is certainly possible, and while not anticipated, represents one of the unforeseen risks for a tropical medicine program in an American medical school. The major way to deal with this risk is to insure the research productivity of the DGM and establish a track record of grant support by engaging

faculty with proven abilities. However, such an emphasis does not provide for the needs of young new researchers, and we face a situation in which not only is training difficult to support but career opportunities for trainees are limited. It is no wonder then that many departments of medicine have not rushed into establishing divisions such as ours, and those that have launched such programs are largely chaired by individuals with first-hand experience in tropical and infectious diseases.

In spite of all of this, it is not our inclination to be fainthearted. We believe the reasons elaborated above to begin our DGM remain valid today, that the group should and can grow, and that support will come to the well-qualified and creative investigator.

As Louis Pasteur said in a somewhat different context, chance favors the prepared mind. We would add to this the principle that the prepared mind must take chances; we are currently recruiting a molecular geneticist.

CYCLES AND FASHIONS IN BIOMEDICAL RESEARCH

JOSHUA LEDERBERG

My task was to collect some of the threads comprising the fabric of fundamental biology and to comment on the health and medical applications thereof. As shorthand for that conception, the elaboration of biology and pathology from first principles of chemical and physical structure, I will caption it a reductionist or reductive model.

The starting point of my own thought was very well stated by Drs. Kennedy and Lehninger, who talked about the promissory notes that reductive biology had been tendering for a number of years. Dr. Kennedy quoted Dr. Charles Huggins: "Whose lives have been saved by a Warburg apparatus?" I suspect that is not such a difficult question to answer. My variant is, "How many lives have been saved in the last twenty years by the 'double helix'?"—an expression that stands as proxy for all of modern reductive biology.

In 1944 Avery, MacLeod, and McCarty reintroduced DNA to the

JOSHUA LEDERBERG graduated from Columbia College with a B.A. degree in 1944. He enrolled in the university's College of Physicians and Surgeons while he worked as a research assistant in genetics. After two years he terminated his medical studies and moved to Yale University where he received his Ph.D. in genetics in 1947. Dr. Lederberg spent the next ten years in the Department of Genetics, College of Agriculture, at the University of Wisconsin, where, in 1957, he created and became Chairman of the Department of Genetics at the university's medical school. Dr. Lederberg moved to Stanford University School of Medicine in 1959 as Professor of Genetics, as well as of Biology and Computer Science, and Chairman of the Department of Genetics. In 1978 he became President of the Rockefeller University. His fields of interest include genetics, chemistry, and evolution of unicellular organisms and of man; computer models of scientific reasoning; exobiology and the origin of life; and applications of scientific understanding to public health and policy. In 1958 Dr. Lederberg shared the Nobel Prize for studies on the organization of genetic material in bacteria.

biologists' consciousness. This development stood against the presumption of the prior two decades that proteins were everything: they were enzymes, and they were sources of such exquisite specificity in every other realm, why not in the genetic material as well? But as is well known, the experiments of these investigators gave the first and eventually irrefutable, direct evidence that genetic specificity resided in the chemical structure of DNA. In the brief interval from 1944 to the beautiful elaboration of the structure of the DNA molecule, the double helix, by Watson and Crick in 1953, thinking and experiments in biology were unassailably revolutionized. Little biological research today is not deeply informed by these conceptions.

Nevertheless, until just now, one might have sought in vain for important public health or specific therapeutic applications of that knowledge. As a geneticist, I would be the first to recall many important applications of chromosome and cell biology, e.g., the delineation of genetic syndromes and the further illumination of pathogenetic processes. Starting with Garrod's insights, the development of medical genetics followed soon upon the rediscovery of Mendelism in 1900. It is all the more paradoxical that hardly anybody's health for twenty-five years after 1953 depended on knowing that the DNA structure was a double helix. How can such a revolutionary and fundamental insight of reductive science have had such a delayed impact on our major health problems?

Today we are just beginning to see a flood of practical applications in the pipeline, and one or two have materialized. The molecular genetic prenatal diagnosis of sickle cell disease is one of the first medical applications that explicitly depends on the knowledge of DNA structure: Y. W. Kan's work is an epitome of the DNA revolution.

The biotechnology industries that are founded on recombinant DNA likewise depend on that reductive base. Even with appropriate skepticism about the pace of development of these industries in the next year or two, no one doubts the large number of forthcoming therapeutic innovations. Human proteins such as pituitary hormones, interferon, insulin—and many others today unknown—are accessible in no other fashion.

So the texture of my question has changed in the last few years—an authentic turning point in our perspective of history of this phase of medical science. Let me state it a bit differently: the phase of application having arrived, why did it take so long? or need it have taken so long? Some people think such a question is both impatient and petulant, but I think it ought to be addressed.

Over the last thirty or forty years of medical history, one can, of course, trace a host of important innovations. The whole style of medical practice has sharpened, and it is far more attuned to critical scientific inquiry. Physiological and metabolic inquiry, to understand disease process and

management of the care of the patient, from the informed perspectives from immunology and endocrinology as well, is a new common standard. Looking for more specific indicators, I have had some trouble trying to authenticate the most important specific changes in medical practice during that period of time. Once one gets past the antibiotics, which may be regarded as the culmination of the last prereductive era of medical science, it is hard to find a predominant single item in the modernization of medical care.

The use of steroids ranks high, despite caveats about iatrogenic complications. As is typical of many innovations, these complications now loom far larger than first expected. In any event, the initial discovery of the use of steroids in medicine, as with other advances, was closer to serendipity than reductionist planning.

My own conjecture is that one of the most important changes in medical practice is the management of the body fluids. I have had some difficulty, however, in getting quantitative data on the history of medical practice with respect to routine fluid infusion therapy. Few will question that this therapy has been a life-saving addition to the armamentarium, if only for the infantile diarrheas. Drinking saline water may in fact become an equally efficacious medical technology!

Water does not sound like a very sophisticated medical entity. There are a few things one puts into the water, but they are not particularly complex from a chemical standpoint, and I doubt that one would invoke reductive biology as the route of discovery in this field. But it is all the more reason to seek the different threads that have informed medical practice. We do lack the kind of critical history that would enable us to judge what has happened there, as well as in many other important changes in practice. Paul Beeson's comparison of textbooks of medicine is an indispensable way of looking at medical history; but it is almost too comprehensive, and few people will take on the assessment of the most important improvements. In my own view, we are seeing, in this decade, the completion of two cycles of medical science and practice. With the DNA revolution we are well into the third.

The first cycle rested on the scientific foundations of medical microbiology laid just a century ago. This was based on the specific recognition of germs as living organisms and as agents of disease: the methods that we owe to Pasteur and Robert Koch, the taxonomy of microorganisms, obtaining them in pure culture and identifying them as etiological agents, the development of vaccine prophylaxis, and antimicrobial therapy. This cycle represented a revolutionary scientific as well as medical finding. It took from 1880 till the 1940s and 1950s to approach an asymptote (Table 1).

We well know how mortality from infectious disease has changed since the turn of the century. While, indeed, much of that change can be

TABLE 1
Three Major Cycles of Biomedical Progress

Cycle	Dates	Description	Developments
Infectious disease	1880–1940 . . .	Reductive—germ theory	Vaccines Antibiotics
Human physiology	1922–1980. . . . . convergence 1980s	Reductive in aim; semi-empirical in practice	Insulin Cortisone Diuretics Psychotropics
Molecular biology	1944–1980	Reductive!	Enzyme inhibitors DNA diagnosis — Atherosclerosis Cancer Transplant rejection

attributed to larger cultural and social developments, it is not a question of "either/or"; and one can hardly dispute the importance of scientific knowledge about what is contaminating our water supplies, or about which vaccines would be effective. Our standards and expectations are much higher today. Even if, after earlier successes, the opportunities for rapid public health improvement are less today than sixty or eighty years ago, we do not want to stop now. Just think how deprived we would be if we had to rely on these very general measures of sanitation and vaccination, and were barred from the much-derided high technology of medical care.

The second cycle I would date to about 1922. It evokes the names of D. D. Van Slyke and J. L. Gamble, i.e., systematic application of human physiology and chemistry in medicine. Many of the specific interventions that are part of medical and surgical practice stem from physiology: the understanding of what the various organs of the body do and how they communicate with one another. Physiology, like much of biology, is informed by medical observations and vice versa. It deserves more honor than it now gets, judging from the departmental arrangements at many of our medical schools. Perhaps just because so much physiology has been incorporated in internal medicine, there is a structural problem fitting physiology as basic science into the organization of many medical schools.

If one then looks back at the variety of important introductions into management over this period of time and asks what the role of reductive science was, one can see that critical exploitation rather than initial discovery has been more significant. An outstanding example is seen in contemporary psychiatric medicine. One cannot describe the development of the now indispensable agents used in the treatment of schizophrenia and depressive illness as having stemmed in any way from a reductive model. Quite the contrary! The empirically demonstrated efficacy of agents like chlorpromazine and lithium then demanded the attention of investigators into the biochemical foundations of the mode of action of the drugs. Their discovery was empirical and preceded the neurochemical theory that is just now emerging.

It is a consequence of our successes against infections that now our priority health problems are heart disease, cancer, and psychiatric illness. The inherent intricacy of these problems, which are rooted deeply in the molecular and cellular structure of the human organism, outreaches the existing base of applicable scientific knowledge. This ignorance has frustrated the building of a theoretical program for the control of these killers comparable with the advances in the golden age of bacteriology.

This frustration is partly obscured by a number of valuable piecemeal advances in all of these fields, by the proliferation of high-technology diagnostic machines, and by the development of scientifically trained, sophisticated specialties to make these accessible to patients. This technological revolution has also carried a heavy price tag, and there now exists some political pressure for cost-reduction that would better be directed to benefit-improvement. The training of these specialists has been the main contribution of academic basic science institutions to today's "half-way technology" in medical care. As I have indicated, most of the important new drugs of the past thirty years have been discovered through empirical, not rational, procedures and in industrial, not academic, laboratories. Empirical as they were, these discoveries also depended on an infrastructure of scientific knowledge to calibrate how aspirin, chlorpromazine, or thiazides could best be employed. Equally important, a host of spurious remedies would be firmly planted in our medicine cabinets without the critical authentication of efficacy and safety that must be informed by the most rigorous scientific judgment.

In the exploitation of such new drugs, we have had to call upon every resource that science could offer, from the analytical methodologies to the critical frame of mind. We have had to organize new kinds of experiments, to define the proper scope of these interventions, to search for their side effects, and so forth. This ramification is, in a way, as indispensable as the initial discovery. It is reaching down toward the development of a reductive infrastructure for medicine, rather than having built on a deductive foundation for the initial discovery of these useful

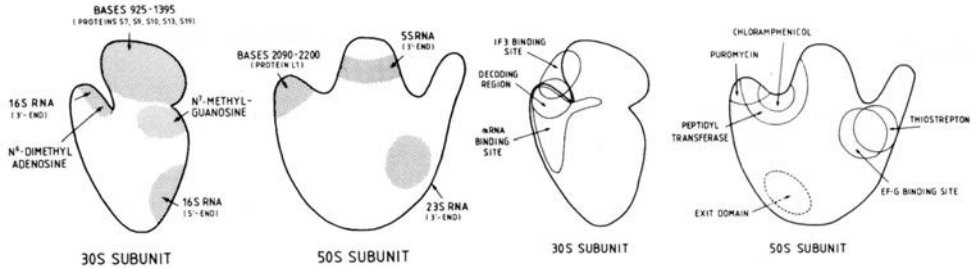
agents. With the exception of prenatal diagnosis, which did start from first principles of genetics and the cytogenetics, very few medical advances have been conceived from prior knowledge of the biology of the organism.

My question about the double helix relates to the third cycle, just at its zenith of scientific accomplishment and burgeoning potential for application. In times past, I might have leaned on the problematical structural relationships of basic sciences to clinical medicine, to account for the imputed delay. The question, it has become apparent, understated the complexity of the task.

To illustrate an essential cellular organelle, the ribosome of *Escherichia coli* (none of this my own work) is sketched in Fig. 1. These cartoons show the structure of the ribosome from four quarters. The important point is that the ribosome is composed of no less than 55 different protein subunits. Ribosomes tend to fall apart into a 30 S and 50 S major component. The *S*'s and *L*'s are on the two respective columns. At this point, every one of those has now been isolated. The amino acid sequence of the majority has been worked out, at least in some degree. Especially revealing is the self-assembly of this organelle: if you mix the different protein constituents with three molecules of specific ribosomal RNA, the ribosomes will self-assemble from these parts. Whatever magic is in the structural organization of the cell derives from the chemistry of its parts. But what complex chemistry!

The extraordinary effort that has been required in order to get to this stage of knowledge has involved: the mechanical labor of developing methods for the purification of these particles; the separation of their protein constituents in ways that do not chemically alter them; and the analysis of these particles, one by one, in order to determine their chemical composition—always in such a way that their biological integrity would not be degraded. Rather than being impatient about it taking from 1953 until now, one marvels that it has been possible to go that far in the molecular dissection of this very important particle.

So it was not enough to proclaim that the structure of DNA was a double helix and to learn the code by which protein structure was determined. That was the revolutionary opening of the door to a vast array of further investigations of the amazing variety of structures in the cell. From these, one can then expect to see a variety of applications in human pathology. We already know of genetic diseases of bacteria that result from mutations in different ribosome constituents. Environmental factors also influence ribosomal structure and function. Analogous human diseases are bound to become evident, following the same principles. Unfortunately, there remains a host of technical problems in trying to do the same thing with the ribosomes of eukaryotes. A few of the units have been found. The general structure of the ribosomes is not fundamentally different, but in this case, we must fish these things out of cells that have



Ribosomal Proteins

Proteins of 30S Ribosomal Subunits			Proteins of 50S Ribosomal Subunits		
Designation	**Mol. Wt.**	**Binding**	**Designation**	**Mol. Wt.**	**Binding**
S1	65,000		L1	22,000	
S2	27,000		L2	28,000	+
S3	28,000		L3	23,000	
S4	25,000	+	L4	28,500	
S5	21,000		L5	17,500	
S6	17,000		L6	21,000	+
S7	26,000	+	L7	15,500	
S8	16,000	+	L8	19,000	
S9	17,500		L9		
S10	17,000		L10	21,000	
S11			L11	19,000	
S12	17,000		L12	15,500	
S13	14,000		L13	20,000	
S14	15,000		L14	18,500	
S15	13,000	+	L15	17,000	
S16	13,000		L16	22,000	+
S17	10,000		L17	15,000	+
S18	12,000		L18	17,000	+
S19	14,000		L19	17,500	+
S20	13,000	+	L20	16,000	+
S21	13,000		L21	14,000	
			L22	17,000	
Sum	405,000		L23	12,500	+
			L24	14,500	+
			L25	12,500	+
			L26[c]	12,500	
			L27	12,000	
			L28	15,000	
			L29	12,000	
			L30	10,000	
			L31		
			L32		
			L33	9,000	
			L34		
			Sum	549,000	

FIG. 1. Ribosomal subunits of *Escherichia coli*, reproduced with permission of authors and publishers. The four illustrations are from H. G. Wittman. "Architecture of Prokaryotic Ribosomes," *Annual Review of Biochemistry* 52(1983):in press. The tabular material is from D. E. Metzler. *Biochemistry. The Chemical Reactions of Living Cells.* New York: Academic Press, Inc.,1977, p. 929. (A plus sign in table indicates direct binding to ribosomal RNA.)

a lot of aggressive enzymes, which tear things apart as soon as they are taken out of their normal niche.

I conclude that it is asking too much to expect reductive advances in medical practice until we can fill in the infrastructure between information that is in the DNA, and the way the cell is finally designed and built.

Without correctly assembled ribosomes, proper protein synthesis in the cells cannot continue. Ribosome assembly also presents an exciting challenge from the standpoint of its regulatory mechanisms. Here there are fifty-five different proteins, whose synthesis is precisely coordinated. One finds hardly any unassembled leftover constituents within the *E. coli* cell under a very wide range of conditions. Some of the protein constituents are able to turn off the synthesis of others at various levels, some at transcription and others at translation, and in that way the system is kept in elegant balance. The details of these interactions again involve intricate geometrical and physical patterning of the reacting macromolecules.

Our knowledge of this organelle is matched in some measure by what we know of how cell membranes and several other organelles are put together. However, the cell membrane is not a homogeneous, chemically consistent structure, and thus it presents still further challenges to elucidating its adaptations to the various roles it must play for different kinds of cells in their own circumstances.

Further glimpses into "complexity" come from work on a single bacterium, *E. coli.* Again, a very important part of the message is that in a comprehensive presentation, the details are unreadable. Figure 2 shows the *E. coli* genomic map as of two years ago. About 1,000 genetic factors have been identified in *E. coli,* each known well enough to admit the name of a protein or some enzymic or regulatory function. Most of the morphogenetic variants in the human species would not qualify so well, because of ignorance of the protein or regulatory process involved.

This map is organized into 100 intervals called "minutes," in the *E. coli* jargon. The reason for such a unit is that the process of fertilization, i.e., the transfer of genetic information from a male cell to a female cell, is rather prolonged in *E. coli;* it takes about 100 minutes for entry, from the beginning of the chromosome to the end. Jacob and Monod showed us how to use the time of entry of a gene for mapping. Finer methods which, in increasing measure, comprise the direct examination of DNA sequences are available today.

These hundred minutes of *E. coli* correspond to about 4 million base pairs: it would take about 1,000 pages of this book to inscribe them one by one. So far, we know sentences, here and there, adding up to about a dozen pages. We can infer from the local density of the map that the *E. coli* genome has sufficient information to encode about 5,000 different

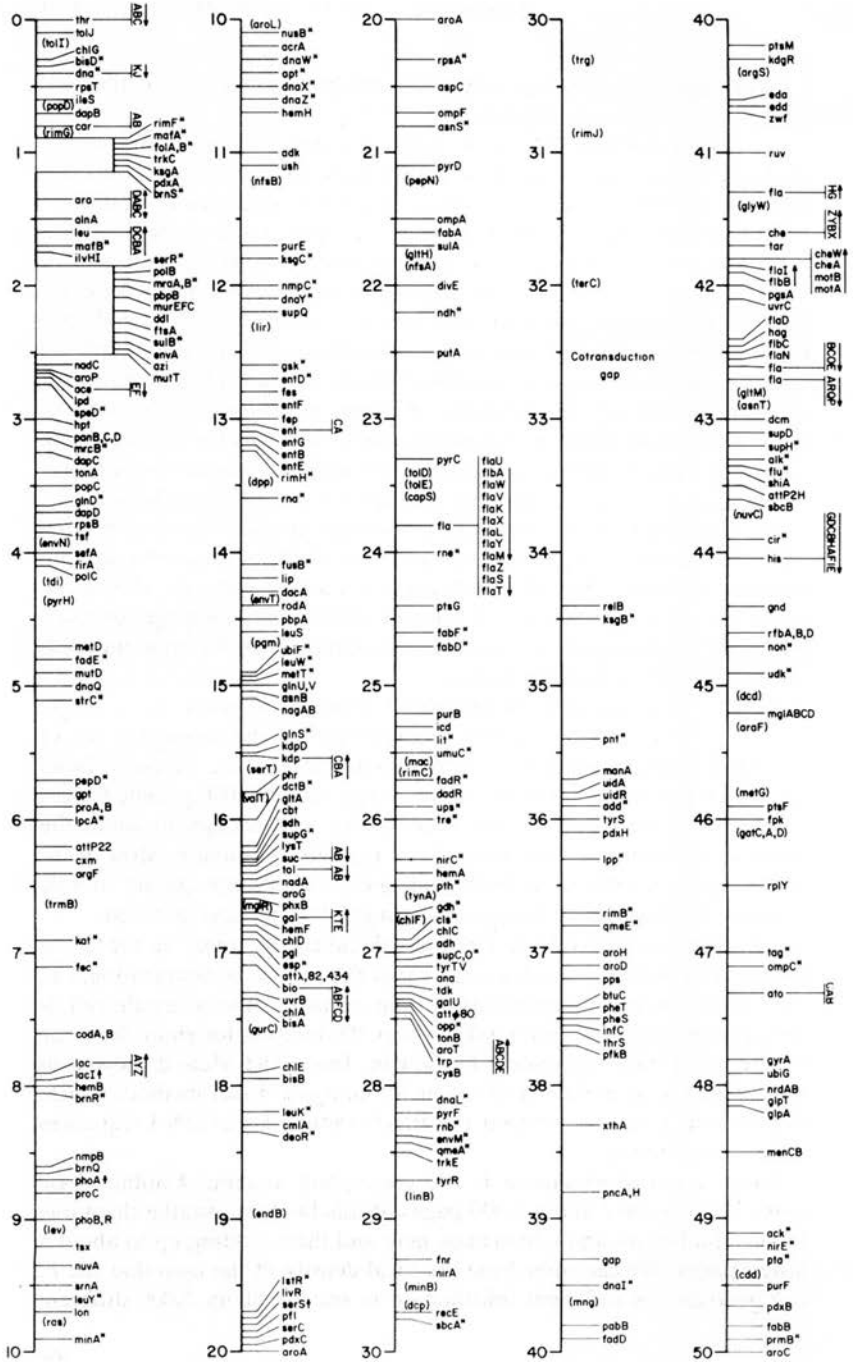


FIG. 2. Linkage map of *Escherichia coli* K-12. Reproduced with permission from Bachmann and Low, *Microbiological Reviews* 44(1980):1–56.

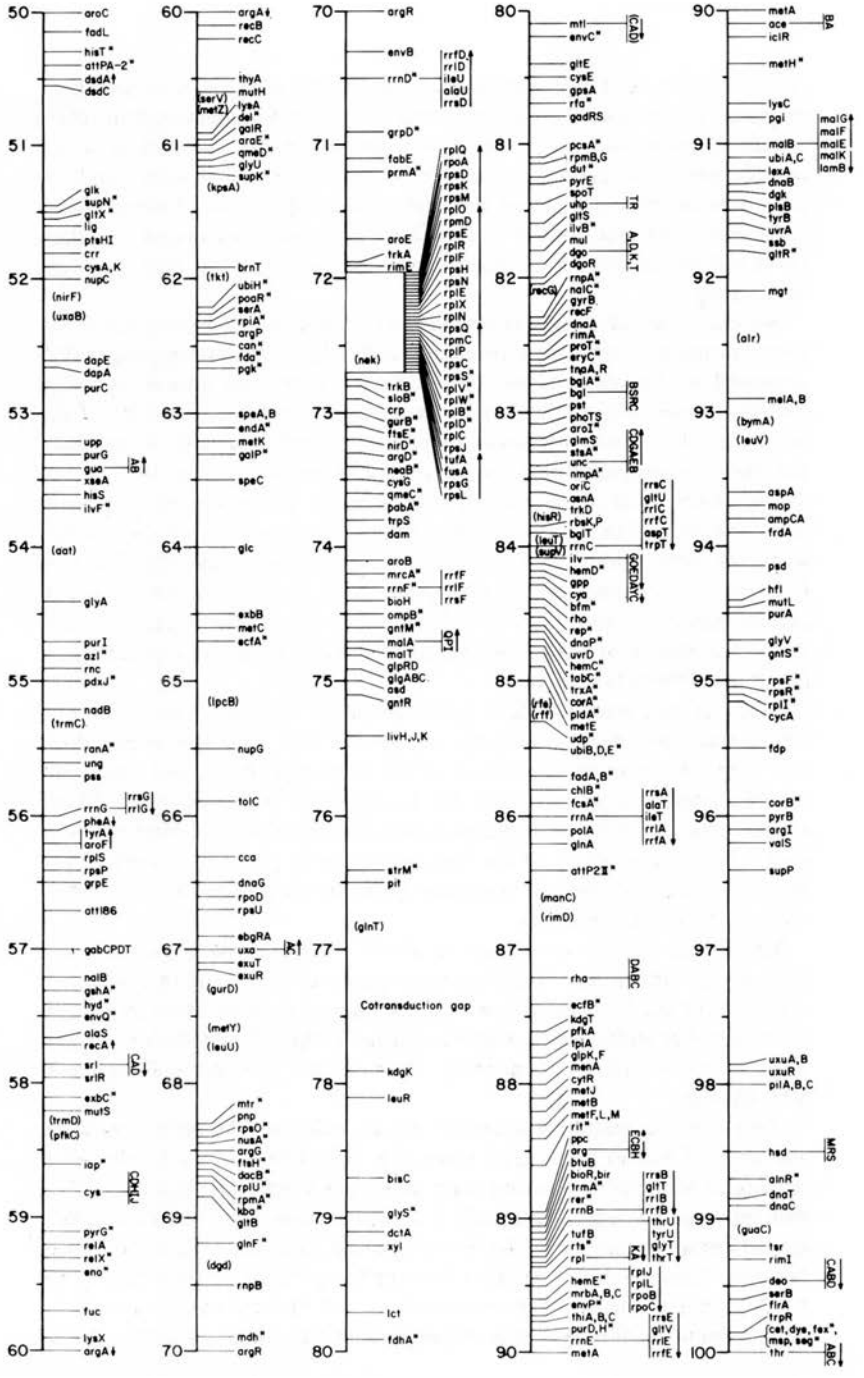


FIG. 2 (*concluded*)

protein chains. As I have indicated, about a fifth of those have now been mapped. The map also embraces about 100 known regulatory sites (there are doubtless many more). These are responsible for the rate at which specific genes are expressed. We know the sequences of some, and the picture is beginning to hang together. About 200 or so of these chains (generally 1,000 nucleotides or less) have now been sequenced, i.e., their DNA is fully known. These chains represent somewhat less than 1 percent of the map.

We might consider some other interesting objects whose complexity has been examined. Figure 3*a* shows the title head of a fascinating paper that appeared in *Nature* just about a year ago. There are almost as many authors as elements in the article—a reflection of the complexity of the enterprise they had undertaken. The paper itself is almost unreadable, but that is a compliment! Its main content is restated in Fig. 3*b*.

Obviously, print is an unsatisfactory medium for transmitting this sort of information. The figure is printed from a computer data base of DNA sequence data, courtesy of the SUMEX computer facility at Stanford University. As shown on the title page of the paper, the mitochondrial human genome comprises 16,569 base pairs. The polymorphism within the human species is already giving rise to some very interesting discussion about our ancestral lineages.

Study of the mitochondrial genome shows that there are 5 protein chains that have been previously recognized, and we know where these are. Eight other sequences also produce messenger RNA and putatively code for structural proteins, but we do not know what those are. There are 22 transfer RNAs, and there are two ribosomal RNA components as well. Thus, the structure of the mitochondrion is about half worked out in terms of the allocation of particular proteins, thoroughly worked out in terms of its DNA sequences.

Recall that the mitochondrion is about 30 seconds of *E. coli*, about a half percent of the size of the bacterial genome. Of course that means it is 1,000-fold less by comparison with the human genome! It is still not the most complex entity so far studied: phage T7 has almost 40,000 nucleotides, recently fully sequenced by J. J. Dunn and his colleagues at Brookhaven.

Here now the reductive program can be laid out. The human genome has about 3 billion nucleotide units in it. The DNA of each cell, when unpacked, is about two meters long, about the height of the person. If all that information were structural, it would encode for 10 million genes: the information content of the *Encyclopaedia Britannica*. These are large but quite finite numbers. Modern biology has given us an opportunity for the first time to measure the complexity of our challenge and examine the implications of the reductive strategy that has been so successful in

unlocking the fundamentals of living processes.

Most people now believe that about 1 percent of the genome is actively coding DNA. Hence, to get a reductive understanding of the human body, we must investigate about 100,000 different protein entities. So far, there are about 1,000 to which we could attach names. Of the ones that we can name, about 100 have been isolated from human sources. Talking about the amino acid sequence of a protein is proxy for a depth of understanding of the relationship of structure to function like the heading of a chapter, one for hemoglobin, another for collagen, and so forth.

To elucidate 100,000 proteins is then a $100 billion enterprise, with present day technology. That figure will be mitigated with further technological advances, but mere purification is already tedious and costly. Some proteins will be elusive, perhaps vanishingly scarce, although still very important in the economy in certain kinds of cells. We are now skimming the cream in terms of what is most accessible, abundant, stable, and so forth. We may wonder whether we will ever be able to afford to go through this entire reductive base. Regardless, does anyone advocate delaying further attention to specific medical problems until the reductive base is complete?

This measure of the size of the enterprise demands a sense of priorities as to which part of the landscape has the most important treasures. (We are not always going to guess right, because of the unpredictability of the insights that most rapidly lead to important applications.)

In this setting I am preaching to the choir about the need to promote better mutual understanding of the problems and methods of clinical observation and fundamental laboratory investigation. Part of the answer is the scientific training of clinically oriented people. The converse, I believe, is equally important but has been neglected even more: that is, the exposure of biological scientists to health problems. This should not be thought of solely as a way to accelerate practical results, although I believe it is an indispensable part of that mission. The history of science is replete with examples of the testing of reductive theories by confrontation with facts and observations from nature, sometimes with revolutionary impacts on the narrowly structured models that science must use. Today's natural history is clinical observation: recall that Avery's work on DNA was impelled by his effort to systematize pathogenic strains of pneumonia, each of which demanded a unique vaccine.

Robust biological theory is an urgent requirement for our understanding of environmental hazards and for the establishment of economically viable policies of regulation. We face the perplexing challenge of predicting hazards to human health before they materialize; and this goal can only be realized with much more solid predictive methods with which to interpret laboratory experiments and translate these into quantitative

standards of exposure for regulatory purposes. To do this will require a vast extension of comparative toxicology as a biological discipline. In the long run, this application of reductive biology to preventive health may be more productive than anything likely to emerge in therapeutic medicine.

Perhaps the greatest difficulty with the long-standing promissory notes is the extent to which they give rise to an underestimation of the abrupt

Sequence and organization of the human mitochondrial genome

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The complete sequence of the 16,569-base pair human mitochondrial genome is presented. The genes for the 12S and 16S rRNAs, 22 tRNAs, cytochrome c oxidase subunits I, II and III, ATPase subunit 6, cytochrome b and eight other predicted protein coding genes have been located. The sequence shows extreme economy in that the genes have none or only a few noncoding bases between them, and in many cases the termination codons are not coded in the DNA but are created post-transcriptionally by polyadenylation of the mRNAs.

FIG. 3*a*. Title head. Reproduced with permission from *Nature* 290(9 April 1981).

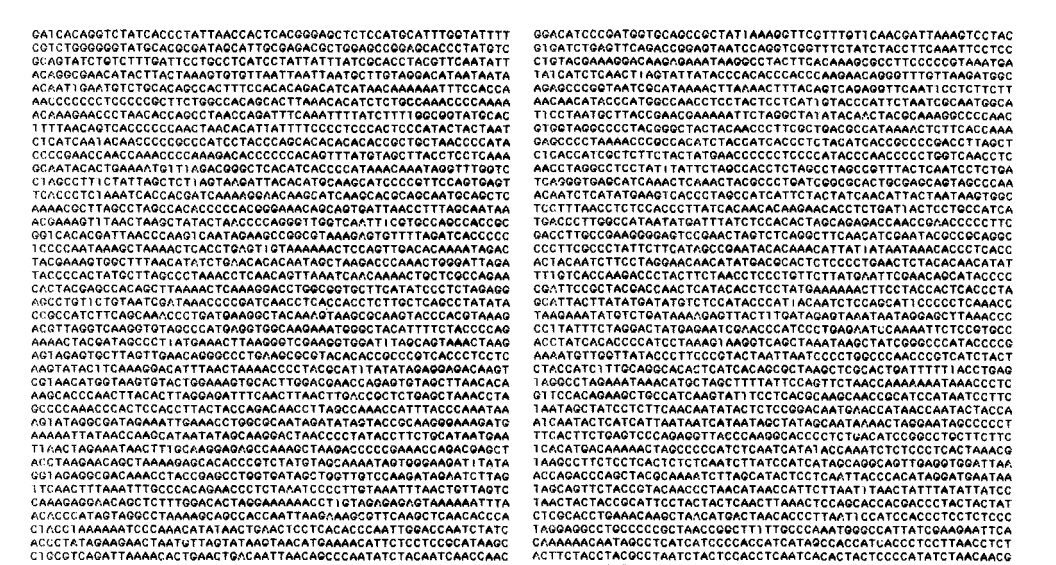

FIG. 3*b*. Sequence and organization of human mitochondrial genome. Reproduced with permission from a far more readable figure in *Nature* 290(9 April 1981).

FIG. 3*b* (*concluded*)

changes in the human condition that will follow from the success of the third cycle in preventing the major threats of heart disease, cancer, and other constitutional diseases. This success is bound to engender many secondary problems: we are already facing an older population—and the dilemmas of work, retirement, and social security policy that then emerge. I have no doubt we prefer these problems to the miseries of premature bad health and disability; but even now they are swept under the rug.

Most of my discussion, and this conference, has centered on the health problems of the United States. Parasitic diseases, whose victims live mostly far away, have had disgracefully low priorities in this country's research efforts. This is the more tragic, for there is no more productive arena for authentic "technological fixes." Yes, that is a problematical phrase, whose problematics come from careless disregard of the social and political obstacles to innovation; but it is hard to see that anything but good would come from a vaccine for malaria or from the control of schistosomiasis or sleeping sickness. The application of reductive molecular biology to the organisms of parasitic disease is a fascinating challenge to a new band of "Microbe Hunters," and there is every prospect of successes to match those of the first wave of microbiology. Similar principles also apply to plant improvement. Despite the complexities that attend farming practices in underdeveloped countries, there will be enormous gains from the development of new crops truly better adapted to the agronomic circumstances of poor countries around the world. Population control technology must be even more sensitive to the human incentives and constraints to its adoption; even so, much fundamental work is needed to offer people better means to implement their intentions, day by day.

Our federal research grants system is supposed to be motivated in the long run by the payoff of the use of scientific advance for health applications. It is a paradox that the frantic hewing to the committed line of a grant, ever since (in the name of accountability!) the project replaced the talented person as the rationale for awards, works to frustrate the broadening of outlook of clinicians and scientists alike. Our research institutions—and these too are given short shrift next to projects in the priorities of funding—in principle could provide both shelter and cement for interlevel and interdisciplinary exploration. Our ability to make these provisions is being seriously eroded both by the general stringency of funding and by the particular ways in which it is administered. There is no easy way to retrench; but if our national aim is to bring our current third cycle to its most fruitful consummation, we will have to reform the ways in which the diverse contributors to creative insight and to practical development are encouraged to cohere.

DISCUSSION

DR. SEYMOUR KETY: I have a comment. Actually, I thought it was going to be on Dr. Motulsky's talk, but it appears to be on Dr. Hartl's talk.

There was a story that Toscanini came to Philadelphia as a guest conductor of the Philadelphia Orchestra, and in the rehearsal he noticed that the concertmaster was making faces. He stopped the orchestra and said, "Concertmaster, I don't understand why you look so unhappy. Don't you like my conducting or perhaps you don't like the baton?" "No, you are the greatest," was the reply. Then Toscanini said, "Perhaps you don't like the music we are playing?" And the concertmaster said, "No, that is my favorite composer. It's just that I don't like music."

The interesting thing about genetics is that there are people who just don't like genetics. I remember in an earlier decade people would argue about genetics and disliked genetics because if something was genetic you couldn't do anything about it. Now they are worried because there is genetic engineering and you can do something about it.

DR. ROBERT BERLINER: I was not around at the inception of the Department of Human Genetics at Yale, which occurred a year or two before I moved there from NIH, but a decision was made to establish a department of human genetics, and it was largely made up by moving people around from other departments—people who had acquired an interest in genetics of one sort or another. Among these people were some pediatricians, including Leon Rosenberg, who has been chairman since it started. A large fraction of the department was from microbiology and consisted of people who had become bacterial geneticists and were thinking of moving toward becoming eukaryote geneticists. There were several people from the Department of Biophysics and Biochemistry, and a number of other people from the Department of Medicine who were mainly interested in fibroblasts.

DR. JOHN BOWERS: Is this department listed as a clinical department?

BERLINER: It is listed as both. It does have clinical activities, mostly through the Department of Pediatrics, although it does, of course, have its own genetic counseling and cytogenetics work and so on. But the majority of the department faculty are in basic genetics. There are a large number of people with secondary appointments from other departments—Department of Biology, Department of Molecular Biology, Biophysics, and Biochemistry.

DR. FREDERICK ROBBINS: There have been several comments here on the educational system and the deplorable state of education, particularly in science and math. The National Academy has made the problem essentially one of its top priority issues. They held a colloquium, a two-day affair, where they had Caspar Weinberger speak, among others. They had the governor of North Carolina. There was a kick-off for a commission, which the National Science Foundation

is supporting, on which Donald Fredrickson is a member. The commission is directed at this issue, to try to activate the system to correct these horrendous deficiencies, which were clearly pointed out at the colloquium. They did get quite a lot of interest. Whether or not anything will come of this, I don't know. But it is a little like the old Sputnik days. People are scared.

DR. EUGENE KENNEDY: I have a question. In the case of the enzymes, the primary structure, of course, is only the beginning of the story. You need to know about the secondary and higher forms. But maybe there is some room for optimism. Let us say there are 5,000 enzymes in *E. coli.* We will call them enzymes. One would be very surprised if it were necessary to have 5,000 primary structures before the rules for folding could be understood; perhaps one could have 500 structures, and then the beginnings of the understanding of folding would be already apparent. Maybe, to get a substantial understanding, one would not need to go the whole route.

DR. JOSHUA LEDERBERG: I hope so.

DR. ARNO MOTULSKY: Do you think it might be possible that, just as the early Mendelian geneticists very well understood the gene without understanding its structure, we might glean from current approaches new insights which we don't dream of today and which don't require the full understanding of all the details?

LEDERBERG: That is what I lumped under "physiology." I think of that level of inquiry as something other than the most fundamental chemical-physical understanding of intracellular process (but I have no quarrel with calling that cell physiology). Our opportunity to advance in such areas is happenstance. Think what it took for Mendel: the idiosyncrasies of faithful mechanical segregation of chromosomes at meiosis. But we must look for such opportunities wherever we can.

DR. KENNETH WARREN: I would like to make two comments about oral rehydration because I share Dr. Lederberg's opinion that this is one of the greatest answers in modern medical science.

First of all, I think it all came about through the work on cholera. To look at it reductively, if we didn't know about cyclic AMP, we would not have done the research that got us to the point where we understood the original concept of cholera—that the gut mucosa was destroyed and was leaking fluid. Then investigators discovered it was the secretion of fluid through activation of cyclic AMP. The next step in the application I don't know. But in any event, the addition of glucose to the fluid aided in the oral rehydration.

My second comment concerns the dogmatic approach of most physicians. They think only in the way they have been trained. It has been very difficult to get oral rehydration into use. The greatest single obstacle is the American physician. People all over the world will tell you that physicians in the developing world use Nelson's textbook of pediatrics. I have been at meetings recently where these people begged us to get Nelson to change from the total use of intravenous infusions to oral rehydration for infants in hospitals in general. Until Nelson does that, people in the developing world won't use it. This is a very good example of the dogma of physicians. Semmelweis also is an example. He committed suicide because he couldn't get people to see the obvious.

BERLINER: The idea of the need for rehydration, that glucose would enhance

absorption from the GI tract, anteceded the discovery of the fact that cyclic AMP was involved. There was a physiologist-biochemist who found that cotransport of glucose and sodium was a major means for removing of electrolytes across the intestinal mucosa. This development gave others the idea that if you added glucose to the solution you would get different retention as far as the need for saline was concerned. That goes back to Sir William Brooke O'Shaughnessy, in the 1880s, who discovered that the main problem in cholera was loss of fluids.

LEDERBERG: No one else found it. It was a secret for eighty years.

There is another dogma that has also continued in the field. I guess that is what is wrong with it. I don't want to be pejorative about physiology, because it is true for medicine also. This dogma is the kind of higher level generalization which is empirically grounded at that level of organization of the system, and whose physical principles you don't understand. So you take it for granted. That happened in microbiology and it was called detoxification. It was a very important insight into the way that bugs caused disease. It ran through one thing to another so that one could understand the pathogenesis of a bacterial infection.

Koch also discovered the cholera organism and then started a wild goose chase that took almost eighty years to resolve because of the dogma of the toxin. It was something that killed on intravenous injection. That absolutely obscured and impeded not only research but therapy in cholera for that period of time until an Indian pathologist set up the ileus loop preparation and demonstrated that indeed that was the mode of action of the so-called toxin. It was not a cytocidal effect of any kind. That is almost inevitably going to happen if you work in higher level generalizations that are unanalyzed concepts.

DR. JAMES HIRSCH: It is a fascinating exercise that Dr. Lederberg has gone through. Even though the number 100 million is a very large number, it is also a remarkably small number. It is not something beyond our conception, when you compare it to the Department of Defense budget or even the annual NIH budget. You don't have to go through many orders of magnitude before you get to that level. It is entirely possible that within a generation we will know all of this. If that is the case, it will be a remarkable advance in biological models. I agree that we shouldn't wait until we know all of it. We should try to make use of the advances that have occurred in the last twenty or thirty years. But these numbers and the exercise Dr. Lederberg has gone through make me optimistic that in the not too distant future we may get there.

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