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Nobel Prize Winners in Medicine and Physiology 1901-1950

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Nobel Prize Winners in MEDICINE and PHYSIOLOGY

1901-1950

by

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Henry Schuman · New York

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PREFACE

A HALF-CENTURY OF ACHIEVEMENT IN MEDICAL SCIENCE IS reflected in the awards of the Nobel Prize for Physiology and Medicine. One-fifth of the interest on Alfred Nobel's fortune is to be given annually "to the person who shall have made the most important discovery" in this domain. Winners are selected by the Caroline Medico-Chirurgical Institute in Stockholm. Each Nobel laureate is judged to have made a personal contribution of first-rate importance. Behind and around him there is always a constellation of scientists who have taken part in the same work. Their preliminary researches have made it possible, or their subsequent efforts have made it more fruitful. The winner of the Prize is therefore not only a discoverer in his own right, but a representative—by virtue of his outstanding contribution—of those who have worked toward the same or a similar goal. The configuration of the heavens may be roughly indicated by mapping the principal stars, but the sky would be dim indeed without the rest.

In the following pages each Prize Winner is represented, first, by a short biographical sketch; second, by a passage in which he describes the Prize discovery in his own words; and third, by a brief editorial explanation of the meaning and importance of the work. For the most part the quotation is an excerpt from the Nobel Lecture delivered in Stockholm at the time of the presentation of the Prize.

These Lectures are given to general audiences and should therefore be suitable for general readers, as many of them are. Unfortunately this is not always the case. When the Lecture has been very technical in form, some less complicated version of the same story has been sought for elsewhere in the author's works. Sought for, but not always found. Happily there are only a few cases—Professor Gullstrand's is one—in which the very nature of the discovery requires that the reader should have extensive background knowl-

edge before he can hope for a competent understanding. These few instances must be left to those who can grasp them. The majority of the discoveries are easy to comprehend in outline. No more than this is aimed at here.

Occasionally, too, the Prize Winner has grown bored with his own discovery long before reaching Stockholm—he may have described it already fifty times—and has chosen to talk about something else. Pavlov and Florey are examples: both of them preferred to speak of more recent work. Again, a modest laureate may devote most of his time to expounding the related discoveries of other scientists. In all such cases it is obvious that the Nobel Lecture would have been an unsuitable choice for the present purpose. Actually most of these Lectures are precisely what is needed. Sometimes, too, the choice has been determined by the way in which the work of one Prize Winner can be linked with that of another: as they are here represented, Sherrington's physiological discovery leads on from an anatomical finding by Golgi; there are also other examples.

Except where otherwise shown, all translations have been prepared for their present use. I am grateful to my colleagues, Dr. R. J. Rossiter, Dr. J. A. F. Stevenson, Dr. George Stavraky, Dr. R. G. E. Murray, Dr. Murray L. Barr and Dr. T. H. Coffey for their help and advice.

Lloyd G. Stevenson, M.D.

October, 1952

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Nobel Prize Winners in Medicine and Physiology 1901-1950

1901

EMIL VON BEHRING

(1854–1917)

"For his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and death."

BIOGRAPHICAL SKETCH

EMIL ADOLF (VON) BEHRING WAS BORN IN DEUTSCH-EYLAU, Germany, in 1854 and studied in Berlin. He entered the Army Medical Corps and was lecturer in the Army Medical College, Berlin, in 1888. The following year he became assistant in Robert Koch's Institute of Hygiene. In 1891, when Koch became chief of the new Institute for Infectious Diseases, von Behring accompanied him. Meantime (1890) he had published his important papers on serum therapy. The consequences in medical practice were sensational and von Behring was soon famous. In 1894 he accepted the chair of hygiene in Halle, but a year later transferred to a similar position in Marburg. He received many distinctions and several monetary prizes. In Marburg he established works for the manufacture of antitoxins and a remedy for the tuberculosis of cattle. He died in 1917.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"As already proved by Löffler, then Roux and Yersin, there are animals naturally immune to diphtheria; I have confirmed by my own investigations that this is true of mice and rats, and that these animals tolerate, without appreciable damage to their health, inoculations with cultures which have a sure and deadly effect on much larger animals, such as the guinea pig, rabbit, and wether. . . .

"Furthermore, one can make animals immune which were originally very susceptible to diphtheria. . . .

"1. One of the immunization methods, which I can show to be very reliable on the ground of my own research, has been described exactly by Prof. C. Fränkel [1861-1915; an assistant of Koch's who became professor of hygiene at Halle and did much original work in bacteriology and immunology]. . . . It depends on the use of sterilized cultures, and with the help of this method one can make guinea pigs nonsusceptible in 10-14 days to inoculations that are certain death to normal guinea pigs. . . .

"2. [Von Behring next describes a method of his own, using in place of the sterilized cultures of Fränkel cultures weakened by the addition of iodine trichloride in small amounts. A feeble culture was succeeded by a more active one. Finally a fully virulent culture was tolerated.]

"In both the methods just mentioned, immunity is brought about by the metabolic products bred by diphtheria bacilli in cultures.

"3. But it is also possible to produce immunity through the same metabolic products engendered from diphtheria bacilli in the living animal organism. If one investigates animals dying of diphtheria, one finds an extremely abundant transudate in the pleural cavity. . . .

"In more than 50 separate cases investigated, this transudate never contained diphtheria bacilli; but it possesses properties poi-

* Translated from Emil von Behring, " Untersuchungen über das Zustandekommen der Diphtherie-Immunität bei Thieren," *Deutsche medicinische Wochenschrift,* Vol. 16 (December 11, 1890), pp. 1145-1148.

sonous for guinea pigs. The degree of toxicity is not always the same. . . .

"Those [few] guinea pigs which survive an injection of [10 to 15 c.c. of] transudate . . . are regularly sick for a long time; [here follows a description of their symptoms].

"Now when I awaited the complete recovery of those animals which displayed the symptoms just described to a pronounced degree, then . . . I could establish that they endured without harm inoculations that would kill healthy animals in 3 to 4 days. . . .

"4. An[other] immunization method, one not hitherto employed, can also be traced to the operation of the metabolic products of the diphtheria bacilli.

"*It consists in first infecting the animals and then doing away with the deleterious effect through therapeutic management.* [This was exceedingly difficult. Of the many drugs tried, most were useless. Mention is made, however, of certain compounds which appeared to have cured infected guinea pigs, notably iodine trichloride. Behring reported that treatment with this drug prior to infection did no good.]

"5. [It was reported that prior treatment with hydrogen peroxide seemed to confer some immunity. This alleged success had nothing to do with immune products resulting from the metabolism of bacilli.]

"All five of the methods of immunization against diphtheria thus far described are in my opinion not practicable—at least in the form I have given them—for humans.

"But from the scientific viewpoint, and . . . for the understanding of the occurrence of diphtheria immunity, they are capable of affording us worth-while service.

"That is to say, immunity having somehow occurred—and I do not exclude natural immunity—all diphtheria-immune animals have certain characteristics in common which distinguish them from non-immune animals.

"First of all, the living immune animals, as a whole, not only possess protection against infection with the living diphtheria bacilli but are also protected against the deleterious effect of the poisonous substances formed by the diphtheria bacilli in cultures and in the animal body.

"I have undertaken the proof of this in various ways. First I tried it with the solution of an albuminous substance which I separated from old cultures with acidified alcohol; however, I was unable to remove the acid from the resulting preparation without impairing the poisonous effect; I also think it no easily soluble problem . . . to separate other precipitating agents from the precipitate produced. But for the purpose in question I scarcely needed to go after the diphtheria poison, or, perhaps more correctly, the diphtheria poisons; filtrates of old cultures afforded me all I wanted.

"Using my cultures grown in alkaline bouillon, with 10 c.c. normal alkali per liter, I found that after 10 weeks they contained so much poisonous substance that, having been rendered germ-free by filtration, they already called forth characteristic symptoms of diphtheria poisoning with a dose of 1 c.c. in medium-sized guinea pigs; these symptoms did not entirely disappear for 3 to 4 weeks. Furthermore, 3 to 4 c.c. were enough to kill larger guinea pigs in 3 to 8 days . . .

"Now all guinea pigs with established diphtheria immunity . . . endured 3 to 5 c.c. without any discernible disease symptoms or local reaction whatever; on the other hand, guinea pigs that had still not quite recovered from an infection proved to be only very little more poison-resistant than they normally would be. . . . *It is very noteworthy that the immunity can be lost again through the subcutaneous injection of considerable and repeated quantities; this happens with all the more certainty, the less the immunity has been 'established.' At all events, guinea pigs under the influence of the poisonous, germ-free diphtheria culture fare as before against diphtheria infection under unfavorable conditions.*

"The first thought to arise could be this, that the resistance to poison here described depends on 'habituation,' as in the case of alcoholics, morphine addicts, arsenic eaters. . . .

"But such an interpretation is at once controverted by the fact that animals which have never had anything to do with diphtheria poison also possess diphtheria poison resistance.

"If we start out again with the 10-week culture rendered germ-free, then, calculating on the basis of body weight, it is deadly for guinea pigs in the ratio of about 1:100; but mice endure the poison

without any harm when it is injected into them in the ratio of 1:20, and I have injected rats on several successive days with 4 c.c. at a time without the appearance of a reaction worth mentioning.

"A further argument against accepting habituation to the poison [as the explanation] is the circumstance that I have never succeeded, despite the most cautious increase in the dosage of poison from a quite harmless to a higher one, in protecting animals against the diphtheria poison, except insofar as they have later been able to endure a little more of it than they normally could.

"These observations and considerations led me to approach closer to the question whether the origin of the poison resistance really does not depend at all on a characteristic of the living cellular parts of the organism, but rather on a peculiar property of the blood, freed of living cells.

"In order to decide this question I withdrew blood from rats 3 hours after they had had large amounts of diphtheria poison injected into their abdominal cavities, and injected it, or the serum obtained from it, into the abdominal cavities of guinea pigs; no trace of the symptoms of poisoning occurred, whereas the blood of diphtheria-susceptible animals which had received the diphtheria poison, when injected into the abdominal cavity in like amount (4 c.c.), did not, indeed, kill the guinea pigs, yet clearly made them sick.

"For the future, then, I attach importance to the fact that the extravascular blood of diphtheria-immune guinea pigs also has the capacity of making the diphtheria poison harmless. To what extent this occurs, and to what extent therapeutic results can be obtained with the blood of immunized animals—on these points I propose to contribute later. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

In No. 49 (December 4, 1890) of the *Deutsche medicinische Wochenschrift* (German Medical Weekly), von Behring and his Japanese colleague, Shibasaburo Kitasato (1852-1931) announced the discovery of tetanus antitoxin. It was shown that "immunity to this disease . . . depends on the capacity of the blood to render

harmless the poisonous substances produced by the tetanus bacilli."

"In that work," wrote von Behring, "the same was also affirmed for diphtheria immunity, in just the same way as for tetanus, but without the communication of separate investigations, which had shown for diphtheria, too, the equivalent mechanism of the occurrence of immunity." The work had already been done in part by von Behring, and one week later, in No. 50 (December 11, 1890) of the same journal, there appeared the classic paper from which an excerpt is quoted above. It is interesting that a large part of this paper concerns preliminary investigations and relates the way in which von Behring reached the conclusion that the power of resisting the disease does not reside in the cellular constitution of the body but rather in the cell-free blood serum. (This contention was so amply proved a little later that Metchnikoff's discovery of the part played by white blood cells in combating infection was at first rather ill received. See below, pp. 49-50.)

As suggested by the last sentence of the longer quotation, much remained to be done in studying this phenomenon. About a year after publication of the quoted paper the first human case was treated with diphtheria antitoxin. This was a child in Bergmann's clinic in Berlin, Geissler making the injection on Christmas night, 1891. The method was soon widely used and its success was phenomenal. The death rate from diphtheria, as reported by one of the Berlin hospitals, fell from 48 percent to 13 percent, and even better results soon were achieved. Before the discovery of antitoxin the fatality rate in general was about 35 percent, and in laryngeal cases about 90 percent. Since this discovery, mortality has fallen to approximately 5 percent, and in laryngeal cases to 15 percent.

Ability to measure dosage was largely the result of the brilliant work of Paul Ehrlich (see below, pp. 52-55). Further progress was made when the Health Department of New York City adopted the use of cultures for diagnosis and for control of the period of isolation; this was done in 1893 under the direction of Park. In 1913 Schick described the intradermal toxin reaction (skin test) for the determination of individual immunity. In the same year von Behring introduced the use of injections of toxin-antitoxin mixtures in children for active immunization against diphtheria. This proved a most effective means of protection. In 1924, Ramon

brought forward his formalized toxin or anatoxin, commonly known as toxoid, which has largely replaced toxin-antitoxin mixtures.

Not only did von Behring make the most important contributions to the conquest of diphtheria but his introduction of serotherapy opened a whole new field to medicine.

REFERENCES

BULLOCH, WILLIAM. *The History of Bacteriology* (London and New York: Oxford University Press, 1938), and the literature cited there, especially E. Wernicke, "Die Immunität bei Diphtherie," *Handbuck der pathogenen Mikroorganismen von Kolle-Wassermann,* 1913.

1902

RONALD ROSS

(1857–1932)

"For his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and how to combat it."

BIOGRAPHICAL SKETCH

RONALD ROSS CAME OF A THREE-GENERATION ANGLO-INDIAN family. He was born at Almora in the Kumaon hills, northwest Nepal, on May 13, 1857, the eldest of ten children. His father was General Sir Campbell Claye Ross. In 1874 Ronald Ross began the study of medicine at St. Bartholomew's Hospital Medical School. He obtained the M.R.C.S. diploma in 1879 and for a time traveled between London and New York as a ship's surgeon. He then entered the Madras Medical Service and took part in the Burma War. On leave in 1888, he studied bacteriology in London under Klein, and took the D.P.H. Returning to India, he began, in 1892, to take especial interest in malaria; he had already studied mosquitoes on his first tour of service. In 1894 Patrick Manson, the great pioneer of tropical medicine, showed him the malarial parasites discovered by Laveran in 1880. Returning to India in 1895 after his second home leave, Ross carried on an exhaustive study of the problem of the transmission of malaria, constantly advised and encouraged by Manson. A series of frustrations, due to the failure of the authorities to support his work and their maddening tend-

ency to transfer him at crucial moments in his research, dogged him for years. He nevertheless achieved the great success described below. Ross was later sent to Assam to investigate kala-azar. In 1899 he was appointed lecturer in tropical medicine at the Liverpool School and retired from the Indian Medical Service; in 1902 he became professor. In 1912 he left Liverpool to act as physician for tropical diseases at King's College Hospital. He served in various capacities as a consultant during the First World War and after 1918 he practiced in London. He traveled widely, chiefly to advise on antimalaria measures. In addition to his scientific writings and his *Memoirs,* he published books of verse and several romances. In 1911 he became a Knight Commander of the Bath, and in 1918 Knight Commander of the Order of Saint Michael and Saint George. The Ross Institute and Hospital for Tropical Diseases, founded in his honor, was opened at Putney in 1926. He died there in 1932.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"Towards the middle of August [1897] I had exhaustively searched numerous grey mosquitoes and a few brindled mosquitoes. [Unable to obtain literature on mosquitoes, Ross made a working classification of his own and invented simple names. His grey mosquitoes belonged to the genus *Culex,* his brindled mosquitoes to the genus *Stegomyia.*] The results were absolutely negative; the insects contained nothing whatever. . . .

"I had remembered the small dappled-winged mosquitoes [genus *Anopheles*], but as I could not succeed either in finding their larvae or in inducing the adult insects to bite patients, I could make no experiments with them. On the 15th August, however, one of my assistants brought me a bottle of larvae, many of which hatched out next day. Among them I found several dappled-winged mosquitoes, evidently of the same genus as those found about the barracks, but much larger and stronger. Delighted with this capture I fed them (and they proved to be very voracious) on

* From Ronald Ross, "Researches on Malaria," *Les Prix Nobel en 1902.*

a case with crescents in the blood. Expecting to find more in the breeding bottle and wishing to watch the escape of the motile filaments in this new variety, I dissected four of them for this purpose immediately after feeding. This proved to be most unfortunate, as there were no more of these insects in the bottle, and the results as regards the motile filaments were negative. I had, however, four of the gorged dappled-winged mosquitoes left; but by bad luck two of the dissections were very imperfect and I found nothing. On the 20th August I had two remaining insects both living. Both had been fed on the 16th instant. I had much work to do with other mosquitoes, and was not able to attend to these until late in the afternoon when my sight had become very fatigued. The seventh dappled-winged mosquito was then successfully dissected. Every cell was searched, and to my intense disappointment nothing whatever was found, until I came to the insect's stomach. There, however, just as I was about to abandon the examination, I saw a very delicate circular cell apparently lying among the ordinary cells of the organ, and scarcely distinguishable from them. Almost instinctively I felt that here was something new. On looking further, another and another similar object presented itself. I now focussed the lens carefully on one of these, and found that it contained a few minute granules of some black substance exactly like the pigment of the parasite of malaria. I counted altogether twelve of these cells in the insect, but was so tired with work and had been so often disappointed before that I did not at the moment recognize the value of the observation. After mounting the preparation I went home and slept for nearly an hour. On waking, my first thought was that the problem was solved; and so it was.

"Next morning . . . the eighth and last dappled-winged mosquito . . . was killed and dissected with much anxiety. *Similar bodies were present in it.* . . . The objects lay, not in the stomach cavity of the insects, but in the thickness of the stomach wall. . . .

"These two observations solved the malaria problem. They did not complete the story, certainly; but they furnished the clue. At a stroke they gave both of the unknown quantities—the kind of mosquito implicated and the position and appearance of the parasites within it."

CONSEQUENCES IN THEORY AND PRACTICE

In July 1897 MacCallum discovered the sexual phase of the reproduction of the malarial parasite. Manson at once recognized that Ross's pigmented cells were the fertilized female cells, becoming motile after fertilization and burrowing into the insects' tissues for further development. In July 1898 Ross discovered the sporozoids of *Proteosoma,* a malarial parasite attacking birds, in the salivary glands of mosquitoes. The route of infection was thus revealed and the story was virtually complete. Grassi extended the discovery from bird malaria to human malaria, and Italian malariologists worked out most of what remained to be learned. Ross optimistically expected that his discoveries were "to save human life in the gross, perhaps to open continents to civilization," a confidence widely shared. It was largely doomed to disappointment, for the problem has turned out to be an enormously difficult one. Economics, agriculture, and the social conditions of great masses of people have proved important, and often intractable, factors in the control of malaria. Furthermore, there appear to be epidemiological considerations which are not well understood even today. For example, no entirely satisfactory explanation has yet been advanced for the almost complete disappearance of malaria in certain areas, such as parts of the United States and Canada, where Anopheles mosquitoes continue to thrive. Nevertheless the discovery made by Sir Ronald Ross has borne fruit in such measures as the drainage or oiling of swamps and in the "malaria discipline" which, properly inculcated and enforced, has been shown capable of providing a large measure of protection to armies fighting in the tropics. This has been of great value to other groups and individuals exposed to the same danger; combined with the use of quinine, and more recently with other drugs, especially atabrine, it has reduced, although by no means abolished, the greatest hazard of the malaria-infested regions of the globe. The introduction of DDT (see below, pp. 255-259) and other insecticides has given the malariologist new weapons against the mosquito. In several

malarial districts, notably in Cyprus, the most recent results have been very encouraging.

One may be tempted to suggest that Ross's work inspired Walter Reed, Charles Nicolle, and later discoverers of insect vectors in disease; but it should be remembered that earlier workers, notably Theobald Smith and Manson, had already performed a similar service. It will not be forgotten that General W. C. Gorgas, by exterminating mosquitoes in the Panama region, was able to control both malaria and yellow fever.

REFERENCES

MEGROZ, R. L. *Ronald Ross, Discoverer and Creator* (London: Allen & Unwin, 1931).

ROSS, RONALD. *Memoirs: With a Full Account of the Great Malaria Problem and Its Solution* (London: J. Murray, 1923).

1903

NIELS RYBERG FINSEN

(1860–1904)

"In recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light rays, whereby he has opened a new avenue to medical science."

BIOGRAPHICAL SKETCH

NIELS RYBERG FINSEN WAS BORN DECEMBER 15, 1860, AT Thorshavn, capital of the Faroe Islands, and received some of his early schooling at Reykjavik, Iceland. He studied at the University of Copenhagen for eight years and took his degree in medicine in 1890. In the same year he was appointed professor of anatomy in the Surgical Academy. As an undergraduate he had already become interested in the influence of light upon living organisms. His work followed researches of Downes and Blunt on the influence of light upon bacteria, and those of Widmark on the power of the actinic rays to cause inflammation of the skin. In 1893 he published his first essay on the red-light treatment of smallpox. This was followed by other papers on the biological effects of light, including accounts of his work on the treatment of lupus vulgaris, a form of tuberculosis affecting the skin, especially that of the face. In 1895 he established the first Light Institute, at Copenhagen, which received patients from many parts of the world. Originally built and supported by private philanthropy, this Institute was later assisted by the state. When awarded the Nobel Prize, Finsen placed half

the prize money at interest for the benefit of his family and donated the other half to the Institute. He died at the age of forty-three, on September 24, 1904.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"Thanks to the work of Downes and Blunt, of Duclaux, Arloing, Roux, Geissler, Buchner, etc., it is at present [1897] well established that light possesses an energetic bactericidal power. Thus everything argues, at least theoretically, in favor of the use of light in the treatment of superficial cutaneous diseases caused by bacterial infection, and yet this therapeutic procedure has remained unused . . . to this day. . . . [Finsen here reviews some references in the literature to earlier attempts to use light in this way in the treatment of lupus. In some cases this apparently had been conceived as nothing more than a form of heat treatment; in general, Finsen concludes, the light source had been too feeble, the treatments too short and too few.]

"These isolated instances of the use of light for the treatment of lupus are thus of little value and can scarcely provide a basis for further researches. Consequently I have thought it my duty to reundertake the study of this important question from top to bottom.

"As light only exerts its bactericidal effects very slowly, it is necessary . . . to concentrate it by means of mirrors or lenses, at the same time excluding the heat rays of the spectrum, the infrared, red, orange, and yellow, because when concentrated they cause burning of tissues. This exclusion, moreover, curtails the bactericidal action of the light only a very little, for on examining the question more closely one finds that the majority of observers have asserted that the bactericidal qualities are due to the most refractive rays, a fact which my own experiments have confirmed. . . . [At this point Finsen describes the filters he used for this purpose, the means he employed for "straining" and concentrating sunlight, and the apparatus he devised for making use of artificial sources of light to produce "blue-violet" rays. His chief resource for filtering

* Translated from Niels Ryberg Finsen, *La Photothérapie* (Paris: G. Carré et C. Naud, 1899), pp. 85-96.

sunlight was a hollow planoconvex lens filled with an ammoniacal solution of copper sulfate; when he used an electric arc lamp, the rays were made parallel by two planoconvex lenses.]

"Before having this apparatus constructed and perfected, I assured myself by a series of experiments that the bactericidal action of light is really augmented in the degree that its rays are concentrated . . . I made use of flat, rectangular vessels, coating their walls inside with peptone-gelatin or peptone-agar which I sowed with pure cultures [of bacteria]. On the outside of each flask I stuck a sheet of paper, white on one side and black on the other, the white surface being turned to the light in order to prevent the absorption of heat rays, and the black surface applied to the glass to prevent the light from influencing the culture. In addition I cut round holes in this paper across which I wrote on the glass of the vessel . . . figures indicating the time in minutes during which these parts were subjected to the action of light.

"Two identical flasks prepared in this way were simultaneously exposed . . . one to direct sunlight, the other to concentrated sunlight. . . . [The cultures were allowed to grow in the dark for a day or two. It was then found that the concentrated light had had a greater inhibitory effect than direct sunlight. Finsen performed other experiments of a similar nature to test this point. He also found that his blue-violet rays, when passed through the pinna of the ear, had no effect on photographic paper; but that if the ear were compressed between plates of glass until partly exsanguinated —i.e., deprived of blood—the rays then seemed capable of penetrating it. For this reason he devised glass discs to be bound firmly with tapes to the surfaces he wished to expose; these were supposed to prevent blood from absorbing too much of the radiation by forcing it out of the areas under treatment.]

"I have employed the method of treatment by concentrated chemical rays in different infectious skin diseases, but above all in *lupus vulgaris,* an affection which presents particularly favorable conditions for putting this therapeutic procedure to work. It is known that lupus vulgaris is caused by the tubercle bacillus, that it is a local and quite superficial malady. On the other hand it is well established that light is capable of killing the tubercle bacillus. . . .

"When a plaque of lupus has been subjected for a long enough

time to the action of concentrated chemical rays, its margins, previously elevated, become smooth, the redness progressively diminishes, the skin regains its normal color, and ulcerations, when they exist, are cicatrized."

CONSEQUENCES IN THEORY AND PRACTICE

Finsen's use of concentrated radiation from the sun or an artificial light source, with the heat rays eliminated, made available the most refractive rays, the blue and especially the ultraviolet. Ultraviolet light continues to hold a place in the treatment of lupus vulgaris and a few other types of skin disease. The apparatus used and the details of treatment have changed, but the principle remains. X-ray treatment has been substituted in some cases of lupus, particularly in those with marked ulceration and hypertrophy, but the Finsen method, although time-consuming and costly, yields the least disfiguring scars. Sometimes both X rays and Finsen rays are used, and radium, too, has been employed. Local treatment with drugs and the surgical removal of severe localized lesions have been recommended, in combination with the systemic treatment of tuberculosis. Despite variations, a leading place is still reserved for ultraviolet irradiation. The approach to therapy has been altered, however, by the recent introduction of cortisone and ACTH.

The therapeutic use of other forms of irradiation has probably been inspired in part by Finsen's success. Ultraviolet light is now used for a variety of other purposes, including the partial sterilization of a limited, enclosed space; attempts have also been made to reduce the number of upper respiratory infections by ultraviolet irradiation of working places, but with limited and rather dubious success. (The importance of sunlight for health has been confirmed by the discovery that vitamin D_2 is produced by the ultraviolet irradiation of ergosterol, a substance derived from yeast and other plant sources, but also found in animal tissues, notably in the skin; hence the rarity of rickets in sunny climates.) Meanwhile, Bernhard, Rollier, and a number of later workers have extended the use of phototherapy in surgical cases and in several different forms of tuberculosis.

Finsen had earlier (1893) described a method for the prevention of pitting in smallpox by keeping the patient in a red-lighted room, the chemical rays at the other end of the spectrum being excluded. This procedure is now seldom mentioned in the textbooks.

1904

IVAN PETROVICH PAVLOV

(1849–1936)

"In recognition of his work on the physiology of digestion, by which, in essential respects, he has transformed and enlarged our knowledge of this subject."

BIOGRAPHICAL SKETCH

IVAN PETROVICH PAVLOV, WHO CAME OF A FAMILY OF POOR country priests, was born September 26, 1849, in the city of Riazan, in Russia. He began his education in the church school and continued it in the theological seminary. Discovering an interest in the natural sciences, he left the seminary in 1870 and entered St. Petersburg University, where Mendeleev and Butlerov were among his teachers. Subsequently he entered the Medico-Chirurgical Academy and was graduated in 1879. The influence of Professor E. von Cyon and the fame of Sechenov are said to have determined his future career. After graduation he served as Professor S. P. Botkin's *chef de laboratoire* in the Clinic of Internal Medicine at the St. Petersburg Military Medical Academy, where he continued to study physiology and carry on research. In 1884 he went abroad to study, spending two years in further training, partly with Ludwig at Leipzig, partly with Heidenhain in Breslau. He returned to the Military Medical Academy in 1886. In 1888 he discovered the secretory nerves to the pancreas; in 1889 he described his experiments in sham feeding (see below). Not until 1890 did he obtain

a chair, becoming professor of pharmacology. A year later he was also appointed director of the Department of Physiology of the Institute of Experimental Medicine. In 1895 he gave up his chair of pharmacology for that of physiology in the Medico-Chirurgical Academy, which he retained until 1924. In 1902 Bayliss and Starling announced the discovery of secretin, the hormone which incites the pancreas to secrete its digestive juice. The discovery was confirmed in Pavlov's laboratories, but Pavlov himself had concentrated on nervous correlations and the introduction of a humoral (blood-stream) factor seems to have cooled his interest in digestion. At any rate he now turned to his famous work on the conditioned reflex. For the next thirty years he devoted himself to the reflex activity of the cerebral hemispheres. His death occurred in 1936.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"In the year 1852 Bidder and Schmidt had observed that, under certain circumstances, one needs only to excite a dog by the sight of food in order to call forth a secretion of gastric juice. . . . In recent times the French physiologist Richet has had the opportunity of making observations on a patient on whom the operation of gastrotomy had been performed for an incurable stricture of the oesophagus [i.e., a permanent opening had been made from the stomach to the exterior to permit feeding]. Soon after the patient took anything sweet or acid into the mouth, Richet was able to perceive a secretion of pure gastric juice. . . . [These] observations prove . . . that the gastric glands are influenced through nerves by 'distant effect,' since the phenomenon comes to pass without any immediate contact between the food and the gastric mucous membrane. It only remained to make the experiment constant and simple; in other words, to facilitate its reproduction and seek out its proper interpretation.

"As a matter of fact, I am now able to demonstrate experiments to you which yield absolutely constant and unequivocal results. We

* From J. P. Pawlow, *The Work of the Digestive Glands,* translated by W. H. Thompson (London: C. G. Griffin, 1902), pp. 49-51, 54, 71.

have here before us [this is a demonstration lecture] a dog . . . [which] possesses an ordinary gastric fistula with metallic cannula [tube], and has had its oesophagus divided as well, so that the mouth is cut off from all communication with the cavity of the stomach. Its stomach has been washed out . . . and . . . not a single drop of fluid escapes from the fistula. I give the dog food. The animal eats greedily, but the whole of the food swallowed comes out again at the oesophageal opening in the neck. After feeding in this way (. . . 'sham feeding') for five minutes, perfectly pure gastric juice makes its appearance at the fistula, the stream steadily becomes greater and greater, and now, five minutes after the commencement of secretion, we have already 20 c.c. of juice. We may continue to feed the dog as long as we wish, the secretion will flow at the same rate for one, two, or more hours. . . . It is obvious that the effect of the feeding is transmitted by nervous channels to the gastric glands.

". . . We will [now] carry our experiment a step farther by dividing the vagi nerves. . . . In the case of this dog, at the time of making the gastric fistula, the right vagus nerve was divided below its recurrent laryngeal and cardiac branches. In this way, only the pulmonary and abdominal branches on the side in question were thrown out of function, the laryngeal and cardiac fibres remained intact. About three hours before the present lecture, I prepared the left vagus free in the neck, passing a loop of thread round the nerve, but not dividing it. I now pull gently on the thread to draw the nerve outwards, and sever it with a sharp snip of the scissors. At present the pulmonary and abdominal vagi on both sides are paralysed, while on the right side the laryngeal and cardiac fibres are intact. . . . The dog . . . shows no indication whatever of a pathological or otherwise uncomfortable condition. . . . We again offer the dog food to eat, which it eats with increasing greed . . . but in sharp contrast to the previous sham feeding, we do not see a single drop of juice flowing from the stomach. We may feed the dog as long as we wish, and repeat our experiment . . . as often as we desire, but never again shall we see a secretion of gastric juice in this animal as the result of sham feeding. . . .

"[In another dog in the same state] the peripheral end of the

[left vagus nerve in the neck] had been prepared free, placed on a ligature, and for the time being preserved under the skin. After three to four days the stitches were carefully removed . . . when the nerve lay free before us. In this way we avoided appreciable discomfort to the animal before exciting the nerve. By such precautions we invariably succeeded in obtaining a secretion of juice from the empty stomach when the nerve was subsequently excited by slow induction shocks at intervals of one to two seconds. . . .

"[In still another case] we begin to get ready a meal of flesh and sausage before the animal [with gastric fistula and divided oesophagus] as if we meant to feed it. . . . Precisely five minutes after we begin to tease the animal in this way the first drops of gastric juice appear in the fistula. The secretion grows ever stronger and stronger, till it flows in a considerable stream."

CONSEQUENCES IN THEORY AND PRACTICE

Apart from his later work on the conditioned reflex (which he discussed in his Nobel lecture, although the Prize had not been awarded with this in mind), the experiments described in the quotation are probably the most famous of the many which Pavlov performed. His great surgical skill contributed to his success, and he is credited with the introduction of aseptic surgery and the "chronic" experiment into physiology. His new experimental procedures included esophagotomy combined with gastric fistula, as well as a new type of stomach pouch designed to preserve blood and nerve supply; he also used new methods of faradization (application of an induced, or faradic, electric current) and was responsible for a number of other innovations or modifications in experimental techniques. His studies of the secretions of the salivary glands, the stomach, the pancreas, and the intestine—indeed, of almost every aspect of digestive secretion—are too far-ranging for brief summation; hence a portion of his work on gastric secretion has been selected as a specimen of his achievement. Professor Babkin summarizes the facts established under ten headings: "(1) It was demonstrated beyond doubt that vagus was the secretory nerve of the gastric glands. (2) It was shown that 'psychic' gastric secre-

tion was a fact of extreme importance. (3) A typical course of gastric secretion in response to different food substances—meat, bread, milk—was established. (4) For the first time it was demonstrated that the peptic power of the gastric juice varied with the nature of the food ingested and the phase of gastric secretion. (5) The constancy of the acidity of the gastric juice was demonstrated. (6) The stimulation of gastric secretion by food introduced directly into the stomach was shown to be due not to the mechanical but to the chemical stimulation of the gastric glands. (7) New secretagogue substances, e.g., water and meat extract, were discovered. (8) The ability of starch to stimulate a greater output of pepsin was shown. (9) The inhibitory effect of fat on gastric secretion was established. (10) The three phases of gastric secretion—the nervous, the pyloric, and the intestinal—were disclosed."

This represents only a part of Pavlov's work on digestion; one therefore feels no surprise at Babkin's further statement that the sum of this work "is the foundation on which modern normal and pathological gastroenterology is based."

Pavlov's discovery of the part played by the vagus nerve was an important contribution to general knowledge of the autonomic control of internal organs and directed further attention to this interesting question. The reflexes described above are unconditioned reflexes. But it is already apparent, in the references to "psychic secretion," that Pavlov was feeling his way toward his concept of the conditioned reflex, initiated by a stimulus inherently meaningless but rendered effective by association. This concept in turn has had widespread influence on physiology, psychology, psychiatry, and even education.

REFERENCES

BABKIN, B. P. *Pavlov: A Biography* (Chicago: University of Chicago Press, 1949).

STAVRAKY, G. W. "Ivan Petrovitch Pavlov," *Archives of Neurology and Psychiatry,* Vol. 33 (May 1935), pp. 1082-1087.

1905

ROBERT KOCH

(1843–1910)

"For his investigations and discoveries in regard to tuberculosis."

BIOGRAPHICAL SKETCH

BORN DECEMBER 11, 1843, IN KLAUSTHAL, HANOVER, ROBERT Koch was the son of a mining official and the third of thirteen children. He attended the *Gymnasium* of his native town and at the age of nineteen began his medical studies at Göttingen. Here he was influenced by the teaching of Jacob Henle, who had proposed a theory of contagion in 1840. In 1866, at the age of twenty-three, Koch received the M.D. degree. He then interned at the Hamburg General Hospital and in 1869 commenced practice at Rakwitz, in Posen. The following year he volunteered for medical service in the Franco-Prussian War. He resumed civil practice in 1872 in the town of Bomst (pop. 4000), in Wollstein, Polish Prussia; soon he became district physician, assuming responsibility for a large territory. Despite the heavy pressure of his day-to-day work, he found time for microscopy and conducted original research. His first triumph was his demonstration, in 1876, of the complete life cycle and sporulation of the anthrax bacillus. This historic piece of work was the first demonstration of a specific microorganism as the cause of a definite disease. Koch's ingenious contributions to the technique of bacteriology—isolating, mounting, staining, and photographing bacteria—facilitated his own later

studies. In 1880 he was made a member of the Imperial Board of Health. This enabled him to give up his country practice and devote his time to research. The results, which were almost immediate, were of prime importance. In 1881 he introduced steam sterilization. On March 24, 1882, at a meeting of the Berlin Physiological Society, he announced his discovery of the bacillus of tuberculosis. From 1885 to 1891, he was professor of hygiene at the University of Berlin, where much of his time was given up to teaching; in the latter year he became the first director of the Institute for Infectious Diseases, turning his full energies to research. In 1883, as head of the German Cholera Commission, he visited Egypt and India and discovered the cholera vibrio. Later travels in India, Java, Africa, and Italy were occasioned by his studies of trypanosomiasis, malaria, plague, and a variety of other diseases. He and his collaborators were able to show that bubonic plague is transmitted to human beings by the rat-flea. He came back repeatedly to his labors on tuberculosis. Koch died at the age of sixty-seven, on May 27, 1910. His body was cremated and the ashes placed in the Berlin Institute for Infectious Diseases.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"[Jean Antoine] Villemin's discovery that tuberculosis is transmissible to animals [1865] has found varied confirmation, as is well known, but also apparently well-founded opposition, so that, up to a few years ago, it remained undecided whether or not tuberculosis is an infectious disease. [It was commonly blamed on nutritional disturbances.] Since then, however . . . inoculations into the anterior chamber of the eye . . . and in addition, inhalation experiments . . . have proven the transmissibility of tuberculosis beyond a doubt. . . .

"Attempts have been made repeatedly to investigate the nature of tuberculosis thoroughly, but up to now [1882] they have been

* From *Berliner klinische Wochenschrift,* Vol. 19 (1882), pp. 221-230; reprinted in *Medical Classics* (Baltimore: Williams & Wilkins, 1938), Vol. 11, pp. 821-852 (translation on pp. 853-880). The translation given here is modified slightly from that of Dr. W. de Rouville in *Medical Classics.*

fruitless. The staining methods so frequently used with success for the demonstration of pathogenic microorganisms have left this disease in the lurch, and the attempts made to isolate and cultivate the virus of tuberculosis up to the present cannot be regarded as successful. . . .

"In my investigations of tuberculosis, I at first followed the known methods without obtaining any explanation as to the true nature of the disease. However, several opportune observations caused me to abandon these methods and to adopt others which finally led me to positive results. . . .

"The material to be examined is prepared in the usual manner for examining for pathogenic bacteria, and either spread on the cover slip, dried, and heated or cut into sections after fixation in alcohol. The cover slips or sections are placed in a staining solution of the following constitution: 200 c.c. of distilled water are mixed with 1 c.c. of a concentrated alcoholic solution of methylene blue, shaken up, and then 0.2 c.c. of a 10 percent solution of potassium hydroxide is added with repeated shaking. This mixture must show no precipitate after standing for several days. The materials to be stained remain in this solution for 20 to 24 hours. By heating the solution to 40° C in a water bath this time can be shortened to ½ to 1 hour. Following this the cover slips are covered with a concentrated aqueous solution of vesuvin, which is filtered each time before using, and after 1 to 2 minutes rinsed with distilled water. When the cover slips come from the methylene blue, the attached layer appears dark blue and is markedly overstained. During the treatment with vesuvin this blue color is lost and it appears stained a faint brown. Under the microscope all the constituents of animal tissue, that is, the cell nuclei and their products of disintegration, appear brown, while the tubercle bacilli, on the other hand, stain a beautiful blue. Moreover, all other bacteria which I have investigated to date, with the exception of the lepra bacilli [discovered by Hansen in 1875], take on a brown color with this staining method. The color contrast between the brown stained tissue and the blue tubercle bacilli is so striking that the latter, which are present often only in very small number, are nevertheless to be found and identified with the greatest certainty. . . ."

[Koch indicates the diseased tissue, both human and animal,

examined by him in his search for the bacilli. He studied not only a large number of cases of spontaneous tuberculosis, but also many animals infected by inoculation.]

"On the basis of my numerous observations I state it to be proved that the bacteria designated by me as the tubercle bacilli are present in all cases of tuberculous disease of man and animals, and that they may be differentiated from all other microorganisms by their characteristic properties. It does not necessarily follow from this coincidence of the tuberculous disease and the bacilli that the two phenomena have an original association. . . .

"In order to prove that tuberculosis is a parasitic disease caused by the invasion of the bacilli . . . the bacilli had to be isolated from the body and cultivated in pure culture . . . and, finally, through transfer of the isolated bacilli to animals, the same clinical picture of tuberculosis as is obtained by the injection of naturally developed tuberculosis material had to be produced.

"[The solution of the problem] depends on the use of a solid, transparent culture medium which retains its firm consistency at incubator temperature [a method previously introduced by Koch]. . . .

"Serum of cattle or sheep blood . . . is poured into cotton-stoppered test tubes and daily, for six consecutive days, is heated to a temperature of 58° C for an hour at a time. By this means it is possible to sterilize the serum completely in most instances. . . . Then it is heated to 65° C for several hours. . . .

"On this solidified blood serum, which forms a firm transparent culture medium at incubator temperature, the tuberculous material [excised from diseased organs with disinfected instruments] is placed . . . by means of a just previously flamed platinum wire fused into a glass rod. Naturally the cotton plug is removed for only the shortest possible time. . . .

"The test tubes . . . are placed in the incubator and must remain there constantly at a temperature from 37° to 38° C. . . . The cultures resulting from the growth of tubercle bacilli first appear to the naked eye in the second week after inoculation, usually not until after the tenth day, as very tiny points and dry scales. . . . The markedly slow growth which is attained only at incubator temperature, the peculiarly dry and scale-like condition of these

bacillary colonies occur in no other known type of bacteria, so that confusion of the cultures of tubercle bacilli with those of other bacteria is impossible; and after only a small amount of practice nothing is easier to detect at once than accidental contamination of the cultures. . . ."

[The pure cultures thus obtained were used by Koch in a series of animal inoculations, described in detail. The nature of the experiments and the results attained are indicated briefly in Koch's summation.]

"If one looks back over these experiments, it is apparent that a not inconsiderable number of experimental animals that had received the cultures of bacilli in various ways, that is, by simple inoculation into the subcutaneous tissue, through injection into the abdominal cavity, or into the anterior chamber of the eye or directly into the blood stream, had been rendered tuberculous without a single exception; and, indeed, had developed not only a solitary tubercle but an extraordinary number of tubercles proportionate to the large number of infectious germs introduced. In other animals it was possible by the injection of a minimal number of bacilli into the anterior chamber of the eye to produce a tuberculous iritis. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

Tuberculosis is a protean disease, which can affect a number of organs and show a number of different results. Nevertheless some clinicians, notably the great Laënnec, inventor of the stethoscope, had been able to draw upon clinical observations to combine all tubercular processes into a single morbid unity. Later, however, under the influence of Rudolf Virchow, this unity was destroyed and a dualistic conception of tuberculosis grew up on the basis of pathological findings. On March 24, 1882, Koch informed the Berlin Physiological Society that he had discovered the tubercle bacillus. Laënnec's views were thus confirmed and the work of Villemin and other experimenters verified; the dualistic doctrine vanished. Koch could demonstrate tubercle bacilli not only in the lungs but in other infected organs—intestines, bones, kidneys,

lymph glands, and skin. A variety of diseases were thus shown to be one and the same. Improvements in staining technique, introduced by Ehrlich and Ziehl, speeded up the detection of the organisms. Soon thousands of examinations were being made and the classification of these tubercular diseases became clear and certain. All were forms of tuberculosis. The clinical aspect of the disease, once complicated, was greatly simplified. "Chronic pneumonia," "apex catarrh," "apex pneumonia," etc., disappeared from the books.

In the tubercle bacillus doctors had a trustworthy diagnostic sign. Found in sputum or urine, it left no doubt of the diagnosis. Furthermore its presence or absence could be used to check on the effectiveness of treatment and on the patient's progress.

Isolation of the exciting cause of tuberculosis made it possible to study the nature and reactions of the responsible organism. All new therapeutic agents must be tried on the bacillus itself, *in vitro* (i.e., in a test tube) first, then *in vivo* (i.e., in the living body). At the present time a number of promising new agents are being investigated and there appears to be a strong likelihood that effective chemotherapeutic remedies will in course of time be found.

In 1890 Koch announced that he had found a substance that would check the growth of tubercle bacilli both *in vitro* and *in vivo*. This was tuberculin, a glycerine extract of a pure culture of tubercle bacilli; although it proved disappointing as a remedy, substances not unlike it have since been found of real value in diagnosis. It is also possible that the work on tuberculin, which attracted universal attention, may have served as a step toward the discovery of the antidiphtheria serum.

As shown in the quotation above, the tubercle bacillus is difficult to stain and difficult to cultivate on artificial media. It was Koch's great technical ingenuity that enabled him to devise a staining technique by which he could detect the bacillus and a culture technique by which he could grow it. Also worthy of note are the steps by which he proved it to be the causative factor in the disease. As a pioneer in staining, in the use of solid culture media, in sterilization by steam, and in many lesser technical matters, Koch was the principal founder of modern laboratory bacteriology in all its means and methods. He also imposed upon the growing science

certain rigid requirements, known as "Koch's postulates," by which to establish proof of a causative relationship between microbe and disease. Among his own discoveries of this kind, none was more important, or more productive of good results, than his discovery of the tubercle bacillus.

REFERENCES

HEYMANN, B. *Robert Koch.* Leipzig, 1932.
KIRCHNER, M. *Robert Koch.* Vienna, 1924.
LÖBEL, J. *Robert Koch: Geschichte eines Glücklichen.* Zurich, 1935.

1906

CAMILLO GOLGI

(1844–1926)

SANTIAGO RAMÓN Y CAJAL

(1852–1934)

"In recognition of their work on the structure of the nervous system."

BIOGRAPHICAL SKETCH

GOLGI

CAMILLO GOLGI WAS BORN IN CORTENO, IN BRESCIA, ITALY, IN 1844, the son of a medical practitioner. He received his medical training at the University of Padua, where he was graduated in 1865. During his postgraduate hospital course he was attracted to the Psychiatric Clinic of Cesare Lombroso, and his first publications were in the field of psychiatry. It was at this time, however, that Virchow's *Cellular Pathology* (1858) was exerting a great influence on medical scientists. Golgi began to work in the Pavian laboratory of Giulio Bizzozero, the histologist, where he conducted his first studies on the lymphatics of the brain and on the nature of the neuroglia. In 1872 circumstances forced him to take a post in the small hospital for incurables at Abbiategrasso, but despite disheartening conditions he carried on his researches and developed his famous silver-impregnation method of staining nervous tissues

(1873). He applied this method to the central nervous system, discovering the "Golgi cells" and providing evidence for the neuron theory. Meanwhile he had also done useful work in neuropathology. In 1879 he was appointed professor of anatomy at the University of Siena, but left the following year to return to Pavia as professor of histology and general pathology. He continued to conduct important studies in neuroanatomy, but much of his later work was in pathology. In a series of publications from 1886 to 1893 he established the cycle of development of the parasites of quartan and tertian malaria. He received many honorary degrees as well as other awards and was probably the best-known Italian medical scientist of his time. He died in 1926.

RAMÓN Y CAJAL

SANTIAGO RAMÓN Y CAJAL WAS BORN MAY 1, 1852, IN PETILLA, an isolated village in the Spanish Pyrenees, where his father was "surgeon of the second class." The elder Ramón later extended his studies and in time became professor of anatomy at Zaragoza. The son's unfortunate early schooling, under tyrannical teachers, failed to reveal his gifts. It was followed by apprenticeship, first to a barber, then to a shoemaker. His father then undertook to teach him, particularly in osteology, which revealed the boy's talent as a draftsman. Thereafter he studied medicine at Zaragoza and was graduated in 1873. Then came compulsory service in the Spanish army, chiefly in Cuba, until 1875; during this interval he suffered severely from malaria and dysentery. After taking a medical degree at Madrid, he became a demonstrator and then, in 1877, professor of anatomy at Zaragoza; but he was soon forced to interrupt his work because of pulmonary tuberculosis. He married in 1879 and in 1884 was called to the chair of anatomy at Valencia. For a time he worked at bacteriology and serology, but turned to his proper field, histology, and in 1887 was given a chair in that subject at Barcelona. Learning of the Golgi silver stain from Luis Simarra, a neuropsychiatrist of Madrid, Ramón y Cajal developed an improvement of his own which he began to use in the study of the nervous system. This was the first of his several important innovations in staining technique. In 1889 he demonstrated his work

before the German Society of Anatomists, was praised by Kölliker, and was soon acclaimed by German histologists generally. In 1892 he was appointed professor of normal histology and pathologic anatomy at Madrid. International honors now accumulated. There followed many years of intensive labor. By 1923 he had already published 237 scientific papers. He also wrote a large number of books, including not only comprehensive works on the nervous system but popular essays, a treatise on color photography, etc. He died on October 18, 1934, at the age of eighty-two.

DESCRIPTIONS OF THE PRIZE-WINNING WORK

GOLGI *

"I have found two quite different kinds of nerve-endings in the tendons:

"(*a*) The one is represented by peculiar bodies which are quite characteristic in appearance, form, structure, and type of connection with the nerve fibrils, and are unlike any other in the known nervous end-apparatus of our organism; it is very probable, then, that their significance lies in correspondence with the function which muscles and tendons have to perform in common. Since they are at times associated with muscles, at times with tendons, one must, I think, confer on them the name of nervous musculotendinous end-organs.

"(*b*) The other type is represented by bodies which likewise have a peculiar and striking appearance, but which, on the whole . . . find their counterparts in other known nervous end-organs of our bodies, which they resemble not only in anatomical structure but probably in function also. I want to remark at once that I here refer to the so-called end-bulbs of the conjunctiva, the glands, etc.

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* Translated from Camillo Golgi, "Über die Nerven der Sehnen des Menschen und anderer Wirbelthiere und über ein neues nervöses musculo-tendinöses Endorgan," *Untersuchungen über den feineren Bau des centralen und peripherischen Nervensystems* . . . übersetzt von Dr. R. Teuscher (Jena: G. Fischer, 1894), pp. 207-209.

"Just as these two kinds of end-organs are distinguished one from another by form, structure and nerve-fibril connections, so, too, do they differ from one another in their location. The first are always found in deep layers of the tendon origins, at the transition point where muscle becomes tendon; always, too, in relation to the muscular fasciculi. The second, on the contrary, lie as a rule in the superficial layers of the tendons or in the tendinous extensions.

". . . [The] principal anatomical characteristics [of the musculo-tendinous organs] may be summed up briefly as follows:

"In general they are spindle-shaped, and one of their ends is always connected with the fasciculi of the muscle fibers, with the sarcolemma [or sheath] of which their stroma [framework] appears to be in direct union; the other end, occasionally single but usually double, follows the course of the tendon fasciculi and gradually blends with them over a considerable distance.

"Their size varies within fairly wide limits, from 70-80 μ in breadth [μ is short for micron, the millionth of a meter or thousandth of a millimeter] and 300-400 μ in length to 100-120 μ in breadth and over 800 μ in length; the latter, especially if stained with gold, can easily be distinguished and isolated with the help of a simple lens.

"Their outline tends to be very distinct and even appears at times in the form of a slender, glittering border, along which one catches sight of nuclei. . . .

"As far as the structure is concerned, if one disregards the medullated nerve fibers, which penetrate from without in varying number, one must believe them to consist simply of fibrillary connective tissue with nuclei scattered through it. . . .

"The nature of the connection of the little bodies described here with the nerve fibrils is characteristic.

"For the most part there is only one fibril allotted to each of these little bodies, but fairly often two, three, and even four medullated fibrils enter a single one. Entry can take place either at one end, regularly at that which blends with the tendon fasciculi, or also at the side, and indeed precisely at the thickest part of the spindle.

"However large the number of fibrils entering, they proceed to separate, in that they advance to the middle of the body and each

fibril of the second or third order, while retaining the character of a medullated fibril, diverges from the others and turns toward the periphery. . . . All this can be perceived with the simplest means of observation. . . . The further, ultimate conduct of the separate fibrils can only be made clear by the gold reaction. With this method one can now make the following observations.

"After the medullated fibrils have changed to nonmedullated, these bifurcating branches diverge helter-skelter and pursue their further course to the periphery of the body. Having reached it, they form at short intervals, by means of still finer and more frequent divisions, numerous circumscribed, longish, reticular plexuses, which lie parallel with the surface. . . ."

RAMÓN Y CAJAL *

"From the sum of my researches springs a general concept which comprehends the following propositions:

"The nerve cells are morphologic units, the neurons, to use the word sanctioned by the authority of Professor Waldeyer. This had already been demonstrated, as regards the dendritic or protoplasmic extensions of the nerve cells, by my illustrious colleague Professor Golgi; but when our researches began there were only conjectures more or less tenable regarding the way in which the ultimate divisions of the axons and nerve collaterals are arranged. Our observations, with Golgi's method, which we applied first in the cerebellum, then in the spinal marrow, the brain, the olfactory bulb, the optic lobe, the retina, etc. of embryos and young animals, revealed, in my opinion, the terminal disposition of the nerve fibers. These, in their ramifications to several junctures, incline constantly toward the neuronal body and toward the protoplasmic expansions, around which arise plexuses, or nerve nests, very close-woven and very rich. The . . . morphologic dispositions, which vary in form according to the nerve centers one studies, attest that the nerve elements have reciprocal relations of *contiguity* and not of *continuity,* and that communications, more or less intimate, are always established not only between the nervous arborizations but between the

* Translated from Santiago Ramón y Cajal, "Structure et Connexions des Neurones," *Les Prix Nobel en 1906.*

ramifications of one part and the body and protoplasmic extensions of another part. . . .

"These facts, recognized in all the nerve centers with the aid of two very different methods (Golgi's and Ehrlich's) . . . involve three physiological postulates:

"(1) Since nature, in order to assure and amplify contacts, has created complicated systems of ramifications around the cells (systems which would become incomprehensible by the hypothesis of continuity), it is necessary to admit that the nervous currents are transmitted from one element to another by virtue of a sort of induction, or influence at a distance.

"(2) It is also necessary to suppose that the cellular bodies and the dendritic prolongations, like the axis cylinders, are induction apparatus, since they represent intermediate links between the afferent nerve fibers and the axons mentioned. This is what Bethe, Simarro, Donaggio, we ourselves, etc., have confirmed quite recently, in demonstrating, with the aid of neurofibrillary methods, a perfect structural concordance between the dendrites and the axis-cylinder prolongation.

"(3) Examination of the transmission of nerve impulses in the sense organs, such as the retina, the olfactory bulb, the sensory ganglions and the spinal marrow, etc., show not only that the protoplasmic expansions play a conducting role but also that the movement of the nerve impulse in these prolongations is *toward the cell body,* whereas in the axons it is *away from the cell body.* This principle, called *the dynamic polarization of neurons,* formulated a long time ago by van Gehuchten and us as an induction drawn from numerous morphological facts, is not contrary to the new researches on the constitution of nerve protoplasm. In fact we shall see that the framework of neurofibrils makes up a continuous reticulum from the dendrites and the cell body to the axon and its peripheral termination."

CONSEQUENCES IN THEORY AND PRACTICE

The investigations of Golgi and Ramón y Cajal were to a large extent complementary, although on many points they disagreed.

(Golgi's Nobel lecture was largely a series of qualifications of the neuron theory as set forth above by his Spanish colleague.) Ramón y Cajal began his work on the nervous system using the Golgi stain. Between the two men, they worked out the finer details of the structure of nervous tissue in a thorough and comprehensive manner.

In 1873, using his new method, Golgi gave his description of the two main types of nerve cells, since known as Golgi cells type I and type II, the long and short axon nerve cells respectively. In 1874 he described the large nerve cells of the granular layer of the cerebellum, which are also known by his name. He likewise described the structure of the olfactory bulb. His name is attached to the internal reticular apparatus of cells, the nature and function of which have not been fully determined even yet. In addition to this he discovered the muscle spindles which are described in the quotation above. This passage has been selected as a characteristic and important piece of work, and also because knowledge of the receptor organs in muscle was the starting point for a valuable contribution to neurophysiology made by Sir Charles Sherrington (see below, pp. 156 ff; 162).

The discoveries in normal histology mentioned here are only the best known among a large number. Golgi also contributed to the knowledge of nerve pathology. He was able to show, for example, that the disease called chorea is not due to a mere functional disturbance but is associated with definite lesions in the nervous system. It was Golgi, too, who pointed out the microscopic characteristics which distinguish sarcomas from gliomas, two kinds of brain tumor which previously were often confused; this was of practical importance, for gliomas, although "malignant" from their location, do not metastasize (i.e., establish cellular colonies in other parts), as do the more dangerous sarcomas. Here again, it is possible only to single out one or two among Golgi's major contributions to neuropathology. His work on the structure of the kidney and other organs and his important studies of malaria parasites fall outside the limits of the Nobel citation.

The quotation from Ramón y Cajal has been selected as the latter's attempt at a general summation of an important part of his work. The neuron theory, here presented in a condensed form, was

firmly established by his researches. Its importance to subsequent investigators can hardly be assessed in a few words. It underlies the exceedingly important work of Sir Charles Sherrington. It guided the thought of Egas Moniz, who introduced prefrontal leucotomy (see below, pp. 264-270). It is one of the basic theories of modern biological science.

Ramón y Cajal's contributions are also too numerous and too complex for summary treatment. As he himself said, "Unfortunately it is absolutely impossible to condense in a few pages morphological facts the description of which occupies a large number of brochures with hundreds of drawings." It may be mentioned, however, that another Nobel laureate, Robert Bárány (see below, pp. 84-88), in attempting to connect the function of the labyrinth apparatus of the ear with cerebellar function, was initially dependent on the Spanish histologist's account of the nerve connections involved. It is safe to say that there is no neurologist or neuroanatomist of recent times who does not owe him a similar debt.

"Even more lasting than his wealth of recorded observations will be the improved methods of Cajal and his disciples. First, in 1888, he increased the applicability of the Golgi stain. In 1903 he developed his own reduced silver nitrate stain. . . . In 1913 he introduced the gold sublimate stain. . . . His eminent pupils Achucarro and Hortega [introduced] the silver carbonate stains. . . .

"These methods in the hands of Cajal and his students have clarified much of the embryology of each cellular element in the nervous system. Furthermore, the finer details of gliomas revealed by these stains, with the accumulating light from embryology, have given the neurosurgeon useful correlations of structure and biologic characteristics of brain tumors." *

* Wilbur Sprong, "Santiago Ramón y Cajal: 1852-1934," *Archives of Neurology and Psychiatry,* Vol. 33 (1935), pp. 156-162.

REFERENCES

GOLGI

CHOROBSKI, JERZY. "Camillo Golgi: 1843-1926," *Archives of Neurology and Psychiatry,* Vol. 33 (1935), pp. 163-170.

DA FANO, C. "Camillo Golgi," *Journal of Pathology and Bacteriology,* Vol. 29 (1926), pp. 500-514.

RAMÓN Y CAJAL

CANNON, DOROTHY F. *Explorer of the Human Brain: The Life of Santiago Ramón y Cajal (1852-1934)* (New York: Schuman, 1949).

RAMÓN Y CAJAL, SANTIAGO. *Recollections of My Life,* translated by E. Horne Craigie and Juan Cano (Philadelphia: American Philosophical Society, 1937), 2 vols.

SPRONG, WILBUR. "Santiago Ramón y Cajal: 1852-1934," *Archives of Neurology and Psychiatry,* Vol. 33 (1935), pp. 156-162.

1907

CHARLES LOUIS ALPHONSE LAVERAN

(1845–1922)

"In recognition of his work regarding the role played by protozoa in causing diseases."

BIOGRAPHICAL SKETCH

ALPHONSE LAVERAN WAS BORN IN PARIS ON JUNE 18, 1845. HIS father, a military surgeon, was a professor at the school of Val-de-Grâce. Having completed his preliminary education in Paris, Laveran matriculated as a medical student at Strasbourg, where he was graduated in 1867 with a thesis on regeneration of nerves. In 1874 he, too, joined the staff of the Val-de-Grâce School of Military Medicine. In 1878 he was sent to Algeria, where he remained, in the service of the French army, until 1883. During this period, while at Bône and at Constantine, he carried out his studies of malaria, which led to the discovery of the causative organism, the malarial parasite. In 1884 he was appointed professor of military hygiene and clinical medicine at Val-de-Grâce, where he remained for ten years. For a short time he was engaged in administrative medical and sanitary work at Lille and at Nantes, but with a view to resuming his scientific studies he retired from his administrative position in 1897. He then entered the Pasteur Institute. Here he soon became a professor, and devoted the rest of his life to a continuation of his work in tropical medicine and parasitology. The

recipient of many scientific honors, he was one of the founders, and first president, of the Société de Pathologie Exotique. His work was terminated only by his death, which took place in Paris on May 18, 1922.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"On arriving at Bona in 1878 I had the opportunity of making autopsies on subjects who had died from pernicious attacks, and I was struck with the fact that melanaemia [the presence of a black pigment in the blood, causing a brown coloration of certain organs] was a lesion peculiar to and very characteristic of paludism [i.e., malaria, or marsh fever, from the Latin *palus,* marsh]; my attention was naturally directed to this lesion, which I had never met in any other disease. [Although often described in connection with malaria before this time, the color change here mentioned had not generally been considered either as constant, or as peculiar to the disease.]

"Melanaemia is specially very pronounced in individuals who died from acute paludism (pernicious attacks); the colour which it gives to certain organs, particularly to the spleen, the liver, and the grey substance of the brain, is almost always sufficient to show from microscopic examination if death is the result of paludism. . . .

"Some observers have been able to maintain that occasionally no single characteristic alteration was found in individuals who had died of pernicious fever.

"This assertion does not stand a strict examination, and could only be put forward at a time when the importance of melanaemia was not known. It might be affirmed on the contrary, that in these cases there always remain lesions specially pronounced in the spleen and liver. The spleen increases in volume and weight, but the increase is not always considerable. . . . The shape of the organ is modified, the edges are rounded; the spleen tends to take a globular form, which is explained by the softening, the pulpiness of the

* From Alphonse Laveran, *Paludism,* translated by J. W. Martin (London: New Sydenham Society, 1893), pp. 5-9.

splenic parenchyma [the specific substance of the spleen, supported and held together by fibrous elements]. It often happens that the mere act of grasping the spleen to pull it out from the abdomen causes rupture of the distended and thin capsule; the fingers sink into splenic pulp.

"The colour is characteristic; instead of the normal red colour the spleen shows in the inner parts, as well as on the surface, a brownish tint which has been compared to chocolate and water.

"If you examine a drop of splenic fluid with the microscope you will find in the midst of the blood, and the elements proper to the spleen which are separated, the existence of pigmented elements in great numbers, and free granules of pigment; the pigmented elements are either leucocytes [white blood cells] loaded with pigment [i.e., "melaniferous," the term used hereafter], or hyaline bodies of irregular shape: one finds in those preparations of the spleen pigmented granules much more numerous than in blood taken from the vessels of other organs. . . .

"[Similar changes are then described as they are seen in liver, kidney, and brain tissue.] The other tissues have a normal tint, but by histological sections it is easy to see that the capillary vessels contain pigmented elements more or less numerous, and that melanaemia is really, as the etymology implies, a general alteration of the blood, which is only more pronounced in the spleen, in the medulla of bones, and the liver than in the other viscera, which is naturally all the more apparent as the tissues are more vascular.

"When one examines a drop of blood taken from the dead body of a palustral subject in the ordinary conditions of autopsy—that is to say, twenty-four hours after death—one sees in the midst of the blood numerous pigmented bodies. Many of these elements are melaniferous leucocytes, the nuclei of which can be coloured and stained with carmine; but besides these leucocytes, hyaline pigmented irregular bodies are seen, which can only be coloured slightly, or not at all, by carmine, and which do not contain any nuclei. These latter elements have great analogy in their dimensions, and often in their shape, with melaniferous leucocytes, and it can easily be understood that they may have been confused with them. If the blood is taken shortly after death the parasitic elements characteristic of paludism can be recognised.

"In 1880, as I was trying to account for the mode of formation of the pigment in the palustral blood, I was led to see that besides melaniferous leucocytes, spherical hyaline corpuscles without nucleus could be seen, and also very characteristic crescent-shaped bodies.

"I had proceeded thus far with my researches, and was still hesitating whether these elements were parasites, when on November 6th, 1880, on examining the pigmented spherical bodies mentioned above, I observed, on the edge of several of these elements, moveable filaments or flagella [literally, "whips"], whose extremely rapid and varied movements left no doubt as to their nature.

"I published in 1881 the observation of the patient in whose blood I saw the flagella for the first time. . . .

"The very fact that I can quote the day on which I observed the flagella for the first time shows how characteristic these elements are. It was natural to suppose that these parasitic elements, for the most part pigmented, were the cause of palustral melanaemia, and also the cause of the phenomena of paludism. Numerous facts soon came to confirm this hypothesis."

CONSEQUENCES IN THEORY AND PRACTICE

The citation for the Nobel Prize in 1907 refers to the sum of Laveran's work "regarding the role played by protozoa in causing diseases." (The protozoa include all the unicellular animal organisms. Literally the word means "first animals.") Since the terms which govern the award require that it be given for recent work, or for work recently seen to be of importance, it is probable that this phrasing was chosen to comply with the rule by including Laveran's later studies; nevertheless it was in fact the reward for his quarter-century-old discovery of the malarial parasite. It is, of course, quite true that this discovery, the first of the kind, stimulated interest in protozoal disease agents, and that although Laveran himself made no other such epochal discoveries he did open the field to other workers and he also made solid contributions of his own toward extending our knowledge of similar organisms. Dur-

ing his years at the Pasteur Institute he collaborated with Professor Mesnil, and together they published an important work on trypanosomes and trypanosomiasis. (G. H. Evans and D. Bruce were chiefly responsible for showing that trypanosomes cause sleeping sickness.) Laveran likewise published the first treatise on leishmaniasis (leishmania are protozoans which cause kala-azar, oriental boil, etc.) and investigated many of the flagellate parasites of man and animals.

Laveran's discovery of the malarial parasite did not receive immediate recognition from all authorities, but his findings were soon confirmed and extended by others, and his own pathological, clinical, geographical, and therapeutic studies all tended to establish the role of the organisms he had discovered, which later came to be known as plasmodia. Their presence in the blood of malaria patients, their disappearance after treatment with quinine, their absence in healthy persons, and their association with the characteristic malaria pigment made it highly probable that they were indeed the long-sought causative organisms of malaria. This could not be readily demonstrated, as in bacterial diseases, according to "Koch's postulates" (see above, p. 28), because in contrast with bacteria the plasmodia could not be cultivated outside the living body. But further evidence, strongly supporting Laveran's view, was provided by another Nobel laureate, Camillo Golgi (see above, pp. 33, 38), who showed that some plasmodia require forty-eight hours to develop to the stage when the red blood cells are broken down and the parasites are released, that others need seventy-two hours, and that these periods correspond exactly to the afebrile intervals of tertian and quartan fever. The different types of plasmodia and the stages in the plasmodial life cycle were worked out by Italian, American, and English scientists. These workers, including the early Nobel laureate Sir Ronald Ross, built upon the foundations laid by Laveran. The practical significance of knowing what the causative organism is (Laveran) and how it spreads (Ross) has been briefly discussed in an earlier section (see above, pp. 13-14).

1908

ELIE METCHNIKOFF

(1845–1916)

"In recognition of his work on immunity."
(*The award for 1908 was shared with Paul Ehrlich, see below, pp. 51-55.*)

BIOGRAPHICAL SKETCH

ILIA ILICH MECHNIKOV, BETTER KNOWN AS ELIE METCHNIKOFF, son of an officer of the Imperial Guard, was born in the province of Kharkov, Little Russia, on May 16, 1845. Privately tutored at first, he later entered the *lycée* at Kharkov, where his scientific interests, already formed, were stimulated in the direction of physiology and zoology. He found little to satisfy such interests at the University of Kharkov, but after graduation did independent and original work in Helgoland and at Giessen. He was then given a scholarship by the Russian Ministry of Public Instruction, which enabled him to travel and study abroad. He worked for a time at Naples, in association with the young Kovalevsky, then at Göttingen, where he spent a short interlude with Keferstein and Henle. At Munich his preceptor was von Siebold. In 1867 he returned to Russia to become docent at the new University of Odessa. He soon shifted to St. Petersburg as professor of zoology, but worked at intervals in Messina and elsewhere. In 1886 he became director of the Bacteriological Institute in Odessa, but left in 1887 and went to Paris, where he resided till the end of his life. He carried on his work at the Pasteur Institute, of which he became subdirector. His

first paper on phagocytosis was read at a congress in Odessa in 1883; the initial observations and experiments had been made at Messina earlier in the same year.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"Occupied with the origin of the digestive organs in the animal world, we were struck by the fact that certain elements of the organism which do not take any part in the digestion of food are nevertheless capable of engrossing foreign bodies. To us it appeared that the reason for this was that these elements formerly participated in the digestive function. . . .

"Certain lower animals, transparent enough to be observed in the living state, show clearly in their interior a host of little cells provided with mobile extensions. The least lesion of these animals brings an accumulation of these elements right to the spot which has been injured. In the little transparent larvae, one can easily ascertain that the mobile cellules, gathered at the point of injury, often contain the debris of foreign bodies.

"Similar facts, on the one hand tending to confirm our supposition of the origin of the migratory elements, on the other hand suggested the idea that their accumulation in the neighborhood of lesions constitutes a sort of natural defense of the organism. It was necessary to find some method of verifying this hypothesis. Finding myself at this time—more than twenty-five years ago—at Messina, I turned my attention to the floating larvae of starfish. . . . Large enough to undergo some operations, they are, however, sufficiently transparent and can be observed under the microscope in the living state.

"Having introduced pointed splinters into the bodies of these [larvae], I was able next day to see a mass of mobile cellules enclosing the foreign body, forming a thick layer. The analogy of this phenomenon with that which takes place when a man pricks himself with a splinter, bringing on inflammation accompanied by suppuration, is astonishing. Only in the starfish larva, the accumu-

* Elie Metchnikoff, "Sur l'état actuel de la question de l'immunité dans les maladiés infectieuses," *Les Prix Nobel en 1908.*

lation of mobile cellules around the foreign body takes place without the least concurrence of blood vessels or nervous system, for the simple reason that these animals possess neither the one nor the other. So it is thanks to a sort of spontaneous action that the cellules are gathered round the splinter.

"The experiment which I have just presented to you shows the first step, so to speak, of an inflammation in the animal world. But . . . in men and the higher animals, this phenomenon is almost always the result of the intervention of some pathogenic microbe. . . .

"It was therefore necessary . . . to find some higher animal sufficiently small and transparent to be observed alive by the microscope and . . . to subject to some microbe disease.

"After several attempts in this direction, it became possible to study the progress of an infection among the fresh-water animals commonly known as "water fleas." These little crustaceans are very widespread in all sorts of stagnant waters and are subject to several diseases. One of these is occasioned by a little microbe which has the peculiarity of producing spores in the form of needles. Swallowed by the water flea . . . these spores easily wound the intestinal wall and penetrate into the body cavity. But once they have stolen into the organism, the spores provoke around them an accumulation of mobile cellules which correspond to human white blood corpuscles. A struggle occurs between the two kinds of elements. Sometimes the spore succeeds in germinating. A generation of microbes is then produced which secrete a substance capable of dissolving the mobile cellules; but these instances are rather rare. Much more frequent, on the contrary, are the cases in which the mobile cellules kill and digest the infectious spores, thus assuring the immunity of the organism. . . .

"Having established the basis of the theory of immunity, it was necessary to apply it to higher organisms and to man himself. The conditions here being incomparably more complicated than among the little transparent animals, all sorts of difficulties sprang up on every side. Because of the impossibility of submitting even the smallest vertebrate animal, such as a newborn mouse, to direct microscopic examination, it was necessary to proceed by a more complicated route, combining the results of researches on the blood

and on organs removed from the organism, and linking them by thought. Now under these circumstances the door is wide open to all sorts of errors.

"The study of several infectious diseases of man and the higher animals has shown from the first that the facts observed accord well with the theory based on the research on transparent lower animals. In all cases where the organism enjoys an immunity, the introduction of infectious microbes is followed by an accumulation of mobile cellules, white blood corpuscles in particular, which incorporate the microbes and destroy them. The white corpuscles and the other cellules capable of bringing about this result have been designated 'phagocytes'—that is to say, voracious cellules [i.e., eating cells]—and the sum of the function which assures immunity 'phagocytosis.' "

CONSEQUENCES IN THEORY AND PRACTICE

Metchnikoff's theory that bacteria are destroyed by "eating cells," or phagocytes, at first met with strong opposition. The view was then current that resistance to bacterial infection depends upon chemical properties of the blood, and indeed antibodies had already been demonstrated in blood serum. A long controversy ensued, in which, as it now appears, both sides were partly right. In 1903 two British scientists, Almroth Wright and Stewart Douglas, found that the serum of immunized animals contains substances which appear to prepare bacteria for ingestion by the white blood cells; these substances were named "opsonins," from the Greek verb meaning "to prepare food." The opinion then grew up that phagocytosis can take place only when the microbes have first been "buttered," as it were, with specific antibodies. The phagocytes were thus restricted to a secondary role.

In the last ten years, however, the Metchnikoff theory has been partly rehabilitated, and the functions of antibodies and phagocytes have been distinguished more clearly. Most bacteria that cause acute infections injure the human body only when they are *outside* of cells; the bacteria that cause chronic infections, on the other hand, do damage *within* the cells. The former are readily engulfed and

digested, except when they have outer capsules which protect them from phagocytes; the latter, although readily ingested by phagocytes, can go on living inside. Phagocytosis as a defense mechanism is therefore of much greater importance in acute than in chronic diseases. When the bacteria of the acute diseases are well protected by a capsule, this armor may be broken down by the appropriate antibody. But patients treated with "sulfa" drugs and other antibiotics often recover several days before antibodies can be detected in the blood. The drug slows the multiplication of the bacteria, and phagocytes may then destroy them without the aid of antibodies, provided there is a suitable surface upon which to operate. In lung tissue, for example, the white cells pin the bacteria against the walls of the alveoli (air sacs) and then ingest them. The strands of fibrin, which are a common feature of the inflammatory reaction, also provide suitable surfaces for promoting phagocytosis; or the bacteria may sometimes be trapped against the walls of small blood vessels. The proportion of fluid to phagocytic cells during infection limits the efficacy of this process, for phagocytes diluted in fluid are unable to engulf fully encapsulated bacteria. In the peritoneal cavity of the abdomen, and in other "open" sites, phagocytosis is relatively inefficient, since the white cells do not have sufficient contact with one another and with tissue surfaces.

In the intracellular infections, caused by viruses, some bacteria, and certain protozoa, phagocytosis is not of primary importance, because the parasites can survive and even multiply inside the white cells. But in a great many acute infections, caused by extracellular parasites, the invaders may be slowed down by drugs and destroyed by phagocytes before the relatively slow process of the manufacture of antibodies has taken place. Phagocytosis is thus the first line of defense in acute infections.

This summarizes the current view of the importance of Metchnikoff's phagocytes and of the way in which they operate. The activities of the white cells continue to be investigated, however, for there is much which yet remains mysterious about the body's reaction to invading microorganisms.

REFERENCES

METCHNIKOFF, OLGA. *The Life of Elie Metchnikoff, 1845-1916* (London: Constable; Boston and New York: Houghton Mifflin, 1921).
PETRIE, G. F. "The Scientific Work of Elie Metchnikoff," *Nature* (London), Vol. 149 (1942), p. 149.
WOOD, W. BARRY, JR. "White Blood Cells v. Bacteria," *Scientific American,* Vol. 184 (Feb. 1951), pp. 48-52.

PAUL EHRLICH

(1854–1915)

"In recognition of his work on immunity."
(The award for 1908 was shared with Elie Metchnikoff; see above, pp. 46-51.)

BIOGRAPHICAL SKETCH

PAUL EHRLICH WAS BORN AT STREHLEN, A SMALL TOWN IN Silesia, in 1854. He received his early education in his native town and at the *Gymnasium* at Breslau. He also spent his first university semester at Breslau, studying scientific subjects, and then proceeded to Strasbourg, where he took up the study of medicine. While still an undergraduate he attracted the attention of Waldeyer by his application of aniline dyes in histology. After graduation he worked for a year in the Pathological Institute under Cohnheim and Heidenhain. In 1877 he was appointed chief assistant in Frerichs's clinic in Berlin. In 1886 he found that he had contracted tuberculosis, apparently as a result of accidental infection in the course of his researches, and was forced to give up his work for

a year and a half, which he spent in traveling abroad. Returning to Berlin, he worked for a time in a small private laboratory, then obtained a post in the Institute for Infectious Diseases, which he held for several years. When the new Serum Institute at Steglitz was opened, in 1896, Ehrlich was appointed director. From 1899 until his death in 1915 he was director of the Royal Institute for Experimental Therapy in Frankfurt am Main. He was raised to the dignity of Privy Councilor with the title "Excellenz" in 1911. It is convenient to divide Ehrlich's work, as W. Bulloch does, into three parts: (1) the application of stains to the differentiation of cells and tissues for the purpose of revealing their function (1877-1890); (2) immunity studies (1890-1900); (3) chemotherapeutic discoveries (1907-1915). He was the founder of modern hematology, one of the chief early contributors to immunology, and, by virtue of the discovery of "606," the founder of chemotherapy.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"At the very beginning of my theoretical work on immunity I made it my first task to introduce measures and figures into investigations regarding the relations existing between toxine and antitoxine. From the outset it was clear that the difficulties to be overcome were extremely great. The toxines, i.e., the poisonous products of bacteria, are unknown in a pure condition. So great is their potency, that we are obliged to assume that the strongest solid poisons which are obtained by precipitating toxic bouillon with ammonium sulphate, represent nothing more than indifferent materials, peptones and the like, to which the specific toxine attaches itself in mere traces beyond the reach of weighing. . . .

"Their presence is only betrayed by the proof of their specific toxicity on the organism. For the exact determination, e.g., of the amount of toxine contained in a culture fluid, the essential condition was that the research animals used should exhibit the requisite uniformity in their susceptibility to the poison. Uniformity is not

* From Paul Ehrlich, "On Immunity with Special Reference to Cell Life," *Proceedings of the Royal Society of London,* Vol. 66 (1900), pp. 424-448.

to be observed in the reaction of the animal body to all toxines. Fortunately in the case of one important body of this nature, viz., the diphtheria toxine, the conditions are such that the guinea-pig affords for investigations the degree of accuracy necessary in purely chemical work. For other toxines this accuracy in measuring the toxicity cannot be attained. It was necessary for me to try to eliminate, as far as possible, the varying factor of the animal body, and bring the investigations more nearly into line with the conditions necessary for experiments of a chemical nature. . . . The relations were simplest in the case of red blood corpuscles. On them, outside the body, the action of many blood poisons, and of their antitoxines, can be most accurately studied, e.g., the actions of ricin, eel-serum, snake-poison, tetanus toxine, etc. In an experiment of this kind, in which are employed a series of test-tubes containing definite quantities of suspended blood corpuscles, each test-tube represents as it were a research animal, uniform in any one series, and one that can be reproduced at will. By means of these test-tube experiments, particularly in the case of ricin, I was able, in the first place, to determine that they yielded an exact quantitative representation of the course of the processes in the living body. The demonstration of this fact formed the basis of a more extended application of experiments of this nature. It was shown that the action of toxine and antitoxine took place quantitatively as in the animal body. Further, these experiments yielded a striking series of facts of importance for the theoretical valuation of the reaction between toxine and antitoxine. It was proved in the case of certain toxines—notably tetanus toxine—that the action of antitoxines is accentuated or diminished under the influence of the same factors which bring about similar modifications in chemical processes—warmth accelerates, cold retards the reaction, and this proceeds more rapidly in concentrated than in dilute solutions. . . . Yet again insurmountable obstacles seemed to present themselves. . . .

"When, in the case of diphtheria toxines of different stocks, that quantity of toxine bouillon which is exactly neutralized by a certain definite quantity of diphtheria antitoxine (the official German immunity unit . . .) was determined, so that every trace of toxic action was abolished, the figures obtained were not in accord. Of

one toxine bouillon 0.2 c.c., of another 2.5 c.c., were so neutralised by one immunity unit. Such a relation need not have given rise to surprise, because it was well known that the diphtheria bacillus, according to outside circumstances, yields in the bouillon very different quantities of toxine. It was therefore allowable to infer that the different quantities of toxine bouillon, which were saturated by one immunity unit, were exact expressions of the toxicities of the various bouillons, or, to use other words, indifferently whether the bouillon was strongly or feebly toxic, the same multiple of the minimal lethal dose would be constantly neutralised by one immunity unit, so that in every case the law of equivalent proportions would hold good.

"But when looked into more closely, the relations showed themselves to be by no means so simple. In what manner could one obtain a satisfactory estimation of the strength of a toxine? As the constant factor in such an estimation, it was only possible to proceed from a previously determined standard reaction in the case of a definite species of animal, and so we came to regard as the 'toxic unit' that quantity of toxic bouillon which exactly sufficed to kill, in the course of four days, a guinea-pig of 250 grammes weight.

"When we employed this standard unit, or 'simple lethal dose,' to estimate the amount of toxic bouillon neutralised by one 'immunity unit,' the facts which presented themselves were far more surprising than it was possible to have foreseen at the outset. These results were, that of one toxine, perhaps 20, of a second, perhaps 50, and of yet a third, it might be 130 simple lethal doses were saturated by one immunity unit. Since, however, we had previously assumed that the simple lethal dose alone afforded a standard on which reliance could be placed in determining the combining relations of toxine and antitoxine, it appeared from these results that the neutralisation of toxines by antitoxines did not follow the law of equivalent proportions, and, notwithstanding all earlier work in agreement with such a conception of the action, we were obliged to conclude that between toxine and antitoxine a purely chemical affinity did not exist. The seemingly inexplicable contradiction between the results just stated and previous work was very soon explained. When the neutralisation point of toxine and antitoxine was investigated for one and the same sample of poison, the fol-

lowing results were obtained. Immediately on its preparation, fresh from the incubator, it was found that one immunity unit neutralised α c.c. of toxic bouillon, and this quantity represented β simple lethal doses. When the same toxic bouillon was examined after a considerable interval, the remarkable fact was discovered that exactly α c.c. of the toxic bouillon were again neutralised by one immunity unit; but that these α c.c. now represented only $\beta - x$ simple lethal doses. It therefore followed that the toxic bouillon had retained exactly the same combining affinity but possessed feebler toxicity. From this it was evident that the toxic action on animals and the combining capacity with antitoxine represented two different functions of the toxine, and that the former of these had become weakened, while the latter had remained constant."

CONSEQUENCES IN THEORY AND PRACTICE

This is not the place to discuss the importance of Ehrlich's studies on the staining of bacteria, nor his related studies of animal cells, especially blood cells, nor his work in chemotherapy. Like these studies, his investigations in immunology, for which the Prize was awarded, were of basic importance. By the researches described above he established the principles of the standardization of bacterial toxins and antitoxins. The practical methods still in use are essentially the same as his. The first disease to which this contribution applied was diphtheria: an exact gradation of the efficacy of antidiphtheritic serum was achieved. In this regard the conception outlined in the last paragraph above is a fundamental one—that the lethal action of a toxin and its antitoxin-combining power are two separate functions. In his work with the vegetable poison known as ricin, Ehrlich discovered that a latent period exists between the injection of the stimulating "antigen" and the production, as a protective response, of the specific "antibody." He also studied the serum fluctuations in the course of the development of antibodies. Moreover, he investigated the transmission of immunity, which is not truly hereditary, through the placenta and the milk. In the course of this study he was able to distinguish between active immunity, a more or less lasting condition due to the active

manufacture of antibodies in response to antigens, and passive immunity, a transient state due to the transmission of antibodies in the ways already mentioned or by the injection of a ready-made antitoxin. When Bordet's work on hemolysis appeared (see below, pp. 90-95) it was taken up, confirmed, and extended by Ehrlich and Morgenroth, who introduced the terms "complement" and "amboceptor."

This is no more than an indication of the main headings for an appreciation of Ehrlich's work in immunology.

REFERENCES

BULLOCH, WILLIAM. *The History of Bacteriology* (London: Oxford University Press, 1938).

MARQUARDT, MARTHA. *Paul Ehrlich* (New York: Schuman, 1951).

MUIR, R. "Paul Ehrlich," *Journal of Pathology and Bacteriology,* Vol. 20 (1915-1916), pp. 350-360.

Paul Ehrlich: Eine Darstellung Seines Wissenschaftlichen Wirkens (Jena: G. Fisher, 1914). Essays on Ehrlich's achievements in science by thirty-seven contributors.

1909

THEODOR KOCHER

(1841–1917)

"For his work on the physiology, pathology, and surgery of the thyroid gland."

BIOGRAPHICAL SKETCH

THEODOR KOCHER WAS BORN ON AUGUST 25, 1841, IN BERNE, Switzerland. He was educated in his native city, and after his graduation there in 1865 he spent some time in Berlin, London, Paris, and Vienna. In Vienna he was a pupil of Theodor Billroth (1829-1894), the most famous surgeon of his time. Kocher became professor of clinical surgery at the University of Berne in 1872 and for forty-five years was head of the University Surgical Clinic. The first of his contributions to surgery to attract attention was that in which he worked out the method now known by his name for the reduction of a dislocated shoulder. He afterward devised new methods, or modifications of older methods, for operations upon the lungs, the stomach, the gall bladder, the intestine, cranial nerves, hernia, and so on—all this in addition to his famous work on the surgery of the thyroid gland, described below. He also invented many instruments and appliances. "Kocher's forceps" remain in general use. It is an indication of his scientific objectivity that he was always ready to abandon any of his own techniques or gadgets in favor of improvements introduced by other surgeons. Thus it is said that in his later years he performed the Bassini operation for hernia in preference to his own. In his

work on the thyroid, Kocher showed himself to be not only surgeon and anatomist but also physiologist and pathologist. He was diligent and original in research, expert in operating, and effective in teaching, although he left no surgical "school" behind him. His clinic was for many years a mecca for visiting surgeons from all parts of the world. "With the death of Kocher," wrote Sir Berkeley Moynihan in the *British Medical Journal* obituary in 1917, "the world loses its greatest surgeon."

DESCRIPTION OF THE PRIZE-WINNING WORK*

"It was due . . . [in part] to strict asepsis that one of the most difficult, before Lister [one of] the most dangerous, operations, the removal of the thyroid gland, so often appearing urgently necessary because of severe respiratory disturbances, could be performed without substantial danger. We ourselves have contributed a series of three hundred and more goiter operations without a death. Important as this result has been for suffering humanity, it has been far surpassed by the knowledge of the vital *physiological* function of the thyroid, growing up afresh on practical and clinical grounds. . . . In the spring of 1883, at the Congress of the German Surgical Society [Gesellschaft für Chirurgie], we announced that some thirty of our first one hundred thyroidectomies, which we could follow up and investigate, presented a quite definite, characteristic disease-picture, which we designated simply with the name *cachexia strumipriva* [literally, a bad condition due to removal of a struma, or goiter]. This appeared in its completely distinct form only in those patients from whom we had removed the whole thyroid gland; with no more than transitory signs, on the other hand, where all goiter tissue had supposedly been removed, but where in point of fact a piece had remained behind, which grew larger.

"Isolated observations on the connection of cretinoid disturbances with changes in the thyroid gland had already been made by early investigators. . . . [Kocher here mentions the observations on sporadic cretinism of Felix Plater (1536-1614), but not those

* Translated from Theodor Kocher, "Über Krankheitserscheinungen bei Schilddrüsenerkrankungen geringen Grades," *Les Prix Nobel en 1909.*

of Paracelsus, who linked cretinism and endemic goiter. Also mentioned are T. B. Curling, who in 1850 suggested that cretinism was due to thyroid deficiency, Hilton Fagge, Sir William Gull, W. M. Ord, etc., and his own contemporaries, the Reverdins, who in 1882 published a short notice on the "bizarre" changes displayed by certain patients after thyroid operations. J. L. Reverdin (1842-1908), also a Swiss surgeon, was best known for his plastic operations, particularly skin grafting.]

"At the time (April 1883) when, in Berlin, I described cachexia strumipriva as the *constant* result of total excision, on the ground of numerous observations, and warned against such excision because it always leads to consequences displaying a well-marked cretinoid character, a brilliant discourse was delivered at the same congress by a first-rate surgeon on the advantages and technique of total excision. . . .

"Further corroborative information on the nature and conduct of the new disease soon followed my contribution. On reviewing their operations the Reverdins recognized the relation of cachexia strumipriva to the myxedema of the English [Gull, Ord, etc.]. . . . At a famous meeting of the Clinical Society in London (November 23, 1883) Felix Semon . . . referred to my work and mentioned a confirmatory case, following total excision by Lister; and Ord read a letter I had written to him on the etiology of the disease and the connection of myxedema with cachexia thyreopriva.

"The impulse was thereby given for the splendid investigations of the Clinical Society Committee, which came to the conclusion that myxedema and sporadic cretinism are identical, and probably cachexia strumipriva also, and that close connections exist with endemic cretinism. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

Myxedema, due to deficiency of thyroid secretion, had been given its name by W. M. Ord, who read Kocher's letter to the Clinical Society. Cretinism, a form of idiocy and dwarfism with the general symptoms of myxedema, is due to congenital atrophy or absence of the thyroid gland and is also called congenital myxe-

dema. Cachexia strumipriva, following total excision of the thyroid, is operative myxedema. As indicated in the text above, it was Kocher's description of the latter condition, together with his perception of its cause and its relation to other forms of thyroid deficiency, which made possible the grouping of all these "entities" under a single head. This clarified not only the terminology of the subject but also the thinking and the therapy of both physicians and surgeons. Moreover, Kocher was able to point out that hypothyroidism can be traced not only to absence of the gland, whether congenital or due to an operation, but also to a goiter which has made the gland stop working. Incomplete and debatable evidence as to the function of the thyroid could now be reviewed and supplemented, and in the years which followed Kocher's first pronouncement on the subject great advances were made. Murray, Gley, and Vassale administered thyroid in various forms to overcome deficiency. Attempts to produce the essential constituent, the hormone, in a pure state were long unsuccessful but resulted in showing that iodine plays an important part. In 1914 E. C. Kendall finally isolated the hormone—or the effective part of it—called thyroxin, which was later synthesized by C. R. Harrington and G. Barger. Meanwhile the nature of hyperfunction or dysfunction of the gland, causing exophthalmic goiter, was elucidated by Victor Horsley and others, providing a sound basis for surgical intervention. Kocher did much to perfect the technique of the operation and performed more than two thousand thyroidectomies with less than 5 percent mortality; this represents the resultant of a reduction of mortality from 18 percent to less than $\frac{1}{2}$ percent, the ultimate rate in his clinic. He was also a pioneer in stressing the importance of blood-picture change and coagulation time as means of early diagnosis and prognosis both in hyperthyroidism and hypothyroidism. Finally, he made extensive and careful studies of malignant tumors of the thyroid gland.

In the days before anesthesia and antisepsis, thyroidectomy was so dangerous that it was performed only in cases with severe suffocative symptoms. The control of bleeding remained a serious problem, and only from 1870, when the hemostatic forceps came into general use, was the operation a practical one. Understanding of thyroid physiology and pathology extended the range of surgical

intervention. Kocher made important contributions to this understanding.

The prophylactic value of small amounts of iodine in the prevention of goiter has been shown by D. Marine and others. Thiouracil and related compounds have been introduced for the medical treatment of thyrotoxicosis (poisoning by an excess of thyroid secretion). Radioactive iodine has found a similar use. Yet, whatever the future holds in the prevention and treatment of the various forms of thyroid disease, surgery is still of predominant importance today.

1910

ALBRECHT KOSSEL

(1853–1927)

"In recognition of the contributions to the chemistry of the cell made through his work on proteins, including the nucleic substances."

BIOGRAPHICAL SKETCH

ALBRECHT KOSSEL, ELDEST SON OF A MERCHANT AND PRUSSIAN consul, was born in Rostock on September 16, 1853. After attending the *Gymnasium* there, he studied medicine at the University of Strasbourg, where he was much influenced by E. F. Hoppe-Seyler (1825-1895), one of the pioneers of modern physiological chemistry; he also attended the University of Rostock. He passed his state examination for practice in 1877 and became doctor of medicine in the following year. After assisting Hoppe-Seyler for a time, he was summoned by E. Du Bois Reymond to the Physiological Institute in Berlin. In 1895 he became professor of physiology and director of the Physiological Institute at Marburg, where he remained until 1901, when he took over the Heidelberg chair made famous by Willy Kühne and Helmholtz. A physiologist by training, Kossel devoted his researches almost entirely to chemical subjects. His early investigations were concerned with the nucleic acids; later he turned his attention to the protamines of fish roe (first investigated by Miescher), which are comparatively simple proteins, and made a special study of their six-carbon cleavage products, containing nitrogen, called "hexone bases." He reached a position of pre-eminence by his substitution of the exact methods of organic chemistry for the less precise means employed by older physiologists. He had a number of distinguished pupils, including the Englishman H. D. Dakin. His son, Walther, became a well-

known theoretical physicist. Professor Kossel died in his seventy-fourth year, after a brief illness, on July 5, 1927. At the time of his death he was emeritus professor of physiology at the University of Heidelberg and director of the Heidelberg Institute for Protein Investigation. For more than thirty years he had been editor of the *Zeitschrift für physiologische Chemie,* in which most of his writings appeared.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The first observations in this field [the chemistry of the cell nucleus] were undertaken on the nuclei of pus cells during the sixties of the last century in Hoppe-Seyler's laboratory. It fell to Miescher, a pupil of Hoppe-Seyler's, to isolate this nucleus, and he found in it a substance very rich in phosphorus, which he designated 'nuclein.' [This substance is now known to have been nucleoprotein. Friedrich Miescher (1844-1895) is regarded as the founder of our knowledge of the chemistry of the cell nucleus.] A suitable object for the continuation of this work presented itself in a structure arising from the transformation of the nucleus and preserving its chemical nature, obviously a fundamental part of the physiological functions also—namely, in the head of the spermatozoon. In the course of the next decades evidence accumulated to show that 'nuclein,' or 'nuclein substance,' is actually peculiar to the nucleus. [This view has had to be altered. See the commentary below.] Still other objects were found, which in some way lent themselves to the isolation of the nuclei, e.g., the red blood corpuscles of birds, the cell body of which is soluble in water. Furthermore, the nuclear substance isolated from them could be submitted to chemical investigation in sufficient quantity, and now the characteristics of the nuclear substance were further revealed. Microchemical work completed the demonstration. At the same time it showed that the nuclein substance appertained to a definite part of the substance of the nucleus, which separates itself in the trans-

* Translated from Albrecht Kossel, "Über die chemische Beschaffenheit des Zellkerns," *Les Prix Nobel en 1910.*

formation processes in a very characteristic way, the quantity of which varies in different nuclei, and which has obtained the name 'chromatin' because of its reaction to certain dyestuffs. [The question of the distribution of nuclear constituents is not yet settled, but chromosomes are considered to be almost exclusively nucleoprotein.] Only one difficulty presented itself at first for this doctrine. This was the finding of 'nuclein substance' in animal products which contained no nuclei, and indeed in the vitelline discs [yolk] of eggs and the casein of milk. Strange hypotheses had already been advanced in an attempt to make these facts intelligible, when exact chemical investigation brought enlightenment.

"The chemical structure of these nuclein substances exhibits some peculiarities, which are found in many of the organic constituents of protoplasm, especially in those which take a lively part in metabolic processes. It was observed that such combinations readily break down into a definite number of complete atom groups, which have been compared to building blocks. Such 'building blocks,' in large number and variety and apparently combined according to a definite plan, build the molecule of albuminoid or protein material, also that of starch and glycogen. . . .

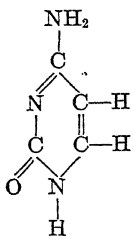
"The nuclein substances also exhibit a combination of this kind. Chemical analysis showed first of all that the nuclein substances can in many cases be separated into two parts, one of which bears the character of a protein or albuminoid material. This possesses no other atom groups than the usual albuminoid substances. So characteristic is the structure of the other part that it has received the name *nucleic acid*. It fell to me to obtain from it a series of fragments, which may in part be detached from the molecule even by *gentle* chemical procedures and which are characterized by a quite specific group of nitrogen atoms. There are here side by side four nitrogen-containing atom groups: *cytosine, thymine, adenine,* and *guanine*.

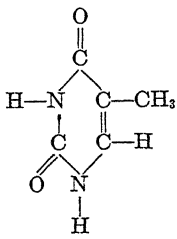
"One of these four bodies, guanine, was already known earlier and in different tissues of the animal organism; e.g., it had been discovered by Piccard in the spermatozoa of salmon. . . . The knowledge of their origin from nucleic acid, which was unexpected and was at first assailed by lively opposition, at once made intelligible separate phenomena which had been encountered without

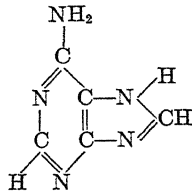
explanation; e.g., it had been observed that guanine and its kindred are found in large amounts in the blood in leukemia. Now this form of disease is distinguished by the fact that unnucleated red blood corpuscles [adult cells] are replaced by [young] nucleated forms. But these latter fall prey in large numbers to decomposition, and accordingly the body fluids are inundated with the disintegration products of the nuclein substances. So, then, the bases named or their nearest conversion products are to be met with in large amounts in the body fluids. Also the contradiction previously mentioned, which seemed to lie in the alleged presence of nuclein substance in vitelline elements and in milk, was now solved. An exact chemical investigation proved that these elements, which because of their unusual behavior and their phosphorus content had been proffered earlier as nuclein substances, possessed another kind of chemical structure. The building blocks rich in nitrogen which I have just named are altogether absent from them. . . . [Nucleoproteins are nevertheless present in eggs, and embryonic tissues are rich in nucleic acids.]

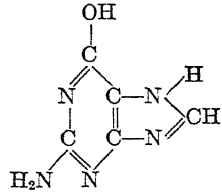
"Now the more was known of the relation to the nucleus of the nitrogen-rich substances, the more also must the question arise of the arrangement of the nitrogen and carbon atoms in their molecule. Two of the four bodies named, adenine and guanine, belong to a group of chemical compounds which today are usually grouped together under the names of alloxur or purine derivatives. . . . Both thymine and cytosine showed a simple composition; analytical and synthetic research lead to the result . . . which the following schema express:

[A number of workers, notably Emil Fischer, contributed to the establishment of these formulae; the mode of writing them has here been altered slightly to conform to recent usage.]


Cytosine


Thymine


Adenine


Guanine

CONSEQUENCES IN THEORY AND PRACTICE

The study of the biochemistry of the nucleic acids, in which Miescher, Altmann, and Kossel were among the pioneers, has assumed ever-increasing importance. Knowledge of the presence or absence of these compounds in certain organic substances has been much extended since Kossel's day, so that some of his assertions, quoted above, are now outdated; nucleoprotein is not peculiar to the cell nucleus, as was then supposed, but is also found in protoplasm. Pentosenucleic acids of the type found in yeast were once thought to be characteristic of plants, deoxypentosenucleic acids of the type found in the thymus gland to be characteristic of animals; but both have been found in plants and animals alike and the distinction of source has been shown to be largely false.

The metabolic activity of the nucleic acids is of great importance. The rate of renewal in different parts of the body varies with age, with X radiation, and with other factors. Questions of growth and of both the normal and pathological function of the organs are involved in the study of these substances. Formation of the body's proteins takes place through the mediation of the nucleic acids. Genes and chromosomes consist of nucleoproteins. A great deal of current research on cancer is also centered on the study of the nucleoproteins. Bacteria are particularly rich in nucleic acids, and nucleoproteins form the substance of plant and animal viruses and of the bacterial virus, bacteriophage. Indeed all self-reproducing or protein-synthesizing units in living organisms are believed to be of this chemical constitution. Studies in the biochemistry of nucleic acids are expected to yield valuable information, not only concerning the mode of action of bacteria and viruses but also concerning genetics, embryology, the normal physiology of the cells, and the pathological deviations from the normal, including cancer.

This general field of biochemical research is of primary importance for the basic knowledge which underlies medicine. Immediate practical applications may appear at any time or, on the other hand, may be long postponed. The fact that thymine, one of the pyrimidine bases discovered by Kossel, has proved clinically effec-

tive in cases of pernicious anemia is probably less important for this immediate reason than because there is some possibility that the basic biochemical defect which results in the disease may be elucidated through the use of thymine. Cellular pathology, initiated by Rudolf Virchow nearly a century ago, gives promise of new and greater usefulness as the mystery of chemical events within the cell is gradually penetrated.

REFERENCES

B., G., "Prof. Albrecht Kossel." *Nature* (London), Vol. 120 (1927), p. 233.

DAVIDSON, J. N. *The Biochemistry of the Nucleic Acids* (London: Methuen; New York: Wiley, 1950).

EDLBACHER, S. "Albrecht Kossel zum Gedächtnis," *Hoppe-Seyler's Zeitschrift für physiologische Chemie,* Vol. 177 (1928), pp. 1-14.

GRAY, GEORGE W. "The Mother Molecules of Life," *Harper's Magazine,* April, 1952, pp. 51-61.

RIESSER, OTTO. "Albrecht Kossel," *Deutsche medizinische Wochenschrift,* Vol. 53 (1927), p. 1441.

1911

ALLVAR GULLSTRAND

(1862–1930)

"For his work on the dioptrics of the eye."

BIOGRAPHICAL SKETCH

ALLVAR GULLSTRAND WAS BORN AT LANDSKRONA, SWEDEN, on June 5, 1862. He studied at the University of Uppsala, for one year at Vienna, and finally at Stockholm, where in 1888 he passed the examinations for the license to practice medicine. He sustained his thesis for the doctorate in 1890, and was named docent in ophthalmology in 1891. He was later called to the new chair of ophthalmology at Uppsala. In geometric and physiological optics he was self-taught. His thesis of 1890 ("A Contribution to the Theory of Astigmatism") already contained the foundations of his most notable work, elaborated in three subsequent publications (1900, 1906, and 1908). One of his most remarkable contributions to ophthalmology was the discovery of intracapsular accommodation, described below; he also invented a number of important instruments and made useful modifications in the design of others. He died in 1930.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"It is . . . necessary to remember that the lens fibers are attached both anteriorly and posteriorly, describing in their course

* From Allvar Gullstrand, "Mechanism of Accommodation," an appendix to *Helmholtz's Treatise on Physiological Optics,* translated from the third German edition by James P. C. Southall (Rochester, N. Y.: Optical Society of America), Vol. 1, pp. 388-390.

arcs which are convex toward the equator. When the points of attachment of the fibers are separated from one another by the increase of thickness of the lens, the arches must be spread, involving the greatest amount of dislocation of particles in the parts of the fibers farthest from the points of attachment. If the lens were always symmetrical, a centripetal shifting would have to occur at the equator. If the point of maximum centripetal shifting on each lens fiber were determined, and a surface passed through all these points, this surface of maximum accommodative shifting would coincide with the equatorial plane. But since the passive lens is asymmetrical, and the change of shape is particularly marked on the anterior surface, the surface of maximum accommodative shifting must be concave toward the front. This conclusion, drawn entirely from the anatomical structure of the lens with respect to its asymmetrical accommodative change of shape, may also be deduced directly from . . . mathematical analysis. The slight change of form of the posterior surface of the lens demonstrates that the points of attachment of the lens fibers adjacent to this surface must, on the average, be less separated from one another during accommodation than those of the fibers lying on the anterior surface. Since, on the whole, the fibers of the posterior surface have their points of attachment situated more toward the periphery on the anterior surface, and toward the center on the posterior surface, and as these conditions are reversed in the case of the fibers of the anterior surface, the distance of the posterior pole of the lens from the anterior point of attachment of the *Zonula Zinnii* must be relatively less changed during accommodation than the distance of the anterior pole from the posterior point of attachment. As a result, the shifting at the anterior point of attachment must occur in a direction approximately corresponding to a tangent to the surface. Consequently, it follows from the anatomical structure of the lens that *the increase of curvature of the anterior surface of the lens during the accommodative change of form is accompanied by an axipetal shifting of the anterior point of attachment of the zonule.* . . . Mathematical investigation demonstrates the presence of a corresponding shifting in those parts of the largest closed isoindicial surface that are nearest to the point of attachment.

"As the surface of maximum accommodative shifting contains

cross or slightly oblique sections of the lens fibers, the rapidity of the centripetal movement of these sections during accommodation must be greater at a point nearer the axis than in the vicinity of the equator. . . . It is true, this mechanism might be impeded by the fact that the fibers lying nearer the axis would be cut obliquely by the surface of maximum shifting in the passive state and perpendicularly during accommodation, provided the centripetal movement could occur to a sufficient extent. But in order to compensate the suggested difference of centripetal shifting, the oblique section must make an angle of 60° with the perpendicular section; and this is manifestly impossible. Another consequence, therefore, of the anatomical structure of the lens is that the equatorial diameters of the smaller iso-indicial surfaces must be proportionately more shortened in accommodation than those of the larger. But according to the mathematical investigation, this is an expression of an increase of the total index; and hence *the increase in total index during accommodation,* as proved by physiological-optical investigations, *may be deduced directly from the anatomical structure of the lens.* The so-called S-shaped curvature of the lens fibers is inferred from the fact that the projection of such a fiber on the equatorial plane is not a straight line; and the reason why in this discussion of the anatomical structure of the lens the possibility of a change in this curvature has not been mentioned is that the only thing which could modify it would be radially directed elevations and depressions. This is a necessity due to the mode of attachment of the lens fibers in rows, so that any mutual shifting of the individual fibers at these points is impossible. On the other hand, it follows again from the anatomical arrangement of the lens fibers that during the accommodative change of form, such elevations and depressions must either originate in the iso-indicial surfaces or must be reversed there, if they are already present. Else they would undergo a reduction of superficial area during accommodation. This might perhaps be possible if the lens were composed of freely movable particles, but is actually impossible because the capability of movement is restricted by the arrangement of the fibers. However, a necessary mathematical consequence of this accommodative change of the iso-indicial surfaces is the variation of the star-shaped appearance of a luminous point.

"A slight increase of the index at any given point may result from the interpenetration of individual fibers between others, even though the physical indices of the individual fibers are not altered. This explains why the smaller iso-indicial surface . . . is apparently a little nearer the anterior pole of the lens during accommodation, because the superficial extent of that portion of it which is nearest the axis is augmented by the forward displacement, and this must involve an interpenetration of fibers from the central region.

"Thus, the dioptric investigation of the lens in accommodation has resulted in finding out the accommodative variations that occur in the substance of the lens. At the same time, it appears that these changes, which for convenience may be grouped together under the name of the *intracapsular mechanism of accommodation,* are not only in complete agreement with the anatomical structure of the lens, but also establish and explain the causal connection between this structure and the variation of the total index of the lens as proved by the change of refraction that occurs when the lens is removed or during the process of accommodation."

CONSEQUENCES IN THEORY AND PRACTICE

For a proper understanding of Gullstrand's contributions to ophthalmology, a thorough knowledge of the anatomy of the eye and of geometric and physiological optics is essential. Certain points, however, may be noted here as of primary importance. The heterogeneous structure of the lens, described in the quotation, had never before been explained on physiological grounds. According to the classical (Helmholtz) theory of accommodation, the action of the ciliary muscle increases the convexity of the lens, especially of the anterior surface, and no function is ascribed to the nonuniformity of the internal parts of the lens structure. Accommodation, representing a gain in the refractive power of the lens, makes it possible to focus on the *punctum proximum,* or "near point," which varies with the amount of accommodation possessed by the eye and is determined clinically by noting the shortest distance at which it is possible to read the smallest test type. Gullstrand was

able to show that this gain in refractive power is only about two-thirds dependent on the increase in surface curvature of the lens; the remaining third is due to a rearrangement of internal elements, as set forth above. This means that approximately two thirds of accommodation is "extracapsular," one third "intracapsular."

Gullstrand's investigation of optical reproduction, begun on the level of pure physics and extended to physiological optics, led him to modify, or supplement, the theory of co-linear reproduction, enabling him to give improved explanations of anisotropic coma and monochromatic aberration. In applying his findings to the human eye he contributed also to present knowledge of the structure and function of the cornea.

In practice, Gullstrand invented improved methods for estimating astigmatism and corneal abnormalities and for locating paralyzed muscles. He improved the design for corrective glasses after removal of the cataractous lens. He devised a reflex-free ophthalmoscope. Perhaps the best known and most useful of his inventions is the slit-lamp. It supplies a brilliant light condensed into a beam, which traverses the parts to be examined, the remainder of the eye being in darkness; the illuminated area is then examined with the binocular microscope. The combination of slit-lamp and corneal microscope makes possible the minute examination of changes in the anterior part of the eye. Exact localization in three planes or dimensions is obtainable with this instrument. Thus the examiner can locate the site of a foreign body or determine the depth of an ulcer. Lens opacities can be located and their progress watched. The very earliest signs of serious inflammations may often be seen with the aid of Gullstrand's slit-lamp. Sometimes a differential diagnosis of great importance can be made when ordinary methods of examination leave doubt. The slit-lamp is now considered an indispensable part of the ophthalmologist's apparatus.

1912

ALEXIS CARREL

(1873–1944)

"In recognition of his works on vascular suture and the transplantation of blood vessels and organs."

BIOGRAPHICAL SKETCH

ALEXIS CARREL WAS BORN IN LYONS, FRANCE, ON JUNE 28, 1873. He became a bachelor of letters of the University of Lyons in 1889, bachelor of science in 1890, and doctor of medicine in 1900. He interned in a Lyons hospital, then taught anatomy and operative surgery at the university as a prosector. He began his experimental work in surgery in 1902 in Lyons, whence he went to Chicago at the end of 1904. In 1906 he became attached to the Rockefeller Institute for Medical Research in New York, where he conducted most of the experiments for which the Nobel Prize was awarded him. This was the first Nobel Prize in medicine for the United States. He was made a fellow of the Institute in 1909, a member in 1912, and retired in 1939 as member emeritus.

During the First World War, Carrel served as a major in the French army medical corps and helped to develop the well-known Carrel-Dakin antiseptic solution for sterilization of deep wounds. In 1935, with Col. Charles A. Lindbergh, he announced the development of a mechanical "heart," in which the heart, kidney, etc. of an animal could be kept alive for study in glass chambers supplied by circulation of artificial blood.

When the Second World War broke out, Carrel joined a special mission for the French Ministry of Public Health (1939-1940). At the time of his death, which took place in Paris, on November 5, 1944, he was director of the Vichy government's Carrel Foundation for the Study of Human Problems.

His writings included the best-selling *Man, the Unknown,* and he was joint author with Georges Dehelly of *Treatment of Infected Wounds* and with Charles Lindbergh of *The Culture of Organs.*

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The idea of replacing diseased organs by sound ones, of putting back an amputated limb or even of grafting a new limb on to a patient who has undergone an amputation, is far from being original. Many surgeons before me have had this idea, but they were prevented from applying it, owing to the lack of a method for re-establishing immediately a normal circulation through the transplanted structures. It was of fundamental importance to first discover a suitable method of uniting the blood vessels of the new organ to those of its host. In 1902, therefore, I began to investigate by what means a vascular anastomosis [union between blood vessels] might be effected without producing either stenosis [narrowing], or thrombosis [plugging by clot formation]. Many surgeons had previously to myself performed vascular anastomosis, but the results were far from satisfactory. I began by using Payr's and Murphy's methods, after which I proceeded to study the principles for a new technique on human cadavers. I next performed some vascular anastomoses on living dogs at the University of Lyons in the laboratory of Prof. Soulier and with the collaboration of Dr. Morel. This study was continued at the University of Chicago in Professor Stewart's laboratory and with the collaboration of Doctor Guthrie. Later, at the Rockefeller Institute for Medical Research, the causes of all possible complications were analysed and greater perfection of methods was obtained. With this modified technique a great many experimental operations were performed

* From Alexis Carrel, "Suture of Blood-Vessels and Transplantation of Organs," *Les Prix Nobel en 1912.*

and their clinical and anatomical results were observed during a period of three and four years. . . .

"In operations on blood vessels certain general rules must be followed. These rules have been adopted with the view of eliminating the complications which are especially liable to occur after vascular sutures, namely, stenosis, haemhorrhage and thrombosis. A rigid asepsis is absolutely essential. Sutures of blood-vessels must never be performed in infected wounds. It seems that the degree of asepsis under which general surgical operations can safely be made may be insufficient for the success of a vascular operation. It is possible that a slight non-suppurative infection, which does not prevent the union of tissues 'per primam intentionem' ['by first intent'], may yet be sufficient to cause thrombosis. The obliteration of the vessel also follows injuries to its walls. The arteries and veins can be freely handled with the fingers without being injured, but it is often harmful to use forceps or other instruments. If a forceps be used, it must take between its jaws nothing but the external sheath. When temporary haemostasis [control of bleeding] is obtained by means of forceps or clamps, these instruments must be smooth-jawed and their pressure carefully regulated. The desiccation of the endothelium [lining membrane] may also lead to the formation of a thrombus. Therefore, during the operation the wall of the vessels must be humidified . . . or be covered with vaseline. . . . As perforating stitches are always used, the endothelial layer is necessarily wounded by the needle. These wounds, however, are rendered as harmless as possible by the use of very fine and sharp round needles. Extremely small wounds are made. The threads are sterilized in vaseline and kept heavily coated with it during the suture. . . . The operating-field is circumscribed by a black Japanese silk towel on which the fine threads can easily be seen. . . .

"*The termino-terminal* [end-to-end] *anastomosis* is effected by bringing the extremities of the vessels into contact, no traction being necessary. The ends are united by three retaining stitches located in three equidistant points of their circumference. By traction on the threads the circumference of the artery can be transformed into a triangle, and the perimeter can be dilated at will. Then the edges of each side of the triangle are united by a con-

tinuous suture whilst they are under tension. During the suture great care is taken to approximate exactly the surfaces of section of the wall. Before the last stitch is made, the remaining vaseline is removed by pressure from the lumen [cavity] of the vessel. In venous anastomoses the ends of the veins are also united by three retaining stitches. A venous suture, however, requires more stitches than an arterial suture, on account of the thinness of the walls. The union of the extremities is made by eversion of the edges, which are united not by their surface of section, but by their endothelial surfaces. An inversion of the edges would be very dangerous and would provoke the formation of a thrombus."

CONSEQUENCES IN THEORY AND PRACTICE

Aiming at successful replacement or transplantation of organs, Alexis Carrel perceived that the chief difficulty was the re-establishment of circulation without hemorrhage or thrombosis. He therefore worked out the method described above; then he proceeded to apply it. Using his new techniques he was able to remove entire organs, such as the spleen or kidney, and replace them either in the original location or occasionally, in still more spectacular operations, in different parts of the body, where they functioned fairly well. He was even able to replace an amputated limb.

Before the introduction of citrate to prevent blood from clotting (see below, p. 146), vascular suture was used in blood transfusions, a donor blood vessel being anastomosed to a recipient vessel. This method has since been abandoned, but it is repeatedly necessary, in the surgery of injuries and wounds, to restore the continuity of divided blood vessels. Here the Carrel technique finds application.

Vascular surgery is now an important specialty. As a result of a congenital malformation, the greatest of the arteries, the aorta, may be so constricted at some point that the blood supply to the lower half of the body becomes inadequate. This condition is often overlooked, as the patient may be active for years and experience little or no difficulty; but the average duration of life is only about thirty-five years. In 1944 C. Crafoord, and in 1945 R. E. Gross, performed the first operations for this condition, known as coarctation

(narrowing) of the aorta. The local constriction is removed and the Carrel method makes it possible to join together the two ends and thus provide an aortic lumen of adequate size.

Certain other kinds of congenital heart disease may now be remedied by somewhat similar techniques. The "blue baby" operation, introduced in 1944 by A. Blalock and H. G. Taussig, involves a rerouting of congenitally misdirected blood flow, using a piece of vein to form a new link between two arteries. In this way it is possible to direct a larger proportion of the blood through the pulmonary circuit, originally by-passed in part, and so to assure sufficient oxidation of the blood as it circles through the lungs.

The domain of vascular surgery is undergoing remarkable extension. Among the surgical techniques which have made this possible, the suture method devised by Carrel is of basic importance. Even with the full resources of present-day surgery the transplantation of organs has not yet become generally practicable. At the present time kidney transplants are being attempted, but the value of this procedure remains in doubt. It appears that tissues do not fare well for the most part when removed from one individual and implanted in another; corneal transplants, having nothing to do with vascular surgery, are the obvious exceptions.

1913

CHARLES RICHET

(1850–1935)

"In recognition of his work on anaphylaxis."

BIOGRAPHICAL SKETCH

CHARLES RICHET WAS BORN ON AUGUST 26, 1850, IN PARIS, where his father, Alfred Richet, was professor of clinical surgery in the Faculty of Medicine. He was graduated in medicine in 1876, and then worked under Marey at the Collège de France. In 1887 he was appointed professor of physiology at the University of Paris. An industrious and versatile worker, he did not limit himself to the usual confines of physiology but also published papers on physiological chemistry, experimental pathology and pharmacology, and normal and pathological psychology. He did original work on gastric secretion. He also investigated the relation between respiration and the area of body surface, and carried out extensive research on animal heat. In addition he studied the effect of chloride deprivation on epilepsy, and of a diet of raw meat in the treatment of tuberculosis. Work begun in 1887 led Richet to the concept of immune serum, and in 1890 he performed the first serotherapeutic injection on a human subject. Richet's attempt to follow this clue in his work on tuberculosis was disappointing, but von Behring and Kitasato pursued it with greater success in studies of tetanus and diphtheria. In 1898, with his collaborator, Héricourt, Richet studied the effect of eel serum on dogs, observing that a condition of

hypersensitiveness could develop. This was followed by his work with P. Portier in 1902 and his own later independent studies of anaphylaxis, described in part below, for which he received the Nobel Prize. In his later years Richet's inclination toward the study of psychology increased. Side by side with this, he nurtured an interest in clairvoyance, telepathy, and materialization—an interest that he did not find incompatible with rigid mechanistic determinism. He followed the development of aeronautics very closely and actually designed an airplane. He was the author of a number of novels and plays. He was also active in pacifist movements. Richet died of pneumonia on December 4, 1935.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"*Phylaxis,* a word but little used, means, in Greek, protection. And the word *anaphylaxis* will then signify the contrary of protection. Thus, through its Greek etymology, anaphylaxis means a state of the organism in which . . . , in place of being protected, [it] has become more sensitive. [Richet coined the word *anaphylaxis* in 1902.]

"To state the ideas precisely, we are going to examine what takes place in an individual receiving a poison.

"Let us suppose the dose a moderate one, and the individual restored, after some days, to his original state, at least to all appearance. If, then, the same dose of the same poison is injected anew, what is going to happen?

"We can suppose three cases.

"The first, the simplest, is that nothing has been changed in his organism, and that on receiving the same dose as a month ago, exactly the same phenomena will reappear under the same conditions. . . .

"The second possibility is that the organism may have become less sensitive. In other words, a certain state of habituation, or insensibility, has been produced by the preceding intoxication; so that a stronger dose has become necessary, at the second injection,

* Translated from Charles Richet, "Conférence Nobel sur l'anaphylaxie," *Les Prix Nobel en 1913.*

to produce the same effect. It is the case of immunity (relative). . . .

"These two cases: unmodified sensitivity or *stability,* diminished sensitivity or *habituation,* had been known for a long time. But I have shown that very frequently, under certain conditions which I have been able to specify, a third modality is seen: it is increased sensitivity, of such a kind that the first injection, in place of protecting the organism, makes it frailer, more susceptible, it is *anaphylaxis.*

"Let me tell you under what circumstances I observed this phenomenon for the first time. I may be permitted to enter into some details on its origin. You will see, as a matter of fact, that it is not at all the result of deep thinking, but of a simple observation, almost accidental; so that I have had no other merit than that of not refusing to see the facts which presented themselves before me, completely evident.

"In equatorial seas one comes across Coelenterates [a sub-kingdom of animals comprising the Actinozoa and Hydrozoa] called Physalia (Portuguese men-of-war). These animals are formed essentially of a sac full of air, which allows them to float like a leather bottle. Associated with this sac is a bucco-anal cavity, furnished with very long tentacles, which hang down in the water. These tentacular filaments, sometimes two or three meters in length, are armed with little "gadgets" which adhere like suckers to objects which they encounter. And in the interior of each of these innumerable suckers there is a sharp little point, which penetrates the foreign body touched. At the same time this point imparts a subtle poison, very active, contained in the tentacles; so that the contact of the Physalia's filament is equivalent to a multiple injection of poison. The moment you touch a Physalia, you feel an intense pain, owing to the penetration of this venomous liquid. . . .

"Now, in the course of a cruise made on the yacht of Prince Albert of Monaco, the Prince advised me, as well as our friends Georges Richard and Paul Portier, to study the poison of these Physaliae. We saw that it dissolves readily in glycerine, and that on injecting this glycerinated liquid one reproduces the symptoms of Physalian poisoning.

"Having returned to France, and no longer being able to obtain

Physaliae, I thought of studying comparatively the tentacles of Actiniae [sea anemones] . . . which can be obtained in abundance; for the Actiniae swarm on the rocks of all the European coasts.

"Now the tentacles of the Actiniae, treated with glycerine, yield their poison to the glycerine, and the extract is toxic. Working with Portier, I then sought to determine the toxic dose. This was difficult enough, because this poison acts slowly, and one must wait three or four days before knowing whether or not one has reached the fatal dose. With the solutions that I was using, a kilo of glycerine to a kilo of tentacles [a kilo, or kilogram, is a little more than two pounds], it required, after filtration, about 0.1 of liquid per kilo of live weight to bring about death.

"But certain dogs escaped, whether because they had received too weak a dose, or from some other cause. And at the end of two, three, or four weeks, as they seemed altogether restored to their normal state, I made use of them for a new experiment.

"Then an unforeseen phenomenon presented itself, which to us appeared extraordinary. If the dog, injected beforehand, received an extremely weak dose, for example 0.005 per kilo, he immediately exhibited dreadful symptoms: vomiting, bloody diarrhea, syncope, loss of consciousness, asphyxia, and death. Repeating on different occasions this fundamental experiment, we were able to establish, in 1902, these three principal facts, which are the very foundation of the story of anaphylaxis: first, an animal injected beforehand is enormously more sensitive than a new animal; second, the symptoms which supervene on the second injection, characterized by a rapid and total depression of the nervous system, have no resemblance to the symptoms produced by the first injection; third, this anaphylactic state requires an interval of three or four weeks to establish itself. It is what is called an incubation period.

"After the initial facts of anaphylaxis had been solidly established, the domain was enormously enlarged at once, thanks to the beautiful experiments of clever investigators.

"In 1903, Arthus, of Lausanne, showed that if a rabbit is given an intravenous injection of serum, this first injection of serum is anaphylactogenic—that is to say that three weeks after the first

injection the rabbit has become very sensitive to the second injection. Thus the phenomenon of anaphylaxis was generalized; and in place of being particular to toxins and toxalbumin was extended to all albumins, whether toxic on first injection or not. [Albumin-protein. Arthus observed a local reaction since known as the 'Arthus phenomenon.']

"Two years later, two American physiologists, Rosenau and Anderson, established in a remarkable memoir that the anaphylactic phenomenon is seen after every injection of serum, even when the quantity injected is minuscule, be it 0.00001 c.c., the tiniest quantity, but sufficient to give an animal anaphylactic sensitivity. They gave examples of anaphylaxis with all the organic liquids: milk, serum, egg, muscular extract. They indicated the specificity of this reaction, and finally they clearly established that of all animals the guinea pig appears to be the most sensitive to the anaphylactic reaction.

"In 1907, I made an experiment which notably clarified the pathogenesis [the mode of origin] of anaphylaxis. In taking the blood of a sensitized animal, and injecting it into a normal animal, the anaphylactic state is developed. Thus the anaphylactogenic poison is a chemical substance contained in the blood.

"Such, as it seems, are the principal phases through which our knowledge has passed."

CONSEQUENCES IN THEORY AND PRACTICE

Richet was not the only investigator to report intensified results from a preliminary conditioning expected to create, if anything, a state of immunity. Thus Edward Jenner had long ago noticed a similar occurrence in performing vaccinations, and von Behring had observed that a second injection of diphtheria toxin seemed at times to have a greater toxic effect than anticipated. But the regularity of the phenomenon was Richet's discovery; he not only observed and named it but clearly expounded as a general principle what had been noted from time to time in the past as an exceptional and bizarre occurrence. Furthermore, he showed that it was not a mere intensification of an ordinary toxic action but was a specific effect with characteristic signs and symptoms.

The term "anaphylaxis" may refer to increased susceptibility to an injection under the conditions described above; more commonly it means the reaction to a foreign substance, usually a protein such as animal serum, following a previous introduction, by injection or otherwise, of the same substance. The effect is the same regardless of what substance is used to cause it, but the conditioning is specific for each substance. Often the preliminary introduction of the substance in question has taken place accidentally or obscurely, or the sensitivity may be inherited; in other cases there is a clear history of the previous introduction. Because spontaneous or hereditary cases occur, and because the history and other indications are often unreliable, test doses are introduced into the skin or the eye before serums are injected. Anaphylactic shock, which is sudden and often fatal, or the slower "serum sickness," may be avoided by the use of a type of serum different from the one previously introduced. The risks connected with serum treatment may also be overcome, as A. Besredka has shown, by desensitization—that is, by beginning with extremely small doses and gradually increasing them.

Antigens causing reactions akin to those of anaphylaxis may gain entrance to the body by ingestion, by inhalation, by injection, from a focus of infection, or from external contacts. Proteins are the commonest, but not the only, antigens. The list includes the pollens, danders and many other air-borne substances of animal and vegetable origin, foods, drugs, therapeutic serums, and bacteria and their products. Diseases of allergy now form an important division of internal medicine. They include not only asthma, hay fever, and serum sickness but also contact dermatitis in a wide variety of forms. This whole domain of medical science and practice finds its starting point in the investigations of Charles Richet.

1914

ROBERT BÁRÁNY

(1876–1936)

"For his work on the physiology and pathology of the vestibular apparatus."

BIOGRAPHICAL SKETCH

ROBERT BÁRÁNY, AN AUSTRO-HUNGARIAN, WAS BORN IN Vienna, on April 22, 1876. He was educated chiefly in the city of his birth, and was graduated in medicine in 1900. After two years spent at various German clinics in the study of internal medicine and psychiatry, he returned to Vienna, where he soon restricted his work to otology (the study of diseases of the ear) and related problems as they affect certain parts of the brain. He became famous for his studies of the vestibular apparatus in the ear and of the cerebellum (the "little brain," or that part of the brain behind and beneath the larger cerebrum; see below). In 1913-1914 he was awarded a number of international prizes, culminating in his selection as Nobel laureate. The confusion which accompanied the outbreak of the First World War caused postponement of the 1914 award until 1915. At that time Bárány was a Russian prisoner of war in Siberia. Through the intercession of the Swedish Red Cross, however, he was released, and the award presented to him through diplomatic channels. After 1917 his work was done at Uppsala University. He died in 1936, at the age of sixty.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"As a young otologist I practiced in the clinic of Privy Councillor Professor Politzer in Vienna. Among my patients there were many whose ears I had to flush out. A number of these patients complained of dizziness after the flushing procedure. It naturally occurred to me to examine their eyes, and there I observed marked nystagmus [involuntary, spasmodic motion of the eyeballs, a jerky rolling of the eyes]. I made a note of this observation. After a while, when I had collected about twenty observations, I compared them and was surprised to find the same observations recorded every time. Then I recognized that a general law must underlie these observations. I did not yet know, however, the basis of the conformity to law. Chance came to my aid. One of the patients whom I syringed explained to me: 'Doctor, I only get dizzy when the water is not warm enough. When I flush out my ears for myself at home and use warm enough water, I don't get dizzy.' Thereupon I called the attendant and instructed her to give me warmer water for the flushing process. She explained that the water was warm enough. I retorted that if the patient found the water too cold, we had to adjust ourselves to the patient. The next time she put very hot water in the bulb of the syringe. When I syringed the patient, he cried out: 'But Doctor, the water is much too hot; now I'm becoming dizzy again.' Hurriedly I observed the patient's eyes, and noticed that now the nystagmus was exactly opposite in direction to that seen earlier when syringing with water that was too cold. Then in a flash it became clear to me that naturally the temperature of the water was responsible for the nystagmus. I drew some conclusions from this at once. If the temperature is to blame, then, to be sure, water of exactly body temperature must produce no nystagmus and no dizziness. Experiment confirmed this conclusion. I said further, if it is a matter of water temperature, then nystagmus must be producible by syringing in normal people, too,

* Translated from "Nobel-Vortrag . . . von Dr. Robert Bárány," *Les Prix Nobel en 1914-18.*

and not merely in people with suppurations of the ear. This inference also proved to be right.

"On the ground of my previous studies, I did not doubt for a moment that as regards this nystagmus it was a question of a reflex initiated in the semicircular canals. [The three semicircular canals, or ducts, which are membranous, are contained in corresponding bony canals in the internal ear within the skull; the canals lie in planes approximately at right angles to one another. Their function, briefly stated, is to initiate the reflexes which cause us to right ourselves involuntarily by compensatory movements, in response to changes in velocity or direction of motion. These reflexes effect movements of eyes and limbs. There are also reflexes which influence the tone, or steady, continuous action, of the muscles responsible, in their coordination, for posture.] Thence the further conclusion was also obvious that the semicircular canals being destroyed, this reflex must fail to appear. I now sought a case of this kind in the rich material of the Vienna ear clinic. I had soon found a case of severe suppuration of the middle ear, showing no nystagmus reaction on long-continued flushing with quite cold water. I diagnosed destruction of the labyrinth (with respect to the semicircular duct apparatus); in point of fact the operation showed the expected finding. This made clear the significance of the new reaction for the diagnosis of diseases of the inner ear. Yet a series of cases was required for corroboration. This was forthcoming. . . . I had already perceived the significance of the caloric reaction, and yet I did not know how to explain it. I thought it over in vain. Then one day an idea struck me. I remembered the water heater, and my astonishment, as a child, when I found the water just above the fire quite cold, but right at the top the bath-oven was so hot it burned the fingers. The labyrinth now represented in my mind the water heater—i.e., a vessel filled with fluid. The temperature of this fluid is naturally 37° C—the body temperature. I squirt cold water at one side of the vessel. What must happen? What must naturally occur is that the water lying against this wall is cooled down; in this way it acquires a higher specific gravity than the surrounding water and sinks to the bottom of the vessel. On the other hand, water still at body temperature takes its place. If I syringe the ear with hot water, then the motion must be precisely

contrary. But the motion of the fluid must be altered if I alter the position of the vessel. And it must be changed to the exact opposite if I turn the vessel through 180°. The test which had to be the crucial experiment for this theory occurred to me at once. If syringing, be it with cold fluid or hot, succeeded in evoking nystagmus precisely opposite in direction for two positions of the head differing by 180°, then the theory must be the right one. I now went to the clinic and undertook the experiment. As it turned out, the anticipated result appeared with the greatest clearness. Two positions of the head, encompassing between them 180°, gave directly opposite nystagmus reactions. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

"Bárány's caloric test," the first result of his study of the vestibular apparatus, consists in irrigating the canal of the external ear with either hot or cold water. This normally causes stimulation of the vestibular apparatus resulting in nystagmus. In vestibular disease, the response fails relatively or entirely. This method for diagnosing disease of the semicircular canals is the most widely used of several "Bárány tests" and has borne his name to clinics and hospitals the world over. But this was not the end of his investigations. Starting from the work of Ramón y Cajal (see above, pp. 33-40), who traced the communications of the vestibular nerve, and from the studies of the Dutch comparative anatomist Louis Bolk, Bárány concluded that influences on the musculature of the whole body which result in disturbances of equilibrium pass from the semicircular ducts by way of the cerebellum. The study of these disturbances, and the belief that there is definite localization in the cerebellum for movement, led him to devise certain tests for the integrity of the control centers, as reflected in movement of the extremities and even of particular joints. A normal subject with his eyes shut will "past point" to the right beyond the spot he attempts to touch, if the right vestibular apparatus has been stimulated with cold water. The direction of "past pointing" is always opposite to the direction of nystagmus. But Bárány found that spontaneous "past pointing" sometimes occurred. If the patient

"past pointed" to the right, stimulation of the vestibular apparatus to induce a swing to the left failed to work; it merely caused the patient to point correctly. Bárány assumed that "there are in the cerebellum four centers . . . namely, a center directing to the right, one to the left, one up, and one down. . . . At any time two of these centers work like two reins, between which the arm, for instance, moves. If both of these reins are stretched equally taut, then the arm moves without fail to each point desired. But now I can pull one rein harder than the other. This happens if I stimulate the semicircular duct apparatus." It is obvious that a lesion of some sort, a local sickness in one of these centers, will act like the cutting of a rein. Attempts to "pull" this rein will fail, as in the instance of spontaneous "past pointing" mentioned above. Hence it is possible to use Bárány tests not only for diagnosing certain ailments in the inner ear but also for investigating some of the activities of the cerebellum.

1915–1918

No Award

1 9 1 .

JULES BORDET

(1870–)

"For his discoveries in regard to immunity."

BIOGRAPHICAL SKETCH

JULES (JEAN BAPTISTE VINCENT) BORDET, FAMOUS BELGIAN bacteriologist and immunologist, was born on June 13, 1870, at Soignies, Belgium. He studied at the University of Brussels, where he was graduated as doctor of medicine in 1892. In 1894 he went to the Pasteur Institute, Paris, where he was *attaché* or *préparateur* in Metchnikoff's laboratory until 1901, when he founded the Pasteur Institute in Brussels and became its director. In 1907 he was appointed professor of bacteriology at the University of Brussels. His numerous and important contributions to immunology made him widely known. He was elected a foreign member of the Royal Society in 1916. His colleague, Octave Gengou, co-author of the paper quoted below, was also a Belgian; he afterward (1902) extended the work on complement fixation which is described in the quotation. From the considerable range of Bordet's work in immunology this particular contribution has been selected as of outstanding importance to medicine.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The serum of numerous animals contains alexin [now generally known as "complement," the name given to it by Ehrlich],

* Translated from J. Bordet and O. Gengou, "Sur l'existence de substances sensibilisatrices dans la plupart des sérums antimicrobiens," *Annales de l'Institut Pasteur,* Vol. 15 (1901), pp. 289-302.

that is to say, an ill-defined material, its chemical constitution still unknown, to the presence of which is attributed that property which serums in general possess of exercising a destructive influence on diverse cellules and on certain microbes. The alexin loses its activity when the serum which contains it is heated to 55°. This material is to be met with, in quite comparable amounts, in the serum of normal animals and in that of vaccinated animals: artificial immunization does not modify it appreciably, either in quantity or in character.

"When an animal is vaccinated against the cholera vibrio [bacteria], the organism elaborates a particular substance, the preventive or *sensitizing* material [amboceptor], the presence of which can be detected in the serum and which resists quite elevated temperatures. By itself, it is not at all bactericidal for the vibrio. But it favors considerably, and in a specific way, the destructive action which the alexin can exercise on this microbe. One can also say that the specific vibrio-killing property of cholera serum, although due primarily to alexin . . . , results from the collaboration of two substances, on one hand the alexin, on the other the favoring (sensitizing) material with which only the serum of vaccinated individuals is endowed in large degree. . . . [These ideas were established by Bordet in 1895. He applied them, first, to cholera serum, secondly, to specific hemolytic serums. He supposed the phenomenon to occur more generally, but the method he had used for these instances was not generally applicable. In brief it was this. Cholera vibrios are destroyed (bacteriolysis) to a very marked degree by immune serum from a vaccinated animal, to a very slight degree by normal serum. The power of either serum may be abolished by 55° of heat. But adding to normal, feebly active serum a small amount of preheated immune serum, inactive in itself, results in a strongly bactericidal mixture. Hence, the conclusion, as above, that it contains a "sensitizer" (amboceptor) which adds to the otherwise slight power of the "alexin" (complement) in the normal serum. A similar method applied where hemolysis, rather than bacteriolysis, was the revealing change. But where neither of these changes took place another method was needed.]

"As a preliminary, we must recall to the reader an experiment

related a year ago in these *Annales* [Bordet, in May 1900], and of which the following is the principle:

"If one adds to a suitable quantity of the serum of a normal animal, such as the guinea pig (serum recently obtained, unheated, thus containing alexin), some red cells (of a rabbit for example) [which have been] strongly *sensitized* (that is to say, mixed with some hemolytic serum, active vis-à-vis these cells, and which has been heated to 55°), one observes . . . the destruction of the corpuscles. At the end of a certain time some *sensitized* cholera vibrios (added to cholera serum preheated to 55°) are added to the mixture, which is incubated at 37°. One ascertains that the vibrio . . . retains its normal form. Consequently one can affirm that at the moment when the vibrios were introduced, the mixture no longer contained alexin. . . . [This could be reversed—i.e., the "alexin" could be used up by "sensitized" vibrios and would then fail to hemolyze "sensitized" corpuscles.]

"These experiments have established . . . two quite distinct ideas: (1) Corpuscles or microbes, *under the influence of sensitization, acquire the power of absorbing alexin avidly,* and thus of making it disappear from the surrounding liquid. (2) In the same serum, *the same alexin* can provoke either hemolysis or bacteriolysis. . . . [The authors assert as the aim of the present paper to show that] *to denote the existence of a sensitizer in an antimicrobic serum* one can use the property with which this substance is endowed of causing the absorption of the alexin by the microbe which it affects . . .

"[Serum from a horse vaccinated against bacillus pestis, the cause of plague] is heated to 56° for half an hour, at the same time as some serum from a normal horse; this heating renders the alexin inactive. A 24-hour culture of bacillus pestis on gelose [gelatinous part of agar-agar, a solidifying agent used in culture mediums] is diluted in quite a small amount of a physiological solution of NaCl; one thus obtains a very turbid emulsion, rich in microbes. Some serum is also prepared, well cleared of corpuscles by centrifugation, from a normal guinea pig bled the day before. This is the alexic serum [i.e., serum containing alexin, or complement]. The following six mixtures are prepared in test tubes: (*a*) This tube contains: 2/10 c.c. alexic serum; 4/10 c.c. bacillus pestis emul-

sion; 12/10 c.c. antiplague serum (preheated to 56°). (*b*) [The same as *a* except that] it contains, in place of antiplague horse serum, 12/10 c.c. of normal horse serum (preheated to 56°). (*c*) [The same as *a* but without bacillus pestis emulsion.] (*d*) [The same as *b* but without bacillus pestis. These four mixtures contain the same dose of alexin.] (*e*) Contains 4/10 c.c. plague emulsion; 12/10 c.c. antiplague serum. (*f*) Contains 4/10 c.c. plague emulsion; 12/10 c.c. normal horse serum. These last two tubes are the same, respectively, as *a* and *b*, except that they do not contain alexin.

"One waits about five hours, while the mixtures remain at laboratory temperature (15-20°). Then one introduces into the different tubes, at the same moment, 2/10 c.c. of the following mixture: 2 c.c. of serum (previously heated for half an hour to 55°) from a guinea pig treated in advance with three or four injections of 4-5 c.c. of defibrinated rabbit blood; 20 drops of defibrinated rabbit blood. In other words each tube receives two drops of *very strongly sensitized blood.*

"Here is the result of the experiment: Hemolysis appears very quickly, with very similar rapidity, in the tubes *b, c, d.* After 5-10 minutes these mixtures no longer contain intact corpuscles. In the tube *a,* which contains, besides alexic serum, the bacilli and the antiplague serum, *hemolysis does not occur.* The corpuscles remain intact for days at a time. They also remain intact . . . in the tubes *e* and *f,* which do not contain alexin. Thus we see, first, that the bacillus pestis mixed with normal horse serum does not absorb alexin (or absorbs it only to an insignificant degree); second, that the same bacillus, in the presence of antiplague serum from a vaccinated horse, fixes the alexin with great avidity, and makes it disappear from the surrounding liquid; third, the antiplague serum, without the addition of bacilli, leaves the alexin perfectly free.

"Consequently it is necessary to conclude that the serum of a horse vaccinated against the bacillus pestis contains a *sensitizer which confers on this microbe the power of fixing alexin* [complement]."

CONSEQUENCES IN THEORY AND PRACTICE

Bordet and Gengou formed an effective team and worked together for years. (The organism called Hemophilus pertussis, the cause of whooping cough, was originally known as the "Bordet-Gengou" bacillus, after its discoverers; it was first described by them in 1906-1907.) But the fundamental work which made possible the discovery set forth in the above quotation had been carried out by Bordet some years earlier. His publication of 1895 had shown two different substances to be involved in the phenomenon of bacteriolysis. That the terminology has changed makes little difference. It was Bordet who discovered that two factors, not a single antibody as previously supposed, are concerned in the lytic (destructive) action. One of these substances is present both in normal and fresh immune serum and is thermolabile (subject to alteration or destruction by heat), the other is peculiar to the immune serum and is thermostable (heat-resistant). He called these, respectively, "alexine" (from the Greek *alexo,* "I ward off") and "substance sensibilisatrice." These terms have been replaced by the names given to the substances by Ehrlich, "complement" and "amboceptor." It was found, chiefly as a result of Bordet's further experiments, that lytic action is not limited to bacteria. Red blood cells are destroyed by a similar mechanism, hemolysis.

"The possibility of . . . a practical test [using immune serum] was first made known by R. Pfeiffer (1894), who found that the bacteriolytic destruction of cholera vibrios in the peritoneum was so specific that this method could be employed for the differentiation of cholera vibrios from vibrios otherwise indistinguishable. Bordet (1895) utilized this principle and applied it *in vitro* [in the test tube] instead of *in vivo* [in the living animal]. . . .

"Of particular medical importance is the so-called complement fixation test. . . . Gengou (1902) showed . . . that 'sensitizers' (amboceptors) are developed in the blood-serum of animals which have been injected with milk, and that such sensitizers are also capable of fixing complement. . . . [I.e., Gengou further generalized the discovery.]

"These facts were extended by C. Moreschi (1905), who showed that complement fixation occurs in the presence of normal serum mixed with the serum of an animal injected with normal serum, and he demonstrated that extraordinarily small quantities of serum (1/100,000 c.c.) can be detected by this method of diagnosis. M. Neisser and Sachs (1905) recommended the method for the diagnosis of blood in medico-legal work. In 1906 Wassermann, Neisser, and Bruck published their historic account in which they described the discovery of antibodies to syphilis antigen in the serum of syphilitic monkeys. In the same year Wassermann and Plaut (1906), by demonstrating syphilitic antibodies in the cerebrospinal fluids of general paralytics [see below, p. 126], proved this disease to be syphilis, and Wassermann, Neisser, Bruck and Schucht (1906) demonstrated similar antibodies in the blood-serum of syphilitics. Since that time the 'Wassermann reaction' has been practised to an enormous extent in the diagnosis of syphilis and is regarded as a test of deadly accuracy. The complement fixation test has been permanently accepted also in the case of the diagnosis of glanders." *

* William Bulloch, *The History of Bacteriology* (London and New York: Oxford University Press, 1938), pp. 281-283.

1920

AUGUST KROGH

(1874–1949)

"For his discovery of the regulation of the motor mechanism of capillaries."

BIOGRAPHICAL SKETCH

AUGUST KROGH WAS BORN AT GRENAA, IN JUTLAND, DENMARK, on November 15, 1874. He studied zoology at the University of Copenhagen, receiving the M.A. degree in 1899. Even before this, beginning in 1897, he had been carrying on research in the physiology laboratory under Christian Bohr, with whom he continued to work for some years. In 1902 he took part in an expedition to Greenland to study arctic animals. Krogh early turned his attention to studies in gaseous pressures, first in natural waters, afterward in animal physiology. His doctoral thesis (1903) dealt with the respiration of frogs. Much of his subsequent work on the pressures of oxygen and carbon dioxide in the blood was carried out in collaboration with his wife, Dr. Marie Krogh. That the affinity of blood for oxygen depends upon carbon dioxide pressure was demonstrated in 1904 by Bohr, Hasselbalch, and Krogh. In 1908 Krogh became associate in animal physiology at the University of Copenhagen, but had no laboratory until 1910 and did not become titular professor until 1916. His investigations, in some of which Lindhard was associated, were concerned chiefly with the physiology of respiration and blood circulation, but covered a wide range of interests.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The current view of the capillary circulation, at least until a few years ago, was . . . that blood is flowing continuously through all [capillaries] at rates which are determined by the state of contraction or dilatation of the corresponding arterioles, and that the dilatation of an arteriole will cause a rise of pressure in the corresponding capillaries, which will become passively expanded, to contract again by their own elasticity when the pressure is reduced. . . . An increase in [arterial and arteriolar] current must always be accompanied by a corresponding increase in capillary pressure, and when the requirements are small the quantity of blood in a large number of the capillaries would serve no useful purpose. A much more effective distribution would obviously be obtained if the capillaries themselves were contractile, if in a resting organ only a limited number of capillaries . . . were kept open. . . . This hypothetical conception was to me personally the starting point and guide in the experimental study of capillary contractility. . . .

[Krogh here reviews earlier work on the subject, beginning with S. Stricker (1865) and extending to H. H. Dale and A. N. Richards (1918). Most of this work was based on direct microscopic observations of capillaries. Sources of error inherent in the method were not sufficiently guarded against. V. Ebbecke, however, and at the same time (1917) Cotton, Slade, and Lewis, had published evidence based on the local vasomotor reactions of the skin and internal organs, and Dale and Richards had compared the actions of three "depressor" drugs, leading to the conclusion that two of them, histamine and adrenaline, must produce relaxation of the capillary wall.]

"My own first contribution to the problem . . . was published in Danish in 1918 . . . and appeared in the British *Journal of Physiology* (1919). . . . I found it possible to observe at least the superficial capillaries of muscles both in the frog and in mammals through a binocular microscope. . . . Resting muscles observed

* From August Krogh, *The Anatomy and Physiology of Capillaries* (New Haven: Yale University Press, 1922), Silliman Memorial Lectures, Lecture II.

in this way are usually quite pale, and the microscope reveals only a few capillaries at fairly regular intervals. These capillaries are so narrow that red corpuscles can pass through only at a slow rate and with a change of form from the ordinary flat discs to elongated sausages. When the muscle . . . is stimulated to contractions a large number of capillaries become visible and dilated. . . . Since capillaries, even in a group fed by the same arteriole, do not all behave in the same way, the changes obviously cannot be due to arterial pressure changes. . . .

"[Measurements showed the average distance between open capillaries in resting muscle to be much greater than in muscle which had just contracted.] The measurement of distances between open capillaries made upon living specimens could not, of course, be very accurate. . . . I had, therefore, to try and devise a method by which the state of the vessels at any given moment could be studied after fixation. This I succeeded in doing by injecting an India ink solution . . . [made] isotonic with the blood and [freed from] toxic substances. . . . When a suitable quantity of India ink is introduced into the circulation of a living anaesthetized animal it is evenly mixed with the blood, and if the animal is suddenly killed by stopping the circulation a few minutes later, and preparations are made from the muscles and other organs, these show the capillaries which were open at the time.

"On frogs I found by this method that there were large differences between different organs in the number of open capillaries. The skin, liver and brain [organs which are constantly active] were always well injected, with all, or nearly all, capillaries open. The tongue was generally white and nearly bloodless, when not stimulated before being removed. The empty stomach and intestines had only a small number of open capillaries. The injection of muscles was variable, but in most of the resting muscles few capillaries only were open, while muscles which had been [stimulated] before stopping the circulation were almost black from the large number of injected capillaries."

CONSEQUENCES IN THEORY AND PRACTICE

It was stated above, in the biographical sketch, that a large part of Krogh's work was concerned with the physiology of respiration and circulation. His primary interest appears to have been respiration, and many of his studies of circulatory mechanisms were aimed at finding out how the circulation carries oxygen to the tissues. Some of his earlier studies had dealt with gas exchange in the lungs. When the organism is under stress, breathing quickens and deepens. In determinations of the amount of blood which the heart pumps around the blood-vessel circuit in one minute, Krogh had found that when muscular work is performed there is a marked increase in the blood flow. Thus the extra oxygen taken in is passed along to the tissues. But a problem remained. Under these conditions of stress the oxygen of each cubic centimeter of blood is used up more quickly than when the body is at rest, so that obviously the demand for extra oxygen is not being met solely by the greater cardiac output. In the experiments described in the quotation, Krogh found that there was a great variation in the number of capillaries which might be open at a given moment. The number of patent vessels was directly related to the activity of the tissue at the time, being much larger in active than in resting muscle. Sometimes in resting muscle he could observe that a tiny vessel was so constricted that the oxygen-bearing red corpuscles could not enter it, the plasma alone being allowed to pass. (This he called "plasma skimming.") In active muscle, on the other hand, a larger number of vascular channels were opened, and they were opened more widely, so that as many red corpuscles as possible might carry their oxygen to the tissues. The extra blood supplied by the greater blood flow through the whole body was passed into as many as possible of the small channels where oxygen is given up *in those parts of the body needing it;* elsewhere the capillaries were constricted. Krogh considered that these changes play an important role in the mechanism for the regulation of the oxygen supply to tissues.

The physiology of the capillaries is a subject of great importance to medicine. Studies in normal and disordered blood pressure re-

quire minute and accurate knowledge of the behavior of the smaller divisions of the arterial tree. Inflammatory symptoms and allergic reactions of certain kinds depend on capillary changes. The permeability of capillary walls is altered in some hemorrhagic diseases. Accumulations of fluids in dropsical maladies are also determined in this way, and changes in the state of the capillaries explain many of the symptoms of shock. August Krogh has made valuable contributions to this basic knowledge of the anatomy and physiology of the capillaries.

REFERENCES

REHBERG, BRANDT P. "August Krogh, November 15, 1874-September 13, 1949," *Yale Journal of Biology and Medicine*, Vol. 24 (1951), pp. 83-102.

1921

No Award

1922

ARCHIBALD VIVIAN HILL

(1886–)

"For his discovery relating to the production of heat in the muscles."

OTTO MEYERHOF

(1844–1951)

"For his discovery of the fixed relationship between the consumption of oxygen and the metabolism of lactic acid in muscle."

BIOGRAPHICAL SKETCHES

HILL

ARCHIBALD VIVIAN HILL, DISTINGUISHED BIOPHYSICIST, WAS born in England in 1886 and was educated at Blundell's School, Tiverton. He won scholarships to Trinity College, Cambridge, where he studied mathematics. One of his teachers was W. M. Fletcher, who was then associated with F. G. Hopkins in investigating the formation of lactic acid in muscle. Hill apparently turned to physiology on Fletcher's urging, and J. N. Langley suggested that he undertake the work for which he afterward received the Nobel Prize. In 1910-1911 he studied in Germany under Bürker

and Paschen. He continued his work at Cambridge until the outbreak of the First World War, in which he served from 1914 to 1919. In 1920 he was appointed to the chair of physiology at Manchester, and from 1923 to 1925 he was Jodrell Professor of Physiology, University College, London. In 1926 came his appointment as Foulerton Research Professor of the Royal Society. As an Independent Conservative he was M.P. for Cambridge University from 1940 to 1945. He was also a member of the War Cabinet Scientific Advisory Committee, as well as of many other scientific and defense committees.

MEYERHOF

OTTO MEYERHOF, ONE OF THE PIONEERS OF PRESENT-DAY BIOchemistry, was born in Hanover on April 12, 1884. His family moved to Berlin and he attended the Wilhelms-Gymnasium there, then studied medicine in Freiburg, Berlin, Strasburg, and finally Heidelberg, where he was graduated in 1909, having written a dissertation in psychiatry. He then busied himself chiefly with psychology and philosophy, publishing a book entitled *Contributions to a Psychological Theory of Mental Diseases* and an essay called "Goethe's Methods in Natural Philosophy." Under the influence of Otto Warburg, he transferred his attention to physiology; while in Heidelberg he also worked at physical chemistry. In 1912 he went to Kiel. Lectures delivered in England and the United States appeared as a book, *The Chemical Dynamics of Living Matter,* which helped to make him widely known. Meyerhof occupied a variety of distinguished positions in German science before Germany's scientific and political decline. By 1929 he had become head of the Department of Physiology in the Institute for Medical Research in Heidelberg. Forced to leave Germany in 1938, he continued his work at the Institut de Biologie Physico-Chimique in Paris. After the invasion of France, in 1940, he escaped with his wife to the United States, where he was appointed research professor at the Department of Physiological Chemistry, University of Pennsylvania. Professor Meyerhof died in Philadelphia on October 6, 1951.

DESCRIPTION OF THE PRIZE-WINNING WORK

HILL *

"In the study of thermal changes [in muscle] the most consistent and valuable results have been obtained by utilising the isometric contraction of the sartorius muscle of the frog. [The sartorius is a straplike thigh muscle. "Isometric contraction" refers to the fact that the two ends of the muscle are fixed, so that the effort of contraction does not actually shorten it.] . . . The isometric contraction has the advantage, firstly, that energy is not liberated in it in any other form than heat . . . and secondly, that . . . movements of the instruments are prohibited. . . .

"The fundamental difficulty . . . is the smallness of the changes involved and their rapidity. In the muscle twitch of a frog's sartorius at 20° the rise of temperature is not more than 0.003° C and the time occupied in the earlier phases (as distinguished from the recovery process) is only a few hundredths of a second. The first requisite therefore is a very sensitive thermometric apparatus and great freedom from temperature changes, the second is extreme rapidity and lightness in the recording instruments. . . . [Hill then discusses thermometric apparatus and concludes that a very light, delicate, and sensitive thermopile is the only possibility. A thermopile is a kind of battery, made of alternating pieces of two different metals; heat applied to the junctions, or couples, gives rise to an electric current, the strength of which is measured by a galvanometer; an indirect measure of the heat is thus provided, and very minute temperature changes are detectable. Because of the nature of the apparatus, these readings cannot be accepted at face value, but the factors which distort the results can be eliminated by a control experiment.] Fortunately it is possible to make a direct calibration of the instruments [i.e., to scale them in such a way that results may be read as degrees of temperature] by liberating in the same muscle, in the identical position on the thermopile at the close

* From A. V. Hill, "The Mechanism of Muscular Contraction," *Les Prix Nobel en 1923.*

of an experiment, a known amount of heat . . . [first killing the muscle].

"One of my earliest observations on the subject was that the galvanometer deflection persists much longer in a live muscle than in a control experiment. . . . This phenomenon can be due only to a delayed production of heat, and I found that this 'recovery' heat as we called it is appreciable only in oxygen, being abolished by keeping the muscle in nitrogen, or by previous exercise violent enough to use up the oxygen dissolved in the muscle. . . . A rough estimate of the magnitude of the recovery heat production made it approximately equal to the total initial heat. [Hill's later work, with the help of W. Hartree, showed its magnitude to be 1.5 times the total initial heat.] This estimate appeared to answer unequivocally a question long debated, on the fate of lactic acid in the recovery process. Fletcher and Hopkins had found [in 1907] that lactic acid is removed in the presence of oxygen, though the same muscle at the end of the recovery process can liberate during exercise or rigor the same amount of lactic acid as before. Was lactic acid removed by oxidation, or by restoration to the precursor from which it came? Previous experiments of my own had shown that the production of one gramme of lactic acid in rigor leads to the liberation of about 500 calories. . . . Peters had proved that the production of 1 gramme of lactic acid in exercise . . . leads to the liberation of about the same quantity of heat. Hence, if the recovery heat were equal to the initial heat, the oxidative removal of one gramme of lactic acid would lead to the production of about 500 calories, which is less than 1/7th of the heat of oxidation of the acid. The conclusion . . . seemed to me to be inevitable—that the lactic acid is not removed by oxidation. . . .

"The most important point brought out by . . . analysis of the initial heat-production is that relating to the influence, or rather to the absence of influence, of oxygen. . . . No difference whatever can be detected between the curves obtained (*a*) from a muscle in pure oxygen and (*b*) from one which has been deprived of oxygen in the most rigorous manner for several hours. The conclusion is important and supplements the observations previously described on the recovery heat-production. Oxygen is not used in the primary break-down at all: it is used simply in the recovery process."

MEYERHOF *

"Let us first of all consider an excised frog's muscle, working in a maximal supply of oxygen; chemical analysis then reveals only this, that a definite amount of glycogen disappears from the muscle, while a quantity of oxygen is taken up and carbonic acid given off quite adequate for this oxidation. [Glycogen is a compound carbohydrate, 'animal starch,' found in most of the body tissues, especially in the liver and muscles.] But we can analyze the connection of events more closely if we first let the muscle work under anaerobic conditions [i.e., without oxygen] and then expose it to oxygen. During the anaerobic phase of work, lactic acid accumulates in the muscle, approximately in proportion to the work done. Simultaneously a corresponding amount of glycogen disappears. . . . In the second oxidative phase, on the other hand, the lactic acid which had been formed disappears, while a quite definite amount of extra oxygen is taken up, and actually the disappearance of lactic acid during this period bears an exact proportion to the increased consumption of oxygen. Meantime the oxygen suffices for the oxidation of no more than a fraction of the vanished lactic acid; the rest, in total fatigue about three quarters of the whole lactic acid, reverts quantitatively into glycogen. I may say . . . that this ratio of oxidized lactic acid to the acid which has disappeared is not constant under all conditions."

CONSEQUENCES IN THEORY AND PRACTICE

The complex of chemical events through which every physiological activity is carried on is a tangled skein to undo, and while a great deal is known about the body's chemistry, it is generally the case that each particular process is understood only up to a point; to push beyond this point is, of course, the object of research, and explanations which remain true in principle are constantly being revised in detail. This is what has happened in the case of Meyer-

* Translated from Otto Meyerhof, "Die Energieumwandlungen im Muskel," *Les Prix Nobel en 1923.*

hof's discovery. A fundamental point of great importance in muscle physiology was revealed by the work for which he won the Nobel Prize; but the chemistry of muscle is rather more complicated than it appeared at the time, and the work of other chemists, with his own later work, has brought about some revision and extension in the explanations which were given then. Hence the brevity of the quotation above.

Some fifteen years before Hill and Meyerhof delivered their Nobel lectures, W. M. Fletcher and F. G. Hopkins (the latter to become a Nobel laureate in 1929 for his work on vitamins) had shown that lactic acid is an essential part of the muscle machinery. It appears only gradually in a resting muscle, but rapidly during work. It accumulates more and more, until, when it reaches a concentration of a few tenths of one percent, the muscle becomes incapable of further contraction. This lactic acid disappears in the presence of oxygen; the fully recovered muscle is then able to work again and to produce as much lactic acid as before.

These changes of accumulation or removal of the acid could be detected only after evoking a series of responses in the muscle. Each change actually represented a summation of many changes. To study the transformations taking place in a muscle fiber during and immediately after contraction, to study the instantaneous and contemporary events, seemed beyond the reach of chemistry. The only change recorded in this flash-of-lightning way was the contraction itself; but this muscle twitch is merely the final result, the end product of activity. The mechanical record of a unit response told little; the chemical record was apparently not to be had. But the investigation of heat production seemed promising, for heat is associated with the chemical events which cause contraction. In the manner, and with the results, so clearly set forth above, A. V. Hill made use of this approach. It then appeared that the working phase of muscular activity, the actual contraction, is not dependent on oxygen, which is required, rather, for the recovery phase. The oxygen requirement for an exertion may even be met after the event; the body may assume an "oxygen debt," which explains the heavy breathing of an athlete when the race is over. Hill's thermal data had now to be fitted into the larger picture of chemical happenings in muscle.

Meyerhof found that as lactic acid accumulates a corresponding amount of glycogen disappears, no oxygen being supplied. This disappearance of glycogen was also observed in the presence of oxygen, but without the accumulation of lactic acid. Carbon dioxide was given off and more oxygen was consumed; but the increased oxygen consumption was only enough to account for the oxidation of a small part of the lactic acid. What happened to the rest? At the time of its disappearance the glycogen content was found to have increased. Meyerhof concluded that glycogen breaks down to form lactic acid in a contracting muscle, that lactic acid plays the dominant part in the actual contraction, and that the small part of it which is then oxidized supplies energy for the reconversion of the remainder into glycogen. That this is not the whole story was soon revealed, and the biochemistry of muscle has commanded much attention ever since. A series of complicated enzymatic reactions has been discovered; furthermore, considerable differences have been found between the mechanism of these events in frog muscle and in mammalian muscle. Embden, Lundsgaard, and Szent-Györgyi have made important contributions to the increasingly complex development, and Meyerhof himself published further studies (1938) on glycogen resynthesis. Half of the Nobel Prize for 1947 was awarded to C. F. and G. T. Cori jointly "for their discovery of how glycogen is catalytically converted" (see below, pp. 248-253).

Although Parnas and Wagner (1914) had shown that glycogen was the precursor of lactic acid, it was Meyerhof who demonstrated that the disappearance of the lactate could not be attributed to oxidation, and who first advanced the view that it undergoes resynthesis to form glycogen. Despite later extensions of knowledge this has remained a basic contribution to the understanding not merely of muscular action but of carbohydrate metabolism generally. (On further contributions of both Hill and Meyerhof, see below, pp. 193, 253.)

REFERENCES

H. [ILL], A. V. "Otto Fritz Meyerhof," *The Lancet,* Oct. 27, 1951, pp. 790-791.

1923

FREDERICK GRANT BANTING

(1891–1941)

JOHN JAMES RICHARD MACLEOD

(1876–1935)

"For their discovery of insulin."

BIOGRAPHICAL SKETCHES

BANTING

FREDERICK G. BANTING WAS BORN ON NOVEMBER 14, 1891, near Alliston, Ontario. He was educated in local schools and then attended the University of Toronto, where he registered as a student of divinity but soon transferred to medicine. He completed his medical studies in 1916 and served overseas as a medical officer from 1917 to 1919. In 1918 he was awarded the Military Cross for heroism under fire. Following a year of the study of orthopedic surgery in Toronto, he commenced practice in London, Ontario, but remained less than a year. Carrying out part-time teaching duties at the University of Western Ontario, he became interested in diabetes. In 1921 he returned to Toronto to undertake research on this problem in Professor Macleod's laboratory, where he was associated with C. H. Best, J. B. Collip, and a number of others.

His research and its successful issue are described below. Insulin was isolated in 1921 and the first patients were treated in 1922. In 1923 Banting became professor of medical research. The Banting Institute was opened in 1930 and Banting was knighted in 1934. In later years he was particularly interested in cancer research. In February 1941, while acting as liaison officer between British and North American medical scientists in the Second World War, he was killed in an aircraft disaster in Newfoundland.

MACLEOD

J. J. R. MACLEOD WAS BORN IN CLUNY, PERTHSHIRE, SCOTLAND, on September 6, 1876. He was educated at the Aberdeen Grammar School and the University of Aberdeen, studying medicine at Marischal College. He was graduated in 1898, was awarded the Anderson Research Travelling Fellowship, and studied biochemistry in Leipzig under Siegfried and Burian. In 1900 he became attached to the London Hospital Medical College, as demonstrator in physiology under Leonard Hill. In 1903 he was appointed professor of physiology at the Western Reserve University, Cleveland, Ohio, where he remained for fifteen years; during most of this time he carried on investigations in carbohydrate metabolism. In 1918 he accepted the position of professor of physiology at the University of Toronto, where the work on insulin was performed. In 1928 he returned to Scotland as professor of physiology at the University of Aberdeen. Here he continued his research both within the University and at the Rowett Research Institute. He also served on the Medical Research Council. In his later years Professor Macleod fell victim to a crippling arthritis. His health gradually became worse and he died on March 16, 1935. His scientific, literary, and educational work was very extensive. He was the author of several books, including a well-known text, *Physiology and Biochemistry in Modern Medicine*. He was very successful as a teacher, and some of the most distinguished medical scientists of the present day in the United States and Canada were trained in Macleod's laboratory.

DESCRIPTION OF THE PRIZE-WINNING WORK

BANTING *

"On October 30th, 1920, I was attracted by an article by Moses Baron, in which he pointed out the similarity between the degenerative changes in the acinus cells of the pancreas following experimental ligation of the duct, and the changes following blockage of the duct with gall-stones. [Acinus cells secrete a digestive juice and are distinct from hormone-producing cells.] Having read this article the idea presented itself that by ligating the duct and allowing time for the degeneration of the acinus cells, a means might be provided for obtaining an extract of the islet cells free from the destroying influence of trypsin and other pancreatic enzymes. [The islet cells secrete the hormone.]

"On April 14th, 1921, I began working on this idea in the Physiological Laboratory of the University of Toronto. Professor Macleod allotted me Dr. Charles Best as an associate. Our first step was to tie the pancreatic ducts in a number of dogs. At the end of seven weeks these dogs were chloroformed. The pancreas of each dog was removed and all were found to be shrivelled, fibrotic, and about one-third the original size. Histological examination showed that there were no healthy acinus cells. This material was cut into small pieces, ground with sand, extracted with normal saline. This extract was tested on a dog rendered diabetic by the removal of the pancreas. Following the intravenous injection the blood sugars of the depancreatized dogs were reduced to a normal or subnormal level, and the urine became sugar free. There was a marked improvement in the general clinical condition as evidenced by the fact that the animals became stronger and more lively, the broken down wounds healed more kindly, and the life of the animal was undoubtedly prolonged. . . .

"The second type of extract was made from the pancreas of dogs in which acinus cells had been exhausted of trypsin by the long continued injection of secretin. [See above, p. 21]

* From F. G. Banting, "Diabetes and Insulin," *Les Prix Nobel en 1924-25.*

"The third type of extract used in this series of experiments was made from the pancreas of foetal calves of less than four months development. Laguesse had found that the pancreas of the newborn contained comparatively more islet cells than the pancreas of the adult. Since other glands of internal secretion are known to contain their active principle as soon as they are differentiated in their embryological development, it occurred to me that trypsin might not be present since it is not used till after the birth of the animal. Later I found that Ibrahim had shown that trypsin is not present till seven or eight months of intrauterine development. Foetal extracts could be prepared in a much more concentrated solution than the former two varieties of extract. It produced marked lowering of blood sugar, urine became sugar free and there was marked clinical improvement. Its greatest value however was that the abundance in which it could be obtained enabled us to investigate its chemical extraction.

"Up to this time saline had been used as an extractive. We now found that alcohol slightly acidified extracted the active principle, and by applying this method of extraction to the whole adult beef pancreas active extracts comparatively free from toxic properties were obtained. . . .

"The extracts prepared in this way were tried on depancreatized dogs and in all cases the blood sugar was lowered. . . . Diabetic dogs seldom live more than 12 to 14 days. But with the daily administration of this whole gland extract we were able to keep a depancreatized dog alive and healthy for ten weeks.

"The extract at this time was sufficiently purified to be tested on three cases of diabetes mellitus in the wards of the Toronto General Hospital. There was a marked reduction in blood sugar and the urine was rendered sugar free. . . ."

MACLEOD *

"The invariable lowering of the blood sugar which was observed to result from the administration of insulin in animals rendered diabetic by pancreatectomy, raised the question as to

* From J. J. R. Macleod, "The Physiology of Insulin and Its Source in the Animal Body," *Les Prix Nobel en 1924-25.*

whether such would also occur in those forms of hyperglycaemia which can be induced by other experimental procedures, such as the injection of epinephrin, piqûre or asphyxia. As the first step in the investigation of this question, Collip injected insulin into normal rabbits and found the blood sugar to become lowered, thus furnishing a valuable method for testing the potency of various preparations and, therefore, for affording a basis for their physiological assay. At the same time it was found that neither piqûre, nor epinephrin, nor asphyxia caused any hyperglycaemia in rabbits in which, as a result of injection with insulin, the blood sugar was at a low level to start with.

"Peculiar symptoms (convulsions and coma) were observed in many of the injected animals, and it was soon possible to show that these were related to the lowering of the blood sugar and that they usually supervened when this was about 0.045 per cent. Sometimes the animals recovered spontaneously from these symptoms, but more frequently the coma became so profound, with marked fall of body temperature, that death occurred. That the lowering of blood sugar is closely related to the occurrence of the symptoms, was proved by finding that the subcutaneous injection of a solution of glucose was followed, almost immediately, by complete recovery, even in cases in which death was imminent from deep coma. It has been found, in collaboration with Noble, that glucose is remarkably specific in this regard. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

Long before 1922 the dietary treatment of diabetes had been developed to a high degree of refinement. This treatment, although it helped to minimize symptoms and prolong life, was far from satisfactory, since only the milder cases could be kept under control and even these very often grew worse. Diabetes was then a severe debilitating disease, ultimately fatal in a great majority of cases, usually rapidly fatal in children. Infections of various kinds were very likely to supervene, surgery was most hazardous, and childbearing was dangerous to both mother and child. After the introduction of insulin it became possible to control most cases,

and all the incidental dangers were diminished or removed. Life was greatly prolonged and useful activity restored. Unfortunately the diagnosis of the disease and the use of the remedy have not been universal even in the Americas and Europe. Full realization of the benefit of the discovery has therefore never been attained. None the less the transformation in the therapy of diabetes has been as striking as any single advance in modern medicine.

At the time when Banting, Best, Macleod, and Collip were carrying on their research in Toronto, other workers were pursuing the same end in several other centers. After the discovery was announced a further impetus was given to this research and valuable results were achieved in the study of carbohydrate metabolism. On the practical side, H. C. Hagedorn and D. A. Scott were responsible for the production of protamine-zinc insulin, which has a prolonged effect. On the side of "pure" research, B. A. Houssay, in the year after insulin was discovered, began his related studies of the function of the pituitary body (see below, p. 244). These are only two examples of the work which followed the stimulus of the Toronto discovery. A "working cure" for diabetes, a therapy of replacement of the deficient hormone, had been introduced by the Toronto group, and the search for underlying factors in the genesis of the disease had been given not only a new stimulus but a new basis in added knowledge from which to proceed.

REFERENCES

HARRIS, SEALE. *Banting's Miracle* (Philadelphia: Lippincott, 1946).

STEVENSON, LLOYD. *Sir Frederick Banting* (Toronto: Ryerson Press; Springfield, Ill.: Thomas, 2nd ed., 1947).

1924

WILLEM EINTHOVEN

(1860–1927)

"For his discovery of the mechanism of the electrocardiogram."

BIOGRAPHICAL SKETCH

WILLEM EINTHOVEN WAS BORN ON MAY 21, 1860, IN THE Dutch East Indies, where his father was a practicing physician. When Willem was ten years old his father died; his mother returned to Holland with her six children and settled in Utrecht. In 1878 Einthoven began the study of medicine at the University, where his teachers included the physicist Buys Ballot, the anatomist Koster, and the great physiologist and ophthalmologist F. C. Donders. He became doctor of medicine in 1885 and was called to Leyden in the same year to succeed Heynsius in the chair of physiology; until 1905 his department was also responsible for the teaching of histology. Einthoven approached physiology as a physicist, no doubt partly, at least, as a result of his training in Utrecht; but his knowledge of anatomy, histology, and optics was also of great value to him in his famous work of devising the modern electrocardiograph and interpreting the data obtained by its use. This naturally led him toward pathological physiology and clinical medicine. Einthoven died in 1927.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The string galvanometer consists of a delicate thread, conducting electric current, stretched like a string in a magnetic field. As soon as the thread is electrified, it deviates from its equipoise in a direction at right angles to the direction of the magnetic lines of force. The magnitude of the deviation is proportional to the strength of the current flowing through the thread, so that this can be easily and exactly measured. . . . [This instrument, invented by Einthoven, is the essential part of the modern electrocardiograph. The "string" of the latter is a fiber of finely spun silver-coated quartz glass, 0.002 mm. in diameter, or about $\frac{1}{4}$ of the diameter of a red blood cell; platinum has also been used in place of silvered quartz. A beam of light, directed through holes in the arms of the magnet, throws the shadow of the string on a photographic plate or film, or on sensitive paper, through a series of lenses which magnify the image. This photographic surface, in a camera of special design, moves at an appropriate speed to record the successive positions of the string in its lateral movements, or deflections. The sensitivity of the string is standardized so that a deflection of a certain magnitude represents a certain strength of current. The record is marked out in horizontal lines (to measure the magnitude of deviation, and hence the strength of current) and vertical lines (to indicate the time intervals). Various technical refinements have from time to time been introduced.]

"Just as every muscle in its contraction generates an electric current, so also in the heart there is an evolution of electricity with every systole [contraction]. This was first described by Kölliker and Müller. The English physiologist Augustus D. Waller then showed that differences in potential developed in the heart are conducted to different parts of the body, and that with a sensitive measuring instrument, the capillary electrometer, one is in a position to observe the variations in potential of the human heart. [The capillary electrometer consists of a capillary tube filled with

* Translated from Willem Einthoven, "Das Saitengalvanometer und die Messung der Aktionsströme des Herzens," *Les Prix Nobel en 1924-1925.*

weak acid; a globule of mercury, placed in the center, moves toward the negative pole when an electric current is passed through the tube, and the image of the mercury is projected for photographic record.] One needs only to lead the current from the hands and feet to the measuring instrument in order to see the variations in electric current, which show the same rhythm as the heart action.

"If one records the deviations of the measuring instrument one obtains a curve, which was called the electrocardiogram. But because of the imperfections of the capillary electrometer the curve directly recorded does not portray in an exact manner the actual variations in potential that have occurred. To get an exact picture, one must construct a new curve based on the peculiarities of the instrument used and the data of the recorded curve, work requiring considerable time. This circumstance stood in the way of the practical application of electrocardiography to the investigation of cardiac patients, and general interest in the ECG first developed later, after the string galvanometer made it possible to register the required pattern directly, easily, and quickly, and with satisfactory accuracy. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

Einthoven first constructed a string galvanometer in 1903. From 1906 to 1921 he gradually improved it. It came into fairly general use in hospitals, and the modern electrocardiograph is based on the same principles. By 1906 Einthoven had observed that different types of heart disease show different, and distinctive, tracings on the electrocardiogram. Between 1908 and 1913 he worked on the interpretation of the normal tracing, so as to provide a secure basis for the understanding of deviations from the normal result. His interpretation of each wave and complex in the recorded curve was worked out during this period, and the Prize was actually awarded not for the invention of the string galvanometer, but "for his discovery of the mechanism of the electrocardiogram."

Einthoven's work was confirmed and extended by a number of other scientists, particularly by Thomas Lewis. Analysis of the

symptoms of heart disease as seen in the electrocardiogram was developed in detail by a generation of cardiologists who had been provided by Einthoven with a precise tool for their study. This method often makes for quicker and more reliable diagnosis. When recorded serially, electrocardiograms may provide decisive evidence in questionable cases of coronary thrombosis. They aid in localizing the site of the area affected by obstruction of a coronary vessel (the area of "infarction"). In this and other forms of heart disease they establish the nature of the disturbances of the heart's rhythm or mechanism. Often they are of great value in following the course of healing, and so help to determine the nature of treatment.

1925

No Award

1926

JOHANNES FIBIGER

(1867–1928)

"For his discovery of the Spiroptera *carcinoma."*

BIOGRAPHICAL SKETCH

JOHANNES ANDREAS GRIB FIBIGER WAS BORN IN SILKEBORG, Denmark, on April 23, 1867. He finished his medical studies in 1890. From 1891 to 1894, after hospital work and some further study with Koch and Behring, he was assistant to C. J. Salmonsen in the bacteriology laboratory of the University of Copenhagen. Then, until 1897, he was associated with the Hospital for Contagious Diseases in Copenhagen, meanwhile (1895) obtaining his doctoral degree with a thesis on the bacteriology of diphtheria. After 1897 he worked at the Institute of Pathological Anatomy of the University and in the army bacteriological laboratory. In 1900 he was named professor of pathological anatomy and head of the Institute. He carried out a large number of official commissions and took part in the direction of numerous institutes and societies. He was co-editor, as well as one of the founders, of *Acta Pathologica et Microbiologica Scandinavica;* he was also co-editor of *Zieglers Beiträge.* Fibiger died on January 30, 1928, in Copenhagen, after a short illness.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The researches I am going to communicate started out from some observations I had occasion to make at the end of the year 1907. At the autopsy of three wild rats . . . which originally had served for subcutaneous injections of tubercle bacilli, the stomach showed itself in the three animals to be the site of severe lesions. The stomach was greatly enlarged, heavy, and of firm consistency. The exterior surface was rough, especially at the fundus [the cardiac end of the stomach, where food is received] and divided by means of furrows into slightly elevated parts, gray-yellow in color. After opening it, one found only localized lesions in the fundus, while the pyloric region was normal. The wall of the stomach was greatly thickened at the fundus . . . the mucous membrane arching toward the stomach cavity in the form of folds and of stout, irregular ridges, prolonged in out-juttings, and of papillomatous polyps [see below]. . . .

"Microscope examination ascertained that the enormous thickening of the walls was caused essentially by a very marked epithelial hyperplasia [excessive growth of the surface layer] and by a severe papillomatosis [overgrowth of tiny, nipplelike processes normally present at the surface] and also, but in a less pronounced manner, by acute and chronic inflammatory lesions. . . .

"At the histologic examination one was struck to see that here and there, in a small number of sections, the superficial epithelium contained cavities of different shapes: circular, oval, or cylindrical. Continuing the researches, it was found that in other preparations these cavities were filled by peculiar bodies, not found in the parts of stomachs first examined. . . .

"These bodies had very distinct contours and complicated structure, making the supposition a probable one that this was a matter of the more highly organized animal parasites. . . .

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* Translated from Johannes Fibiger, "Recherches sur un nématode et sur sa faculté de provoquer des néoformations papillomateuses et carcinomateuses dans l'estomac du rat," *Académie Royale des Sciences et des Lettres de Danemark: Extrait du Bulletin de l'Année 1913, No. 1.*

[In an effort to determine the frequency of this disease, which incidentally had nothing to do with tuberculosis, and also to find new cases for further study, Fibiger examined 1144 rats, with negative results. Back in 1878, M. Galeb had described a nematode, a threadlike worm, as parasitic in rats' stomachs. He had shown that this appeared to be the same nematode already described as early as 1824 as a parasite in a common kind of cockroach, *Periplaneta orientalis*. Feeding nematode-infested cockroaches to rats, Galeb was able to parasitize them. So Fibiger looked for rats and cockroaches together, then examined the stomachs of the rats, but without success. He fed large numbers of cockroaches to rats. No luck.]

"At last, informed that in a locality of the city [Copenhagen] (a great sugar refinery) rats and cockroaches were found en masse, I resolved to examine the rats of this district, too, although the cockroach in question was not the *Periplaneta orientalis* spoken of by M. Galeb, but a different species, the *P. americana*. . . .

"Contrary to all expectation, the result of the examination was positive. . . . [Thus Fibiger's studies could be continued. As it turned out, Galeb's nematode was not the same. Nor, on the other hand, was *P. americana* a necessary part of the story, as Fibiger naturally supposed at first, for the commoner *P. orientalis* would likewise serve his purpose; so that when the sugar refinery burned down, his work was only temporarily interrupted. He had found the required nematode again, and he could show that only a part of its life cycle takes place in the rat, rat-to-rat transmission never occurring. Eggs passed by rats were fed to cockroaches, and the cockroaches were fed to rats. There then appeared to be a proportional relation between the number of parasites and the duration of their life in the stomach, on the one hand, and the degree of anatomic change on the other.]

"In general, the successive development of the anatomical alterations can be represented in the following manner: as the initial phenomenon, simple epithelial hyperplasia, ordinarily followed by acute inflammation. The inflammation ever increasing, the growth of the epithelium in depth, the formation of epithelial papillomata and heterotopia [*heteros,* other + *topos,* place: the presence of these cells in parts where they are normally absent] are added to these

phenomena. As the terminal stage: severe papillomatosis, development of large epithelial crypts with the more or less extensive destruction of the stomach wall. As deviations from this course of development: (1) some cases in which the inflammatory processes are little pronounced or totally absent . . . (2) some cases in which the process becomes malignant in the proper sense of the word, by the development of a cancroid having the faculty of producing metastases [new growths in parts of the body remote from the original tumor]."

CONSEQUENCES IN THEORY AND PRACTICE

Fibiger's discovery of *Spiroptera* carcinoma appeared to be a clear confirmation of the view of Rudolf Virchow, the great pioneer of cellular pathology, that cancerous growths are due to chronic irritation. Here was a tiny worm, a nematode, apparently the source of both mechanical and chemical irritation, and it seemed that Fibiger's careful experiments, only partly indicated in the abstract above, had conclusively shown it to be the cause of a particular kind of cancer in rats. Some believed this was due to non-specific irritation; Fibiger thought it due to specific toxins. There was, it is true, some question raised about the real nature of this disease. Parasites of other kinds were known to cause proliferative diseases, but these came to be regarded as noncancerous. The part originally diseased might set up colonies, so to speak, in remote parts of the body; but these were not true "metastases," resulting from the inherent ability of morbidly overactive cells to establish new foci and multiply afresh, for in each of the new locations parasites were found. Like scattered abscesses, these areas represented the migrations of the causative organism. But the metastases seen in Fibiger's disease were true metastases, containing no parasites: the cells themselves had become malignant. There was likewise some dispute over the microscope evidence of the cells (the finer points of the histology have not been given above). But in the course of time it was generally agreed that the tumor was a true malignant, or cancerous, growth. More recently doubts have been raised about the role of the nematodes. It has been suggested that a vitamin

deficiency was responsible for Fibiger's results, since A. Y. Fujimaki was able to produce stomach tumors, some benign and some malignant, by feeding rats on a vitamin-deficient diet. A. Borrel, who anticipated Fibiger in suggesting that parasites might be concerned in causing cancer, continued to maintain his original view that such parasites could only be the carriers of a virus, the real causative agent.

In earlier studies of cancer it had sometimes been found possible to transplant malignant growths to other animals of the same species. But these studies did not show the origin of the tumors, and the earliest stages of their growth could not be followed. It therefore appeared of great importance to have a method at hand for producing a form of cancer experimentally, although this had been done a short time before in the experiments of J. Clunet by X irradiation. Two years after the publication of Fibiger's work, other scientists, perhaps encouraged by his success, were able to produce experimental cancer in rabbits by the use of coal tar. A number of carcinogenic (cancer-causing) substances have since been isolated from coal tar and have been shown to be related chemically to sex hormones, bile acids, and other substances of biological importance.

Fibiger expressed the hope that some forms of human cancer might be shown to be caused by parasites. He did not believe that he had discovered a general principle of broad application, but only that some small part might be found for parasitology in the genesis of human cancer. Even this modest hope was doomed to disappointment. Bilharziasis, a tropical disease caused by a small worm, produces cancers of the bladder or rectum in about 5 per cent of cases; and cancer of the liver is known to follow another kind of infestation. These instances were recognized before the time of Fibiger's work. The vast majority of cancers cannot be explained in this way.

REFERENCES

OBERLING, CHARLES. *The Riddle of Cancer.* Translated by W. H. Woglom. Revised ed. (New Haven: Yale University Press, 1952), pp. 65-74.

1927

JULIUS WAGNER-JAUREGG

(1857–1940)

"For his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica."

BIOGRAPHICAL SKETCH

JULIUS WAGNER-JAUREGG WAS BORN IN WELS, IN UPPER AUSTRIA, on March 7, 1857. (The hyphen in "Wagner-Jauregg" takes the place of "von," the distinction of nobility discontinued by the socialist regime after the First World War.) He received the degree of doctor of medicine in 1880 from the University of Vienna, where he began his scientific career in the Department of Experimental Pathology and Internal Medicine. In 1883 he joined the staff of the psychiatric clinic. This was apparently a second choice, forced upon him by circumstances, but he soon became deeply interested in psychiatry and was later renowned not only for his research but also for his activity as a teacher. In a publication of 1887 he proposed to produce febrile diseases deliberately as a treatment for psychiatric patients, using malaria and erysipelas. His preliminary trials did not proceed far. From 1889 to 1893 he was professor of psychiatry and neurology at the University of Graz (Austria). In 1890 Koch introduced tuberculin, and Wagner-Jauregg tried it as a fever-producer on patients at Graz. These experiments were stopped because tuberculin had come to be considered dangerous. At this time he was recalled to Vienna as head

of the University Hospital for Nervous and Mental Diseases, and in 1894 he resumed his work with tuberculin. The first malaria inoculations for dementia paralytica were given on June 14, 1917.

Wagner-Jauregg published many early contributions on physiology and pharmacology. Later he was interested in forensic psychiatry, in cretinism, myxedema, and the prevention of goiter. He retired from his professorship in 1928, and he died October 1, 1940, in his eighty-fourth year.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"Progressive paralysis [also called paresis, general paralysis of the insane, dementia paralytica] has always been considered an incurable disease, leading in the course of a few years to dementia and death.

"Nevertheless there was on record a series of cases of progressive paralysis which had been cured; cases in which all the symptoms had disappeared so completely as to permit those affected to be independently active for years, in life and employment. And even if such cases were quite extraordinarily rare, there was a comparatively frequent occurrence of remissions of some duration, in which there was a retrogression, greater or less in degree, of symptoms already developed. Thus, in principle at least, progressive paralysis had to be a curable disease. . . .

"The observation was now forthcoming that in the rare cases of healing and in the frequent remissions of progressive paralysis, a febrile infectious malady or a protracted suppuration often preceded the improvement in the state of the disease.

"Therein lay a hint. These cures following febrile infectious diseases, of which I myself had witnessed striking cases, induced me as early as the year 1887 to propose that this natural experiment be imitated by deliberately producing infectious diseases, and at that time I named malaria and erysipelas as suitable diseases. As a particular advantage of malaria, I stressed the fact that it is possible to interrupt the disease at will with quinine, and did not yet suspect

* Translated from "Nobel-Vortrag von Julius Wagner-Jauregg," *Les Prix Nobel en 1927.*

at that time to what extent the expectation would be fulfilled through inoculation with malaria.

"Apart from an unsuccessful experiment with erysipelas, I did not proceed as yet to the direct execution of this proposal, and furthermore I would scarcely have had the authority at that time to carry it through.

"Instead, starting in 1890, I attempted to imitate the action of a febrile infectious disease by the use of tuberculin, just introduced by Koch, at first not only in progressive paralysis but also in other mental derangements, and as a matter of fact with favorable results in not a few cases. [This was to some extent a forerunner of the protein therapy which later attained great development.]

"Since there were some cases of progressive paralysis among them, my interest soon concentrated on this disease, for a favorable result could not so easily be considered an accident here as in other psychoses.

"After . . . it had been established that the paralytics treated with tuberculin . . . showed more, and more lasting, remissions than an equal number of untreated paralytics, this treatment was carried out systematically . . . and at the same time an energetic iodine-mercury cure, later combined with injections of salvarsan, was instituted. . . .

"The remissions which were obtained by the mercury-tuberculin treatment did not differ qualitatively from those to be obtained by inoculation with malaria. . . . But the number of relapses was large; the lasting remissions were in the minority.

"I tried to enhance the action of the nonspecific treatment by the use of different vaccines . . . without much effect on the frequency of the discouraging relapses.

"In the course of this therapeutic research, I could repeatedly make the observation that particularly complete and lasting remissions took place in just those cases in which, concurrently with the treatment, some incidental infectious disease occurred, for instance pneumonia [or] an abscess.

"Consequently, in 1917, I set about the execution of the proposal I had made in the year 1887, and inoculated nine cases of progressive paralysis with tertian malaria.

"The result was gratifying beyond expectation: six of these nine

cases obtained extensive remissions, and in three of these cases the remission proved lasting, so that this year [1927] I was able to present these cases . . . as having carried on their occupations without interruption for ten years. After the outcome of this first experiment had been followed for two years, I undertook, in the autumn of 1919, to pursue this therapeutic research on a large scale. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

Wagner-Jauregg appears to have contemplated the use of malaria in treating paretic dementia for many years, and when, in 1917, a patient with tertian malaria appeared in one of his wards he considered this as a sign of fate and proceeded to carry out his plan. The tertian variety of the disease is still preferred, although the quartan type has also had its advocates.

Dementia paralytica, perhaps more commonly known as GPI (general paralysis of the insane), or simply general paresis, is a progressive disease of the brain and meninges (brain coverings) due to syphilis. In adults it is usually a late result of an untreated or inadequately treated antecedent syphilis; a juvenile form (juvenile paresis) usually is due to congenital syphilis. The proper treatment of the early stages of syphilis is the only sure means of prevention. Fever therapy is indicated in all cases of GPI, as well as in *paresis sine parese,* meaning the same disease before paralytic signs have occurred but where the mental symptoms and laboratory indications point to neurosyphilis.

Fever therapy since Wagner-Jauregg has taken various forms, ranging from sodoku (rat-bite fever), killed typhoid bacilli, preparations containing colloidal sulfur, and continuous hot-air and hot-water baths, to diathermy. A variety of nonspecific proteins have been employed. Although fever cabinets are widely used, some psychiatrists consider it doubtful that any other fever-producing agent gives results as good as does the malaria treatment. The mortality from malaria is low and it is claimed that about 30 to 40 percent of those so treated show permanent recovery (more than five years). It is especially during the earliest stage that the in-

volvement of the central nervous system is amenable to treatment; no treatment of any kind is capable of restoring damaged brain tissue. Fever therapy, however, combined with an antisyphilitic drug (especially tryparsamide) tends to prolong life and arrest deterioration. The newer drugs for the treatment of syphilis may alter the picture somewhat; but as yet there is no likelihood of dispensing with fever treatment, as introduced nearly thirty-five years ago by Wagner-Jauregg.

1928

CHARLES NICOLLE

(1866–1936)

"For his work on typhus."

BIOGRAPHICAL SKETCH

CHARLES NICOLLE WAS BORN SEPTEMBER 21, 1866, AT ROUEN, where his father practiced medicine. He first attended the *lycée* in his native city, then studied medicine in Paris. In 1893, at the conclusion of his studies, he was named to the faculty of the Medical School in Rouen and appointed physician to the Rouen hospitals. At the instigation of his brother, Maurice Nicolle, a microbiologist, he took the Pasteur Institute course in microbiology in 1892. In 1902 he succeeded Adrien Loir as director of the Pasteur Institute in Tunis. Here he carried out the work on typhus described below, in which he demonstrated the role played by the louse. A later achievement of importance was the distinction he helped to draw, after a visit to Mexico, between classic, louse-borne epidemic typhus and the murine variety, which has its reservoir in rats and is transmitted sporadically to man by the rat flea. (The murine type, under the name of *tabardillo,* has appeared epidemically in Mexico. Nicolle has been credited in France with distinguishing murine from classic typhus. It appears, however, that the most important contributions to the knowledge of murine typhus were made by Maxcy, Dyer, Rumreich, Badger, Mooser, Castaneda, and Zinsser.) In 1932 Nicolle took the place of d'Arsonval in the chair once held by Claude Bernard, Magendie, and Laënnec at the Collège de

France. He carried out extensive work on a variety of infectious diseases. In addition to being known for his studies of typhus he was chiefly distinguished for a number of innovations in technique. He was the founder of the *Archives de l'Institut Pasteur de Tunis.* He wrote not only scientific but literary and philosophic works. He died February 28, 1936.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The center of my observations was the native hospital of Tunis. When I visited this hospital I often stepped over the bodies of typhus patients who had come to be admitted and had fallen down from exhaustion at the door. Now there was a singular event taking place in this hospital, the significance of which no one had understood, and which impressed me. The typhus patients were lodged at this time in the common medical wards. As far as the doors of these rooms they scattered the contagion. Typhus developed on contact with them in the families where they were received, and the doctors required to visit them became infected on contact. Moreover the contagion struck the personnel of the admitting offices of the hospital, the employees whose duty it was to collect the clothes and linen, and the laundresses who washed them. And for all this, a typhus patient once admitted to the common ward did not contaminate a single one of his ward neighbors, not an attendant, not a doctor.

"This observation was my guide. I asked myself what happened between the hospital door and the sickroom. What happened was this: the typhus patient was relieved of his clothes and linen, and was shaved and washed. The agent of the contagion was therefore something attached to his skin, to his linen, and something of which soap and water rid him. This could only be the louse. . . .

"If it had not been possible to reproduce the malady in animals and consequently to verify the hypothesis, this simple determination would have sufficed to make clear the mode of propagation of

* Translated from "Conférence Nobel par Charles Nicolle," *Les Prix Nobel en 1928.*

typhus. Fortunately it was possible to bring experimental proof to bear upon it.

"My first attempts to transmit typhus to laboratory animals, consisting of little monkeys, failed, like similar attempts of my predecessors, and for reasons which it is easy for me to explain to myself today.

"I asked my *maître,* M. Roux, to procure a chimpanzee for me, thinking that an anthropoid might be more sensitive than animals of other kinds. The very day I received it, I inoculated it with the blood of a patient. . . . The chimpanzee showed a fever. With its blood, obtained during this fever, I inoculated a macaque (*M. sinicus*), which also showed a fever. On this macaque I fed lice which I transferred to other macaques. These were infected and later showed themselves to be vaccinated against a trial inoculation. . . . [Monkeys are expensive animals for experiment and Nicolle discovered that guinea pigs, rats, and mice are also susceptible to typhus; most of his later work was done on guinea pigs. He found that lice are incapable of spreading contagion until about a week after taking up blood; he also found that development occurs meanwhile in the digestive tract of the louse, and that the feces become virulent.]

"Typhus is characterized in man by a symptomatic triad: fever, eruption, signs of nervous involvement. In animals, fever is the only sign of infection. . . .

"It sometimes happens, especially when one uses blood, that in a lot of guinea pigs, inoculated with the same dose of the same material, certain ones do not show any fever. At first I attributed this failure to a fault in technique, or else to a greater individual resistance. The repetition of negative results did not permit me to accept these too facile explanations for long. The animals for which the virus is pathogenic present a picture of variable sensitivity, which runs from the very severe, often fatal, typhus of the European adult to the merely thermometric fever of the guinea pig, passing through all the intermediate degrees: typhus of the adult native, benign typhus of the children, still more benign in monkeys. I asked myself if there did not exist, below the already very feeble sensitivity of the guinea pig, a yet slighter degree in which the only sign of infection would be the virulent power of the blood

during the period when the more sensitive animals show the characteristic fever. It was indeed so."

CONSEQUENCES IN THEORY AND PRACTICE

Nicolle transformed the fight against typhus into a fight against the louse. For many years the methods of delousing were elaborate, laborious, time-consuming, and not altogether effective. To a large degree they worked; the difficulty was to apply such methods on a broad enough scale. Particularly in winter, when lice are favored by heavy clothing, crowding, and infrequent bathing, it proved impossible to put a quick stop to outbreaks of typhus, at least among civilian populations. In the past ten years, however, such outbreaks have been effectually suppressed on several occasions by the liberal use of DDT (see below, p. 258).

Nicolle also gave a convincing demonstration of what he called "inapparent disease." He showed that there are instances in which no symptoms whatever appear, yet the blood is virulent on inoculation. This fact has been brought forward to explain the mystery of how the contagion survives between epidemics.

It is interesting that Theobald Smith, Patrick Manson, David Bruce, and the members of the Yellow Fever Commission—demonstrators of insect vectors in disease—were not rewarded with the Nobel Prize. Possibly the theoretical aspect of Nicolle's work, together with its importance in combating typhus during the First World War, influenced the decision to honor him with the Prize.

Typhus has been known for centuries as one of the great epidemic diseases. It has been associated with a massing of people in cities, armies, prisons, and ships. Its alternative names—ship fever, jail fever, prison fever, camp fever, hospital fever—are revealing. It has also been known as war fever, since fatal epidemics have attended most of the great wars. To an important degree typhus is a social disease, requiring a lousy population to feed upon. Present ability to cope with it in an emergency depends less upon prophylactic vaccination and modern treatment than upon powerful new insecticides. Nicolle convicted the louse; Paul Müller, of DDT fame, discovered the means to kill it.

1929

CHRISTIAAN EIJKMAN

(1858–1930)

"For his discovery of the antineuritic vitamin."

FREDERICK GOWLAND HOPKINS

(1861–1947)

"For his discovery of the growth-stimulating vitamins."

BIOGRAPHICAL SKETCHES

EIJKMAN

THE SON OF A SCHOOLMASTER, CHRISTIAAN EIJKMAN WAS BORN on August 11, 1858, in Nijberk, a small town on the Zuyder Zee. He began his studies at the University of Amsterdam in 1875 and was for some years assistant to the professor of physiology there. In 1883 he joined the colonial army in the Dutch East Indies but he was invalided home two years later and resumed his laboratory work, this time as a bacteriologist. In 1886 he returned to the Dutch East Indies as a member of the Pekelharing-Winkler Commission to study beri-beri. This group vainly sought a bacterial

cause for the disease. When his colleagues returned home, Eijkman remained in Batavia as director of a new laboratory for bacteriology and pathology, taking charge of the medical school for native doctors as well. It was during this period that he carried out the work on beri-beri described below. He later studied "tropical anemia," denying it separate existence as a disease entity. He also challenged the assumption that metabolism varied greatly with climate. Among the more important investigations of his later years were his study of fermentation tests and the demonstration of the presence of the colon bacillus in water (Eijkman's test). Ill once again, Eijkman returned home in 1896 and became professor of hygiene at the University of Utrecht; he held this post until 1928. In 1930 he died.

HOPKINS

FREDERICK GOWLAND HOPKINS WAS BORN JUNE 20, 1861, IN Eastbourne, in Sussex, England, where he spent the first ten years of his life alone with his widowed mother, attending a dames' school from the age of six and playing with his father's microscope from the age of eight or nine. After 1871 they lived in Enfield with his mother's brother, James Gowland. For nearly four years Hopkins attended the City of London School, but despite a good record at first he had ultimately to withdraw because of truancy—"sheer boredom" was his own explanation. He then attended a private school. At seventeen he entered an insurance office, but remained for only six months; he then became an articled pupil to an analytical chemist. Later he attended the Royal School of Mines at South Kensington and worked for a few months as assistant in a private laboratory. A few courses at University College and success in examination for associateship of the Institute of Chemistry brought an invitation from Dr. (later Sir Thomas) Stevenson, Medical Jurist at Guy's Hospital and Home Office expert, to assist in his laboratory. While working there, Hopkins took a degree extramurally from the London University. In 1888 he began to study medicine at Guy's. In 1894 he qualified and obtained the London M.B. He then joined the school staff at Guy's but left in 1898, going to Cambridge at the invitation of Michael Foster to develop teaching and research in physiological chemistry. There he

spent the rest of his life, at first with meager facilities, but after 1925 in a well-endowed institute. He was everywhere recognized as *facile princeps* of English biochemistry, which he established almost singlehanded. His honors included knighthood, in 1925; the Copley Medal, in 1926; the Nobel Prize, in 1929; presidency of the Royal Society, in 1931; and the Order of Merit, in 1935. He retired in 1943 and died in 1947. In addition to his dietary studies, his work on glutathione and tissue oxidation, on muscle chemistry, and on uric acid are very well known.

DESCRIPTION OF THE PRIZE-WINNING WORK

EIJKMAN *

"An accident set me on the right road.

"In the chicken-run of the laboratory in Batavia there suddenly broke out a disease which was in many ways strikingly similar to human beri-beri, and hence invited penetrating study. . . . [Eijkman here gives a detailed account of the symptoms shown by the birds: unsteady gait, muscular weakness resulting in falls, collapse, progressive paralysis finally affecting the respiratory muscles, cyanosis, or blueness of comb and skin resulting from insufficient oxygen in the blood, stupor, subnormal temperature, and death.]

"As may already be guessed from the symptoms and the course of the disease, and as microscopic study confirmed, it was a question of a polyneuritis [multiple neuritis affecting the nerves generally and not merely in the local area].

"As regards etiology, our original supposition that, considering the striking epizootic commencement of the disease [epizootic = animal epidemic], we had to do with an infection was not confirmed. Search for infection, using material from sick animals or those that had died of the disease, gave no clear result, while all the hens, including those kept separate as controls, were affected. No specific microbe was found, nor any higher organized parasite.

"Then all at once our opportunity for further researches dis-

* Translated from Christiaan Eijkman, "Antineuritisches Vitamin und Beri-beri," *Les Prix Nobel en 1929.*

appeared, as the disease came suddenly to a stop. The sick hens got better and no new cases appeared. Fortunately suspicion was then directed toward food, and indeed rightly, as it presently turned out.

"The laboratory was still temporary, and very meagerly housed in the military hospital, although it was administered under the civil authority. The laboratory attendant, his motive economy, had now, as I first learned later, obtained cooking rice from the hospital kitchen to use as chickenfeed. Then, the cook having been transferred, his successor objected to military rice going to civilian hens. So it happened that the hens were fed with cooking rice only from the 10th of June to the 20th of November. But the epizootic began on the 10th of July and ended in the last days of November.

"Deliberate feeding experimentation was then undertaken, aimed at further proof of the presumable connection between food and sickness. This definitely showed that the polyneuritis had its origin in the cooking-rice feed. The hens were thereby subjected to the disease after 3-4 weeks, or not uncommonly somewhat later, while the controls fed with unhulled rice remained healthy. We also not seldom succeeded in restoring animals already sick by a suitable change in feeding.

"This difference between rice that had been hulled, and likewise polished, and whole rice did not consist in a lessening in the quality of the former through storage, for cooking rice freshly prepared from whole grain could also call forth the disease. It turned out that rice half hulled—i.e., freed only of the thick hull—which spoils much more easily [and] is attacked by mites, molds, etc., proved harmless in feeding experiments. This rice, which is obtained through simple pounding, still has the inner hull, the so-called silver skin [*Silberhäutchen*] (pericarp), and contains the germ, wholly or in large part. As could then be concluded from many different experiments, the effective antineuritic principle occurs particularly in these parts of rice—and of cereal grains generally. It can easily be extracted with water or strong alcohol and can be dialyzed [i.e., the crystalloid and colloid elements of the extraction can be separated by diffusion through a membrane]. I was able to establish further that it can be used as a remedy either by mouth or by injection."

HOPKINS *

"Early in my career I became convinced that current teaching concerning nutrition was inadequate, and while still a student in hospital in the earlier eighteen nineties I made up my mind that the part played by nutritional errors in the causation of disease was underrated. The current treatment of scurvy and rickets seemed to me to ignore the significance of the old recorded observations. I had then a great ambition to study those diseases from a nutritional standpoint; but fate decreed that I was to lose contact with clinical material. I had to employ myself in the laboratory on more academic lines. I realised, however, as did many others at the last century's close, that for a full understanding of nutrition, no less than for an understanding of so many other aspects of biochemistry, further knowledge of proteins was then a prerequisite; and when I was first called to the University of Cambridge I did my best to contribute to that knowledge.

"As an ultimate outcome of my experiments dealing with the relative metabolic importance of individual amino acids from protein my attention was inevitably turned, without, I think, knowledge, or at any rate without memory, of the earlier work, to the necessity for supplying other factors than the then recognised basal elements of diet if the growth and health of an animal were to be maintained. This indeed must at any time come home to every observer who employs in feeding experiments a synthetic dietary composed of adequately purified materials. . . . A good many investigators using synthetic dietaries have, it is true, from time to time expressed doubts upon the point, but we now know that it was because the constituents they used were not pure and not free from adherent vitamins. In 1906-7 I convinced myself by experiments, carried out . . . upon mice, that those small animals at any rate could not survive upon a mixture of the basal foodstuffs alone. I was especially struck at this time, I remember, by striking differences in the apparent nutritive value of different supplies of casein in my possession. One sample used as a protein supply in a syn-

* From F. G. Hopkins, "The Earlier History of Vitamin Research," *Les Prix Nobel en 1929.*

thetic dietary might support moderate growth, while another failed even to maintain the animals. I found that a sample of the former sort, if thoroughly washed with water and alcohol, lost its power and also, if added to the samples originally inadequate, made them to some degree efficient in maintaining growth. I found further at that time (1906-7) that small amounts of a yeast extract were more efficient than the casein extracts. Similar experiences were encountered when otherwise adequate mixtures of amino acids were used to replace intact proteins. By sheer good fortune, as it afterwards turned out, I used butter as a fat supply in these early experiments. Upon the evidence of these earlier results I made a public statement in 1907 which has been often quoted. I cannot, however, justly base any claims for any sort of priority upon it, as my experimental evidence was not given on that occasion. It was indeed not till four years later that I published any experimental data. In explanation of this delay I would ask you to consider the circumstances of the time. The early experiments of Lunin and others had been forgotten by most; the calorimetric studies held the field and tentative suggestions concerning their inadequacy were, I found, received with hesitation among my physiological acquaintances. It seemed that a somewhat rigid proof of the facts would be necessary before publication was desirable. Thus came the great temptation to endeavour to isolate the active substance or substances before publication, and I can claim that throughout the year 1909 I was engaged upon such attempts, though without success. At this time I was using what is now the classic subject for vitamin studies, namely the rat. As I was concerned with the maintenance of growth in the animal, the tests applied to successive products of a fractionation took much longer than those which could be used in studying the cure of polyneuritis in birds by what we have learned to call Vitamin B_1, so the work occupied much time. I may perhaps be allowed to mention what was for me a somewhat unfortunate happening in the beginning of 1910, as it is instructive. A commercial firm had prepared for me a special extract of a very large quantity of yeast made on lines that I had found effective on a small scale. With this I intended to repeat some fractionations which had appeared promising. I thought, however, upon trial that the whole product was inactive and it was thrown away. The

real explanation, however, was that instead of using butter, as in earlier experiments, I at this moment determined to use lard, and my supply of this, as I learned to understand much later, was doubtless deficient in Vitamins A and D; I was now giving my animals in the main the B Group alone. If I had then had the acumen to suspect that any of the substances I was seeking might be associated with fat I should have progressed faster. Later in 1910, if I may intrude so personal a matter, I suffered a severe breakdown in health and could do nothing further during the year. On my return to work I felt that the evidence I had by then accumulated would be greatly strengthened by a study of the energy consumption of rats, on the one hand when failing on diets free from the accessory factors (as I had then come to call them), and, on the other hand, when, as the result of the addition of minute quantities of milk, they were growing vigorously. These experiments took a long time, but they showed conclusively, as at that time it seemed necessary to show, that the failure in the former group of animals was not due primarily, or at the outset of the feeding, to any deficiency in the total uptake of food.

"My 1912 paper . . . emphasizes on general lines the indispensable nature of food constituents which were then receiving no serious consideration as physiological necessities."

CONSEQUENCES IN THEORY AND PRACTICE

Eijkman and Hopkins are among the half dozen pioneers in the study of vitamins. Eijkman, however, did not at once appreciate the full significance of his important discovery. He did not visualize beri-beri as a deficiency disease, but thought of it as a sort of poisoning, due to a nutritional error, an excess of carbohydrate in a diet of rice; this he considered was counteracted by a protective element, or neutralizing substance, in the rice bran. In 1901, however, G. Grijns put forward the view that the cortical substance in rice filled a universal need for the protection of health; this view was later adopted by Eijkman and the vital substance was eventually identified as vitamin B_1. Since beri-beri, which is characterized by multiple neuritis, edema, atrophy of muscles, and heart symp-

toms, often co-exists with other nutritional deficiencies, there has been some debate as to whether or not one specific factor is the sole cause; there is no doubt, however, that persons with beri-beri are greatly benefited by vitamin B_1 therapy. It took a long time before the practical value of Eijkman's observations for combating beri-beri was appreciated, although on this point Eijkman himself had recognized the significance of his findings. The outlook for a case of beri-beri, if diagnosed early and adequately treated, is nowadays very good. Prevention, dependent on a well-balanced diet, is a more difficult matter, since it calls for the education of the ignorant masses of the people in the eastern countries, where the disease is most prevalent, and for the raising of their economic level—two very large orders. It is asserted, however, that prevention of the overmilling of grain would go far to solve the problem.

Although there are other claimants for the honor, it is now widely accepted that F. G. Hopkins was the first to realize the full significance of the facts and to recognize the necessity for "accessory factors" in the diet. The important work which has since been carried out in vitamin research was initiated by his discoveries. Osborne and Mendel, and McCollum and his co-workers, distinguished between "water-soluble" and "fat-soluble" vitamins. It was shown by McCollum and Davis (1913) that the growth-promoting effect of milk demonstrated by Hopkins depended on two factors: fat-soluble vitamin A and water-soluble vitamin B. Vitamin B was later shown by Goldberger to consist of a mixture of several vitamins. One of these, vitamin B_1, protects against beri-beri; another is the pellagra-preventing vitamin.

It is not possible to review the later history of vitamin research in a brief space. Rickets, and also scurvy, were added to the list of diseases proved to result from specific deficiencies; there were soon several others. Many contributions have been made by physiologists, pathologists, and chemists to the increasing knowledge of nutritional deficiencies. Attention has been given not only to the vitamins but to the need for small amounts of other substances, particularly minerals. Study of these various substances, and the vitamins most of all, has greatly increased our knowledge of physiology as well as our clinical knowledge of disease (for an example in physiology, see below, p. 197, in the article on Szent-Györgyi).

Several Nobel Prizes, in medicine and chemistry, have been awarded for work on vitamins. (For Dam's discovery of vitamin K and the hemorrhagic states related to it, see below, p. 218.) Eijkman and Hopkins were among those who opened the gates of an important field in medicine.

1930

KARL LANDSTEINER

(1868–1943)

"For his discovery of the human blood groups."

BIOGRAPHICAL SKETCH

KARL LANDSTEINER WAS BORN IN VIENNA, ON JUNE 14, 1868. He entered the University of Vienna in 1885 and was graduated as doctor of medicine in 1891. He received his chemical training in the laboratories of Hantzsch in Zurich, Emil Fischer in Würzburg, and E. Bamberger in Munich. Thereupon he turned to bacteriology and pathology, but his approach to these subjects was derived from his thorough training in the fundamental sciences, especially chemistry. In 1896 he became assistant under Dr. Max von Gruber in the Institute of Hygiene at the University of Vienna. From 1898 to 1908 he was an assistant under Professor A. Weichselbaum at the Pathological Institute. In 1908 he was prosector at the Wilhelminspital, where he then served as pathologist from 1909 to 1919, with the rank of professor. After the First World War he left Vienna and went to Holland, to be pathologist at the R. K. Ziekenhuis, the Hague, from 1919 to 1922. In 1922 he became a member of the Rockefeller Institute for Medical Research, in New York, where he continued to work for more than twenty years. In 1939, having reached the mandatory age for retirement, he was made an emeritus member of the Institute, but continued his research with undiminished vigor. Stricken by heart disease while busy in his laboratory, he died two days later, on June 26, 1943, at

the Rockefeller Institute Hospital. He had just completed the preparation of a new edition of his book *The Specificity of Serological Reactions,* which was already a classic. Landsteiner published about 330 papers on his investigations in chemistry, in pathological anatomy, in experimental pathology (infectious diseases), and in serology and immunology. His studies of syphilis and poliomyelitis were particularly important. Probably his most far-reaching work was in immunochemistry, a branch of science which he did much to establish.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The difficulty of dealing with substances of large, complex molecules accounts for the fact that we are still far from the goal of characterizing and determining the constitution of proteins, which rank as the most important constituents of living beings. So it was not the usual methods of chemistry but the application of serologic tests which led to an important general result in protein chemistry, to the knowledge that the albuminous substances differ in the separate kinds of animals and plants and are characteristic for each kind. The diversity is increased still more in that the different organs also contain particular proteins, and consequently special building materials seem to be necessary for each particular form and function of living organisms, in contrast to artificial machines, which can be produced for greatly varied performance from a limited number of materials.

"The question which was raised by the discovery of the biochemical specificity of kinds, and which formed the basis of the investigations to be discussed, was thereupon formulated with the aim of seeing whether differentiation extends beyond the limits of species, and whether the separate individuals of one kind also exhibit similar, if at the same time slight, differences. In the absence of any observations pointing to a circumstance of this sort, I chose the simplest among the research arrangements which offered, and that material which at first glance lent itself to useful application.

* Translated from Karl Landsteiner, "Über Individuelle unterschiede des menschlichen Blutes," *Les Prix Nobel en 1930.*

Accordingly the research which I undertook consisted in letting the blood serum and red blood corpuscles of different people react on one another.

"The result was only in part what was expected. In many tests there was no change to be observed, just as if the blood cells had been mixed with their own serum, but often a phenomenon called agglutination took place, the serum causing the cells of the stranger to form clumps.

"The surprising thing was this, that the agglutination, when present at all, was just as pronounced as those reactions already known, which occur with the interaction of serum and cells from different kinds of animals, while in the other cases there seemed to be no difference in the blood of different people. So first of all there was still the consideration that the required individual physiological differences had not been found, and that the phenomena, when seen, too, in the blood of healthy people, could be caused by illnesses which had been overcome. But it soon became apparent that the reactions conform to a law which is valid for everyone's blood, and that the peculiarities found in separate individuals are just as characteristic as the serologic signs for an animal species. The main point, of course, is that there are four different kinds of human blood [Landsteiner first described three], the so-called blood groups. The number of the groups is due to the fact that in the erythrocytes there exist substances (isoagglutinogens) with two different structures, of which both may be lacking or one or both may be present in a man's erythrocytes. That alone would still not explain the reactions; the effective substances of the sera, the isoagglutinins, must also occur in a definite distribution. This is actually the case, for each serum contains that agglutinin which acts on the agglutinogens that are not present in the cells, a noteworthy fact, the cause of which has not yet been established with certainty. From this arise definite relations among the blood groups. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

Serum from the blood of an animal was known to be capable of causing flocculation (hemoagglutination) and dissolution (hemolysis) of red blood corpuscles in the blood of another animal of different species. That this might also at times occur in mixing serum from one individual with red blood cells from another individual of the *same* animal species (isoagglutination) was observed in 1900 by Ehrlich and Morgenroth. In the same year (1900), Karl Landsteiner and Samuel Shattock, working independently, reported on the incompatibility of different types of human blood. By 1901 Landsteiner had enough data to distinguish three groups and was able to give a clear account of isoagglutination. In 1902, his associate, A. Sturli, working with A. von Decastello, described the fourth group.

The discovery of the human blood groups had important results in (1) clinical medicine and surgery; (2) forensic (legal) medicine; and (3) anthropology.

Isoagglutinogens of two different structures, A and B, occur in red blood corpuscles, either separately, or together (AB). Both may be absent (the O group). An individual's serum cannot normally agglutinate his own blood corpuscles or those of others who belong to the same blood group. Serum from a member of the O group agglutinates the red cells in all the other groups, but the red cells of O group are not affected by any of the four kinds of serum (A, B, AB, O). Serum from a person belonging to A group agglutinates the cells of B-group blood, but not those of A or AB groups. Conversely, serum from B-group blood agglutinates cells of A group but not those of B or AB groups. This knowledge formed the foundation for the development of blood transfusion. Agote, Jeanbrau, and Lewisohn demonstrated the efficacy of adding sodium citrate to prevent coagulation of collected blood before injection into the recipient, a method which helped to make transfusion more generally available. Transfusions are now used for a wide variety of purposes. Lives are saved daily by this means following hemorrhage from injury, operation, gastric ulcer, ruptured ectopic preg-

nancy, bleeding after childbirth; in bleeding due to hemorrhagic diseases of the blood; and in cases of severe anemia, leukemia, etc. Carbon monoxide gas has a great affinity for the hemoglobin in the blood; an infusion of fresh blood provides unaltered hemoglobin. Transfusions have proved beneficial in some cases of chronic sepsis, and "immunotransfusions" have been used against scarlet fever, typhoid, and septicemia. Whole blood transfusion is especially effective in cases of traumatic or postoperative shock due to loss of blood in an accident or during an operation.

In 1910 E. von Dungern and L. Hirszfeld discovered that the groups are inherited according to Mendel's laws, A and B being strongly dominant. In cases of disputed paternity this fact may be of great value. Although a man cannot be proved to be the father of a child by means of his blood group, it is often possible to prove that he is *not* the father. The blood-group determination may also be of use when bloodstains are brought in evidence in criminal cases.

Since the blood groups are unevenly distributed in the various races, Landsteiner's discovery has been useful to anthropology. In experiments on primates he showed that the blood of anthropoids is more closely related than that of lower monkeys to human blood and stated that his results "seem to agree with the theory that man and apes are descendants of a common stock rather than that man evolved from one of the apes."

In 1927 Landsteiner discovered additional agglutinogens in human blood, two of which, M and N, have been of importance in forensic medicine. In 1940 Landsteiner and A. S. Wiener discovered the Rhesus, or RH, factor, which has since assumed great significance. Incompatibility in this respect in the blood of the parents is the cause of a fetal disease (Erythroblastosis foetalis) which may result in abortion, miscarriage, or a dangerous illness of the newborn child.

1931

OTTO WARBURG

(1883–)

"For his discovery of the nature and mode of action of the respiratory enzyme."

BIOGRAPHICAL SKETCH

OTTO HEINRICH WARBURG WAS BORN IN FREIBURG (BADEN), on October 8, 1883. His father was the physicist Emil Warburg (1846-1931). After studying chemistry under Emil Fischer, Warburg obtained his doctorate in 1906 with a dissertation on polypeptides. In 1911 he became doctor of medicine as well, his thesis dealing with problems of oxidation. He has concerned himself chiefly with life processes, insofar as they can be investigated by the methods of physics and chemistry; by his own account he has striven to trace the events of life to the events of the inanimate world. He has never taught, except for imparting instruction to younger investigators working with him, but has devoted his entire time to scientific research. For the past twenty years, apart from a brief sojourn in the United States, he has worked in Berlin-Dahlem in the Kaiser-Wilhelm Institute for Cell Physiology, erected in 1930 by the Rockefeller Foundation. He is best known for extensive investigations on intracellular enzymes and on the metabolism of tumors.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"That iron occurs in all cells, that it is vital, and that it is [the oxygen-transporting part of] the oxidation catalyst of cellular respiration was first apprehended in recent times. It is the valence change of an iron compound—the oxygen-transporting respiratory ferment—on which catalytic oxidation in living substance depends. . . .

"In the investigation of the chemical constitution of the oxygen-transporting ferment, analytical chemistry according to the usual methods has been abandoned, since in view of the almost infinitely small concentration . . . and the fragility of the ferment, they appear hopeless. . . . [This opinion determined the adoption of other methods, but Warburg has since concluded that isolation of this substance is not impossible.] One looks for substances which specifically and reversibly stop the operation of the oxygen-transporting ferment—that is to say, the oxidation in living substance. Now it cannot be otherwise than that a substance which inactivates the ferment reacts with [it] chemically, so that conclusions can be drawn about the ferment's chemical nature from the kind of retarding substances and from the circumstances to which the retardation is subject. . . . It is an advantage that by so doing one investigates the ferment under natural conditions, in the intact, breathing cells. . . .

"The blocking of intracellular respiration by hydrocyanic acid . . . takes place through a reaction of the hydrocyanic acid with the iron of the oxygen-transporting ferment. . . . Hydrocyanic acid retards the *reduction* of the ferment iron. . . . [That carbon monoxide also inhibits intracellular respiration was discovered by Warburg in 1926.] In accordance with the carbon monoxide and oxygen pressures a greater or smaller part of the ferment iron is eliminated from catalysis by combination with carbon monoxide.

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* The first quotation is translated from Otto Warburg, "Das sauerstoffübertragende Ferment der Atmung," *Les Prix Nobel en 1931*. The second consists of excerpts from Otto Warburg, *Heavy Metal Prosthetic Groups and Enzyme Action*, translated by Alexander Lawson (Oxford: Clarendon Press, 1949).

. . . Carbon monoxide bars the *oxidation* of the ferment iron. . . . [It was well known that CO acts on hemoglobin by expelling the oxygen from its union with iron. The inference as to the iron content of the ferment is based on analogies of this kind, and on the evidence, mentioned below, of its absorption spectrum.]

"If one adds carbon monoxide to the oxygen in which living cells are breathing, then . . . respiration ceases. If one exposes [this] to light . . . then respiration is resumed. By exposing living, breathing cells to light, and, alternately, darkening them, one can cause respiration to appear and disappear. In the dark, the iron of the oxygen-transporting ferment is bound to carbon monoxide; in the light, the carbon monoxide is split off from the iron, and the iron is thereby again free for oxygen-activation. This was discovered in 1926 [by Warburg] with Fritz Kubowitz."

[Best known of the iron pigments in the body is hemoglobin, consisting of a protein, globin, to which is added an iron compound called a "heme," or "hematin." Such a chemical group or compound attached to a molecule is called a "prosthetic group." Although it was once thought that the body contains no iron apart from hemoglobin, MacMunn in 1885 asserted, on the basis of spectroscopic examination, that all animal cells contain heme compounds. Warburg's discovery of 1926 was an extension of discoveries made by earlier investigators in the 1890's. The photochemical dissociation of certain iron compounds had been discovered in 1891 by Mond and Langer; a few years later J. S. Haldane and J. L. Smith had observed that light upsets the equilibrium of hemoglobin, carbon monoxide, and oxygen, in favor of oxygen. Other biological iron pigments were later found to behave in this way too, and Warburg found the same result with the respiratory enzyme. This suggested that the enzyme contained a prosthetic group with the properties of a heme.]

* * *

"Probably all carbon monoxide-iron compounds are light-sensitive. . . . On the other hand, up till now it has not been possible to decompose by light a carbon monoxide compound in which the carbon monoxide was joined to any metal other than iron. . . . [What follows is an account of the action of light on the carbon

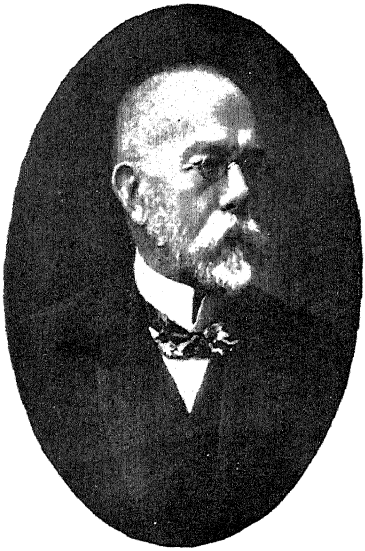
ILLUSTRATIONS

EMIL VON BEHRING

RONALD ROSS

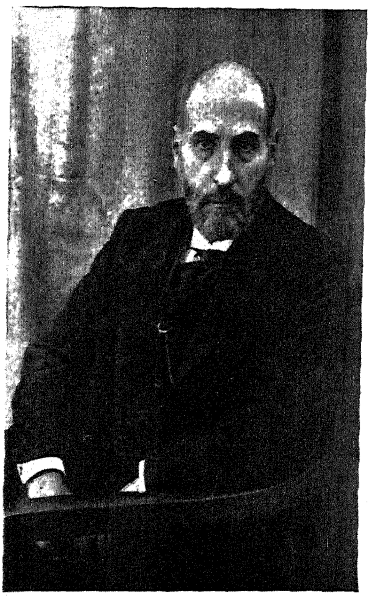
IVAN PETROVICH PAVLOV

NIELS RYBERG FINSEN

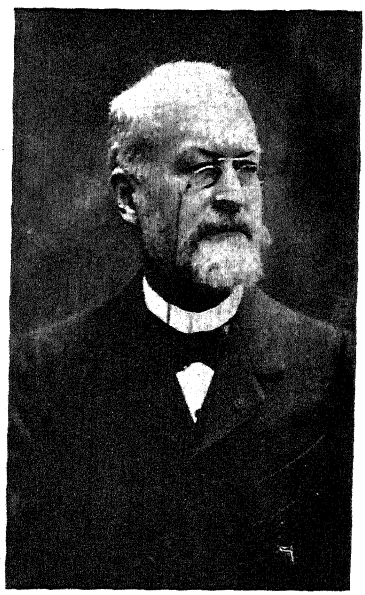


ROBERT KOCH

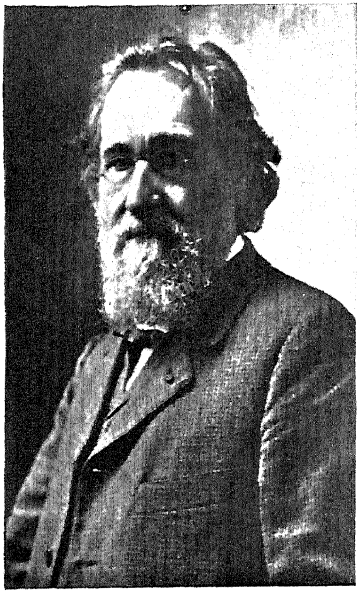
CAMILLO GOLGI



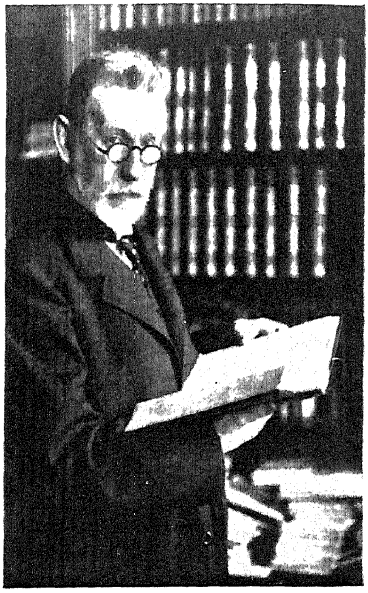
SANTIAGO RAMÓN Y CAJAL



CHARLES L. A. LAVERAN



ELIE METCHNIKOFF



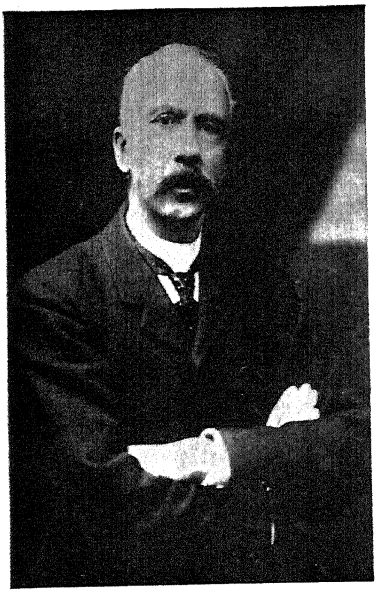
PAUL EHRLICH

EMIL KOCHER

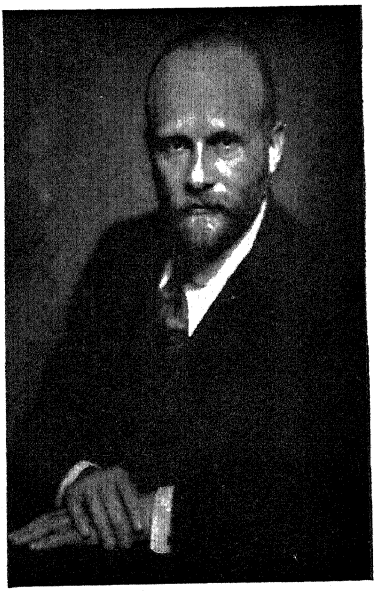
ALBRECHT KOSSEL

ALLVAR GULLSTRAND

ALEXIS CARREL



CHARLES RICHET



ROBERT BÁRÁNY

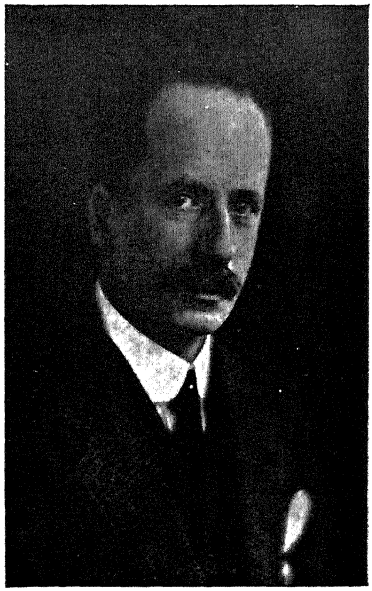
JULES BORDET

AUGUST KROGH

ARCHIBALD VIVIAN HILL

OTTO MEYERHOF

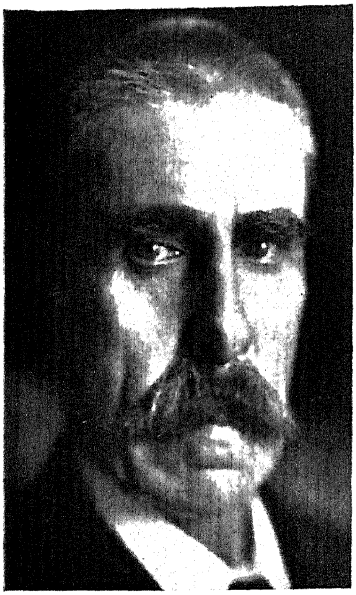
FREDERICK GRANT BANTING



JOHN J. R. MACLEOD

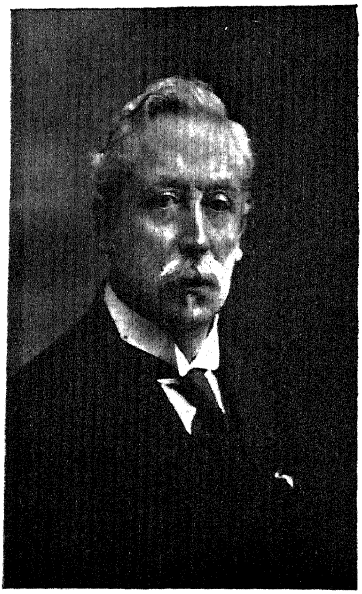
WILLEM EINTHOVEN

JOHANNES FIBIGER

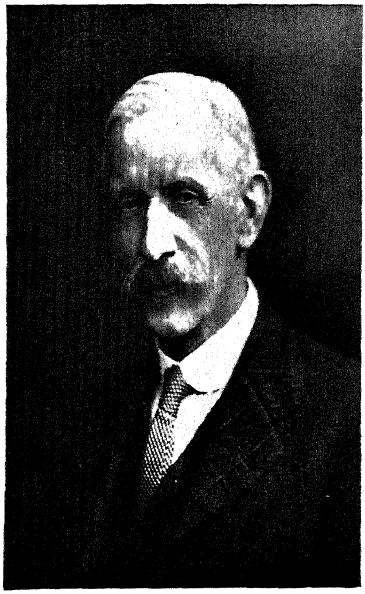


JULIUS WAGNER-JAUREGG

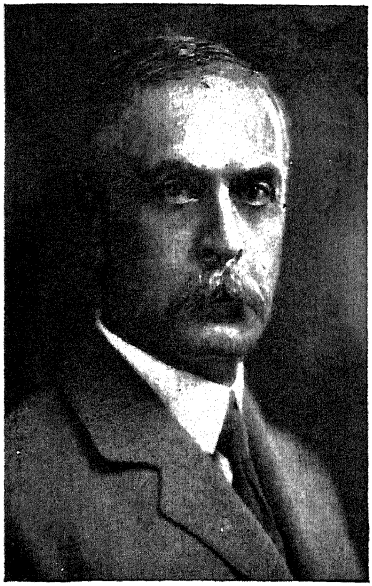
CHARLES NICOLLE



CHRISTIAAN EIJKMAN

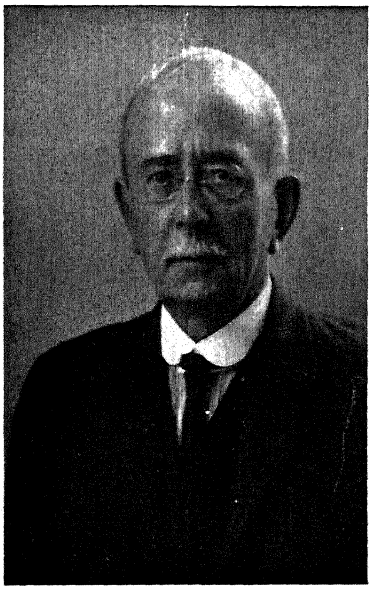


FREDERICK GOWLAND HOPKINS



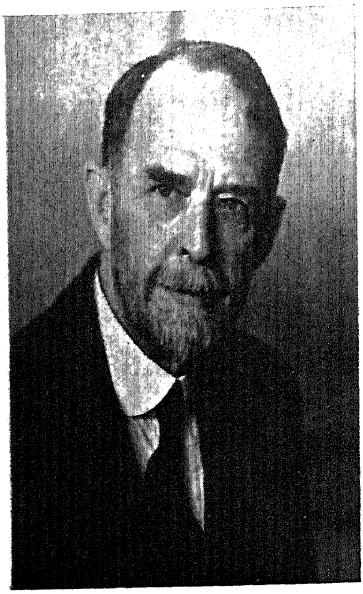
KARL LANDSTEINER

OTTO WARBURG



CHARLES SHERRINGTON

EDGAR DOUGLAS ADRIAN

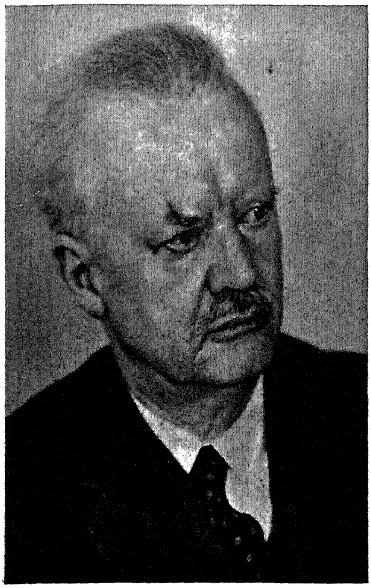


THOMAS HUNT MORGAN

GEORGE HOYT WHIPPLE

GEORGE RICHARDS MINOT

WILLIAM PARRY MURPHY



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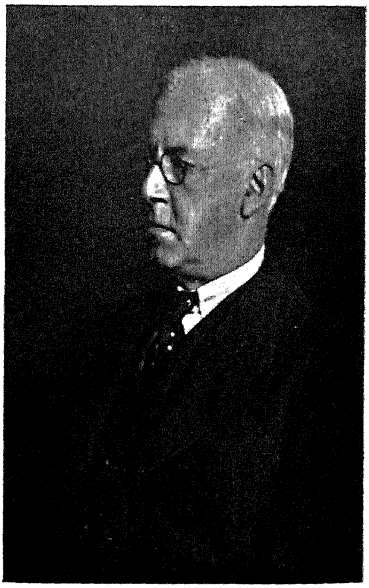


HENRY DALE

OTTO LOEWI

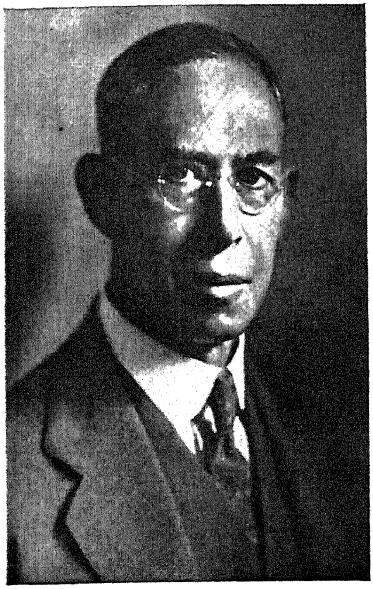
ALBERT VON SZENT-GYÖRGYI

CORNEILLE HEYMANS

GERHARD DOMAGK

HENRIK DAM

EDWARD A. DOISY



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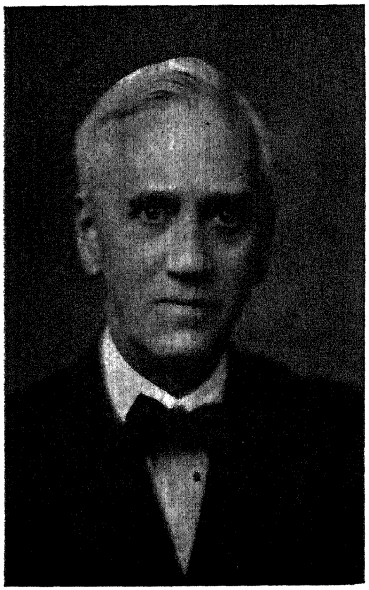
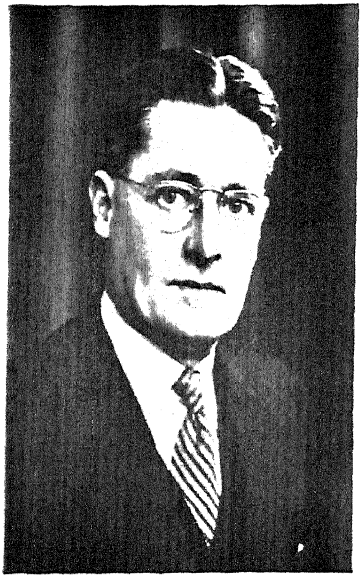
HERBERT SPENCER GASSER



ALEXANDER FLEMING

ERNST BORIS CHAIN



HOWARD WALTER FLOREY

HERMANN JOSEPH MULLER

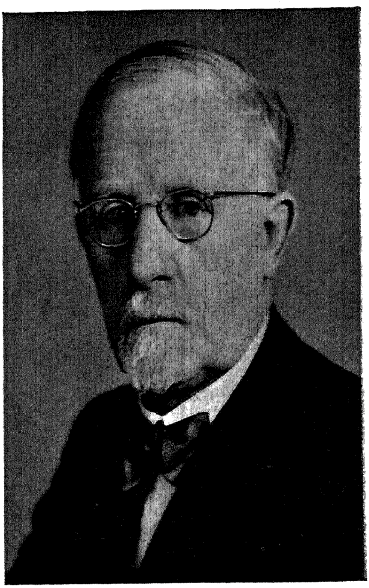
CARL F. CORI

GERTY T. CORI

PAUL MÜLLER

BERNARDO ALBERT HOUSSAY

EGAS MONIZ



WALTER RUDOLF HESS

EDWARD CALVIN KENDALL

PHILIP SHOWALTER HENCH

TADEUS REICHSTEIN

monoxide inhibition of respiration in yeast cells.] A 75-watt metal filament lamp is placed under two conical manometric vessels [a manometer is an instrument for indicating the pressure of gases] which are shaken in a thermostat. Each vessel contains 2 c.c. of a dilute yeast suspension. The gas space contains nitrogen and oxygen or carbon monoxide and oxygen. The light is switched on and off for periods of 20 minutes. . . . The light in the nitrogen-oxygen mixture has no effect on the respiration. The respiration inhibited by carbon monoxide, however, increases with the light and decreases in the dark. [The gas pressures in the manometer indicate the respiration taking place; see commentary below.] This means that the carbon monoxide compound of the oxygen-transporting enzyme is decomposed by light. . . . In order to verify the influence of wave-length on the reaction we selected four regions of the spectrum, made their intensities the same and irradiated yeast cells, the respiration of which had been inhibited by carbon monoxide. Thus with light of the same intensity but different wave-length, we found [in the blue part of the spectrum, strong action; in the green and yellow, weak action; in the red, no action]. This is the experiment which gave rise to the method for the determination of the absorption spectrum of the oxygen-transporting enzyme." [The 'ferment bands' were compared with the bands shown by a variety of hemes, and the close coincidence of the values in certain instances confirmed Warburg's view as to the nature of the prosthetic group of the enzyme.]

CONSEQUENCES IN THEORY AND PRACTICE

Lavoisier believed that oxidation takes place in the lungs. It has long been known, however, that the chemical events summed up in the word "respiration" actually occur in the cells, to which molecular oxygen is transported by the hemoglobin of the red blood corpuscles. In the preface to *Heavy Metal Prosthetic Groups and Enzyme Action,* Warburg writes: "Ever since it has been known that cells respire, the chief problem connected with respiration has been to determine which part of the living matter is auto-oxidizable [i.e., which part undergoes spontaneous oxidation]. If the com-

bustible substances in the cell are not auto-oxidizable, and if the cell material itself is not, with what then does the molecular oxygen, which is absorbed by the respiring cell, react? The answer to the problem lies in the auto-oxidizable ferrous iron complex which is oxidized to ferric iron by molecular oxygen and transformed again to ferrous iron by the reducing action of the cell constituents." This iron complex is the active part of Warburg's *Atmungsferment;* the latter, according to him, is "the enzyme which has contributed more than any other to the explanation of life."

In 1925, D. Keilin confirmed and extended the spectroscopic studies of MacMunn, mentioned above (p. 150). He attributed three of the MacMunn bands to three heme compounds, which he called cytochrome a, cytochrome b, and cytochrome c. The word "cytochrome," which is sometimes used alone to comprehend all three variants, means simply cell pigment. Keilin at first identified cytochrome with Warburg's respiratory ferment, but in 1927 Warburg suggested that the oxygen-transporting ferment oxidizes the cytochrome, which thus forms another stage in the process, a view in which Keilin concurred. Disputes arose, however, first as to whether or not the enzyme is really in part a heme compound, and secondly as to the range of application of Warburg's theory. Warburg himself has discovered that in certain plants the oxygen is transported not by iron but by copper; other heavy metals may at times substitute for iron. He also discovered the first of the "yellow enzymes," which do not contain iron, but he states that "in the aerobic cells . . . the yellow enzymes are intermediate members of the enzyme chain at the head of which stands oxygen-transporting iron."

Warburg has made very important contributions toward understanding the complicated mechanism by which oxidation and reduction, essential to all life, are brought about. The importance to biology and medicine of intracellular chemistry has already been discussed in another connection (see above, p. 66). It may be mentioned here that peculiarities of respiration have been observed in tumor cells and that Warburg's methods have been applied to the study of tumor metabolism. Warburg has designed a manometric apparatus which is now widely used by chemists and biochemists. His "inhibition technique," employing carbon monoxide,

etc., has been used in other respiration studies; and he has demonstrated an ingenious method for determining the absorption spectra of unisolated substances which are present in cells in very small amounts. His "tissue slice" technique is well known to biochemists.

REFERENCES

WARBURG, O. *Heavy Metal Prosthetic Groups and Enzyme Action,* translated by Alexander Lawson (Oxford: Clarendon Press, 1949).

———, ed. *The Metabolism of Tumours,* translated by F. Dickens (New York: R. R. Smith, 1931).

1932

CHARLES SHERRINGTON

(1857–1952)

EDGAR DOUGLAS ADRIAN

(1889–)

"For their discoveries regarding the function of the neurons."

BIOGRAPHICAL SKETCHES

SHERRINGTON

CHARLES SCOTT SHERRINGTON WAS BORN IN LONDON, ON November 27, 1857. He was educated at Queen Elizabeth's School, Ipswich, matriculating in 1881 at Cambridge, where he was admitted to Gonville and Caius College. There he came under the tutelage of Sir Michael Foster and worked in association with Balfour, Gaskell, Langley, Newell Martin, and Sheridan Lea. He published his first paper on the nervous system in 1884, with Langley. After receiving his degree in medicine (M.B.) from Cambridge in 1885, he went to Spain and Italy to study cholera. He continued his work in pathology at Berlin, first with Virchow but for a longer period with Koch. Returning to London, he was made lecturer in physiology at St. Thomas's Hospital, and in 1891 he was appointed Professor-Superintendent of the Brown Institute for Advanced Physiological and Pathological Research, where he succeeded Sir

Victor Horsley. Between 1885 and 1895 Sherrington made several visits to Strasbourg to study under the physiologist Goltz, whose chief interest lay in the function of the central nervous system. In the latter year Sherrington accepted the chair of physiology in the University of Liverpool, where he remained for eighteen years, until he went to Oxford as Waynflete Professor of Physiology. In 1893 he was elected a Fellow of the Royal Society, of which he became president in 1920. He was knighted in 1922. In 1891 he married Ethel Mary Wright. They had one child, Carr E. R. Sherrington, who became a distinguished railroad economist and author. In addition to his scientific papers, Sherrington wrote on more general topics, including public health and the history of medicine, and published a book of verse. His death occurred on March 4, 1952, in his ninety-fifth year.

ADRIAN

EDGAR DOUGLAS ADRIAN WAS BORN IN LONDON, ON NOVEMBER 30, 1889. He was educated at Westminster School and entered Trinity College, Cambridge, with a science scholarship, in 1908. He studied physiology for Part II of the Natural Sciences Tripos and was awarded a first class in 1911. His first research was done in collaboration with Keith Lucas. It was followed by an investigation of the "all or none" principle in nerves, for which he was elected to a fellowship at Trinity College in 1913. Adrian became the ninth Fellow of Trinity to be awarded a Nobel Prize. He took a medical degree in 1915 and worked at clinical neurology, returning to Cambridge in 1919 to lecture on the nervous system. He was made a fellow of the Royal Society in 1923. Two years later he began investigating the sense organs by electrical methods. In 1929 he was made Foulerton Professor of the Royal Society. Probably his best-known works are *The Basis of Sensation* (1927), *The Mechanism of Nervous Action* (1932), and *The Physical Background of Perception* (1947). He has received many honors, including the rare distinction of the Order of Merit, which was also awarded to Sherrington. Succeeding G. M. Trevelyan, the historian, Adrian is now Master of Trinity.

DESCRIPTION OF THE PRIZE-WINNING WORK

SHERRINGTON *

"The receptors played upon by the events of the external world supply their 'drive' to the muscles. In reflex action they do so far more simply and for far more simple purposes than when the trains of reaction they set going have to thread the mazes of the higher brain, and, so to say, obtaining mental sanction, issue in acts remoter from the original stimulus. Yet in both cases the muscles lie at the behest of the receptors, as instruments of their hand.

"We should go too far, however, did we infer that the muscles themselves are instruments entirely passive under drive of the receptors acting on them from without. That they are agents not purely passive is shown by their possession of receptors of their own. On their own behalf they send messages into the central exchanges. This must mean they have some voice in their own conditions of service, perhaps ring themselves up and ring themselves off. Let us attempt to penetrate into the significance of this their 'receptivity.'

"It is a receptivity differing obviously from that of other receptors, rightly more commonly chosen to exemplify receptive function, such as retina, ear, tongue, tactile organs, and so on, for in the case of the receptors of muscle, instead of being stimulated directly by agents of the external world, they are stimulated by happenings in the microcosm of the body itself—namely, events in the muscles themselves. In muscular receptivity we see the body itself acting as stimulus to its own receptors. The receptors of muscle have therefore been termed 'proprioceptors.' [This term was coined by Sherrington.]

"Following the functional scheme of all receptors, we may be sure that the central reactions provoked by the receptors of muscle

* From C. S. Sherrington, "Problems of Muscular Receptivity," Linacre Lecture, *Nature* (London), June 21 and 28, 1924. Reprinted in D. Denny-Brown, ed., *Selected Writings of Sir Charles Sherrington* (New York: Paul B. Hoeber, 1940), pp. 385-390.

will be divisible into, on the one hand, the purely reflex, and on the other hand, those which subserve mental experience.

"Let us turn to the simpler of these divisions, the purely reflex. For that purpose, appeal can be had to what may with justification be regarded as a partially surviving animal—an animal which, its cerebral hemispheres having been removed, is a wholly inconscient and purely reflex automaton. From it no sight or sound evokes evidence of perception. There is total inability to evoke from it any sign of mentality, of emotion, let alone intelligence. It remains motionless hour after hour; yet if planted upon its feet in the upright position it stands, and statuelike continues to stand.

"Now, standing is a postural act, and one of course of high importance. In maintaining posture the muscles, though they perform no external work, are active with an activity often technically termed 'tonus,' a postural contraction. In this maintenance of the erect posture by the decerebrate animal, we meet a co-ordinated posture involving many separate muscles harmoniously co-ordinated reflexly. For this reflex postural act of standing some stimulus must be at work evoking and maintaining it. We have to ask what that stimulus may be.

"If the afferent nerves that pass from a limb to the spinal centres be severed, the standing posture in that limb is no longer fully executed or maintained. The stimulus exciting the posture in that limb must be something which is applied to the receptors of that limb itself. The skin surface of the limb is rich in receptors, one region especially rich being the sole of the foot. On the receptors of the skin of the sole of the foot the external world may evidently be acting as a stimulus in the form of pressure from the ground upon the skin. To test whether that is the source of the reflex posture, the skin of the foot can be deprived of all its receptors by severing their nerves. This is found to exert no obvious influence upon the posture. Nor does severence of all the receptive nerves from the skin of the whole limb, nor, indeed, from that of all the four limbs. The stimulus producing and maintaining the posture is therefore not pressure of the skin against the ground, nor indeed any cutaneous stimulus whatsoever. On the other hand, if, even without interference with the skin nerves, the receptive nerves of the limb-muscles—the motor nerves, of course, remaining intact—

be severed, the reflex posture disappears at once from the limb. The stimulus which produces and maintains the posture is something which is acting on and exciting the receptive nerves of the muscles of the limb.

"What are the muscles which, by their contraction, execute this postural act? The posture keeps the head and neck from sinking, the trunk straightened and the spine supported, the tail from drooping, the limbs from yielding and folding under the superincumbent weight of the body. In a word, this habitual reflex posture counteracts in the various parts of the body the effect of gravity on them in the erect attitude. Experimental analysis shows that throughout the muscular frame of the animal all those muscles, and only those, are in action, the activity of which counteracts gravity in the erect attitude—for example, in the hind-limb the muscles which extend hip, knee, and ankle. The muscles which execute the reflex we may, in short, term 'antigravity' muscles. Even the jaw is included; the lower jaw, which, but for its postural tonus, would drop, is held lifted against the upper.

"If in the limb the receptive nerve of one of these antigravity muscles be cut, that muscle no longer contributes to the reflex posture. On the other hand, severance of the receptive nerves of all the other muscles does not destroy the postural reflex of the muscle the receptive nerve of which remains intact. The stimulus which is the source of this reflex standing is therefore one acting on the receptors of those limb-muscles which are themselves executants of the posture.

"The excitability of a receptor is selective. That is, construction fits the receptor to respond to stimuli of one particular kind only, the so-called 'adequate' stimulus; thus, the retina to light, a taste papilla to 'sweet,' and so on. Hence Pavlov's term 'analyser' for the receptors, because by them the various complex events which play upon the body and cause reactions of it through the nervous system are to some extent analysed. A wave breaking on the shore excites the retina by its reflected lights, the ear by sound vibrations, and, maybe, the skin by the spray dashed up. The wave as 'object' and stimulus from the external world is thus partially analysed by the receptors.

"Seeing that the receptors of muscle are an appendage of an organ mechanical in function, a near supposition is that their adequate stimulus is of mechanical kind. What is the adequate stimulus at work in these antigravity muscles in their posture of standing?

"A muscle representative of the whole antigravity group is the extensor of the knee. Suppose it isolated from the rest and its freed tendon attached to a stiff spring, and to the spring a light lever so fixed that movement of the lever-point is photographically recorded. If then, by its bony attachments, the muscle be pulled against the spring, we can passively stretch the muscle and record the tensile strain developed in it by the stretch. Let us take the case of the muscle paralysed by severance of all nerves both afferent and efferent which connect it with the nerve-centres. The tension developed in the muscle as it is stretched yields a curve resembling that given by various fibrous and elastic tissues of the body, not unlike that given by a strip of indiarubber. Let us repeat the observation, but with the difference that the muscle retains unimpaired its purely efferent motor nerve. The stretching produces the same tensile curve as before, a curve practically indistinguishable from that of the wholly paralytic muscle. Then let us make the observation, with the further difference that the muscle this time retains not only its motor nerve but its receptive nerve as well. We find the muscle yields now a completely different curve of tensile strain. The tension developed by it is much greater, and its curve under equable progressive increase of the stretch runs, tensions being ordinates, convex instead of concave to the abscissa line. The muscle in response to the stretch now replies not merely by passive strain but also by active contraction of its muscle-fibres. In the muscle with its reflex arc intact, the passive pull provokes a reflex contraction of the muscle."

ADRIAN *

"The sense organs respond to certain changes in their environment by sending messages or signals to the central nervous system. The signals travel rapidly over the long threads of protoplasm

* From E. D. Adrian, "The Activity of the Nerve Fibres," *Les Prix Nobel en 1932.*

which form the sensory nerve fibres, and fresh signals are sent out by the motor fibres to arouse contraction in the appropriate muscles. What kind of signals are these? . . . [This question] would have been answered correctly by most physiologists many years ago, but now it can be answered in much greater detail. It can be answered because of a recent improvement in electrical technique. The nerves do their work economically, without visible change and with the smallest expenditure of energy. The signals which they transmit can only be detected as changes of electrical potential, and these changes are very small and of very brief duration. . . .

"The revolution in technique has come about not from any increase in the sensitivity of galvanometers and electrometers but from the use of [amplifiers like those employed in radio] to amplify potential changes. . . . Many workers have contributed to the introduction of this technique in physiology, notably Forbes of Harvard, Gasser of St. Louis [later of New York, winner of the Nobel Prize with Erlanger in 1944], who was the first to use very high amplification, and Mathews of Cambridge. . . .

"Seven years ago [i.e., in 1925] it became clear to me that a combination of the capillary electrometer * with an amplifier would permit the recording of far smaller potential changes than had been dealt with previously, and might enable us to work on the units of the nerve trunk instead of on the aggregate. . . . The problem was then to limit the activity to only one or two nerve fibres. [The difficulty of interpreting the irregular effects from a whole nerve, due to the fact that impulses in the various nerve fibers do not come simultaneously and can therefore nullify or amplify one another, has been likened by Professor Liljestrand to an attempt to construct the separate conversations by listening to the various wires in a telephone cable simultaneously. It was necessary to try to obtain impulses corresponding to one single conversation or one sending station.] In this I was happy to have the co-operation of Dr. Zotterman of the Caroline Institute. We found that the sternocutaneous muscle of the frog could be divided progressively until it contained only one sense organ; this could be stimulated by stretch-

* See above, pp. 116-117.

ing the muscle, and we could record the succession of impulses which passed up the single sensory nerve fibre.

". . . [The signals] consist of nerve impulses repeated more or less rapidly. . . . The waves [recording potential changes] are of constant size and duration, but they begin at a frequency of about 10 a second, and as the extension increases, their frequency rises to 50 a second or more. The frequency depends on the extent and on the rapidity of the stretch; it depends, that is to say, on the intensity of excitation in the sense organ, and in this way the impulse message can signal far more than the mere fact that excitation has occurred. [There had previously been 'good reason to believe that the nerve impulse was a brief wave of activity depending in no way on the intensity of the stimulus which set it up.']

"In all the sense organs which give a prolonged discharge under constant stimulation the message in the nerve fibre is composed of a rhythmic series of impulses of varying frequency. . . . With some kinds of sense organ there is a rapid adaptation to the stimulus and the nervous discharge is too brief to show a definite rhythm, though it consists as before of repeated impulses of unvarying size.

"The nerve fibre is clearly a signalling mechanism of limited scope. It can only transmit a succession of brief explosive waves, and the message can only be varied by changes in the frequency and in the total number of these waves. Moreover the frequency depends on the rate of development of the stimulus as well as on its intensity; also the briefer the discharge the less opportunity will there be for signalling by change of frequency. But this limitation is really a small matter, for in the body the nervous units do not act in isolation as they do in our experiments. A sensory stimulus will usually affect a number of receptor organs, and its result will depend on the composite message in many nerve fibres. . . . [It has been shown in specific instances that] the impulses in each nerve fibre increase in frequency [when the stimulus increases] and more fibres come into action. Since rapid potential changes can be made audible as sound waves, a gramophone record will illustrate this, and you will be able to hear the two kinds of gradation, the changes in frequency in each unit and in the number of units in action."

CONSEQUENCES IN THEORY AND PRACTICE

The contributions of Sir Charles Sherrington to neurophysiology, like the contributions of Ramón y Cajal to neuroanatomy, are so numerous and varied that they are difficult to summarize.* One of Sherrington's earlier achievements was to analyze the distribution of the ventral (motor) nerve roots, recording the muscles activated by each; similarly he mapped out sensory distribution for dorsal roots, with results which have formed the basis of all later work on sensory levels.

Prior to 1894 it was generally assumed that all nerves going to muscle were motor nerves. In that year Sherrington published a paper in which he maintained that one third to one half of the nerve fibers in skeletal muscle nerves are sensory. It was not then established that Golgi's spindles (see above, pp. 34-36) were actually sensory. Sherrington cut ventral nerve roots so as to deprive a particular muscle of motor supply, and found that the spindles remained intact with their myelinated fibers; but interruption of dorsal (sensory) roots at a corresponding level caused these end organs to degenerate and disappear. He found that dorsal root section, unlike the severing of cutaneous nerves, caused an animal to lose awareness of the position of its limbs in space, to lose tendon reflexes (such as the knee jerk) and to become ataxic—i.e., to lose the power of muscular coordination. These experiments laid the foundation of knowledge of the "proprioceptive" system, the mechanism for the sense of position and equilibrium, with the fine adjustment of muscular movements depending on stimuli originating within the organism (Latin *proprius,* one's own). The term is Sherrington's and the whole concept is based largely on his work. These experiments incidentally served to explain ataxia in the clinical condition known as tabes dorsalis, in which sensory pathways at dorsal root level are impaired. In a somewhat similar manner many another Sherrington experiment has explained the find-

* These paragraphs about Sherrington are based in part on John F. Fulton, "Sherrington's Impact on Neurophysiology," *British Medical Journal,* Vol. 11 (1947), pp. 807-810.

ings and guided the thought of the clinical neurologist; his writings have also proved source books for the general physiologist and the psychologist.

Sherrington next studied the reflexes in the spinal and decerebrate state and the reciprocal innervation of antagonistic muscles—i.e., the reflex mechanism which results in the coordinated action of muscles of opposing tendency, such as a flexor and an extensor of the same part. This reflex behavior of antagonistic muscles led to the concept of integration, a theme developed in the Silliman Lectures delivered at Yale in 1904, first published in 1906 under the title *The Integrative Action of the Nervous System* (latest edition, 1947). This is one of the classics of modern physiology, embracing a wide range of work on nervous integration.

Another important contribution was the mapping of the motor areas of the cortex in a more exact manner than had ever been done before. His observations in this field at once accounted for the clinical picture of hemiplegia (paralysis of one side of the body) and for the manner in which recovery takes place. The rigidity (contracture) of hemiplegia was explained by Sherrington's studies of decerebrate rigidity, to be caused by the unantagonized activity of subcortical centers. He then turned to the study of special reflexes, such as the swallowing reflex, and in 1924 discovered the "stretch reflex," which accounts for the constant activity of the antigravity muscles. On the nature of cortical inhibition he published his principal paper in 1925; on the ultimate unit of reflex action, in 1930.

This rapid listing of achievements has taken little account of many observations on the physiological anatomy of the tracts of the spinal cord, of investigations of binocular flicker and sensual fusion, of extensive work on general sensation, and of a host of other special contributions. Sherrington has given to medicine not only a multitude of exact and important observations, but new theoretical concepts of the greatest value and striking advances in laboratory technique, as well as in the teaching and practice of mammalian physiology in general. His work and his ideas have entered into the whole structure of the physiology of the nervous system.

The work of E. D. Adrian built upon and extended Sherring-

ton's researches and demonstrated their value. The latter had shown that stimuli from different points can weaken or reinforce a reflex; he had also determined the effect of repeated stimulations at the same point. A motor neuron receiving impulses from many directions discharges its impulse in one way only, through its axon; of several indications for action, "nociceptive," or pain, reflexes predominate, apparently as a protection for the organism. What is the nature of the nerve impulse in afferent and efferent limbs of a reflex? Adrian and his co-workers answered this question in the manner set forth above, working with the "stretch reflex" originating in a single end organ. By repeated stimulations at the same point Sherrington had demonstrated temporal inhibition and summation. Adrian showed that sense organs can adjust themselves so that a stimulus which produces a rapid succession of impulses when first applied has a weaker effect when sustained. Adrian and Zotterman demonstrated the increase in frequency of the signals sent in to the central exchange as the stretching of a muscle becomes greater; with D. Bronk, Adrian showed that heightened activity in the motor limb of the reflex, or of motor nerves generally, is accompanied by an increase in the number of impulses per second. This analysis of the nerve impulses served to explain earlier results, incomprehensible because of their complexity, by the isolation of functional units; synthesis following analysis put the complex pattern together again. Adrian's work threw much light on the adjustment capacity of the nerve action and the sense organs. His work on the electrophysiology of nerve impulse has been complemented by that of two other Nobel laureates, Erlanger and Gasser (see below, pp. 223-228).*

* For more recent developments see Harry Grundfest, "Potentialities and Limitations of Electrophysiology," a symposium, in D. Nachmansohn, ed., *Nerve Impulse: Transactions of the First Conference, March 2-3, 1950* (New York: Josiah Macy Jr. Foundation, 1951).

1933

THOMAS HUNT MORGAN

(1866–1945)

"For his discoveries concerning the function of the chromosome in the transmission of heredity."

BIOGRAPHICAL SKETCH

THOMAS HUNT MORGAN WAS BORN IN 1866 AT LEXINGTON, Kentucky. He attended the University of Kentucky and was graduated in 1886. He then entered the Johns Hopkins University, where he studied morphology with Professor W. K. Brooks and physiology with H. Newell Martin. In 1890 he received the Ph.D. degree and was Bruce Fellow for the following year. In 1891 he was appointed associate professor of biology at Bryn Mawr College, where he remained until 1904; in that year he was named professor of experimental zoology at Columbia University. In 1928 he became head of the Kerckhoff Biological Laboratories of the California Institute of Technology, Pasadena, California. From 1909 on, Morgan attracted to his laboratory a brilliant group of workers, including C. B. Bridges and A. H. Sturtevant, with both of whom he shared the Nobel Prize money, and H. J. Muller, who was later awarded the Prize himself for his discovery of X-ray mutations (see below, pp. 238-243). The result of the combined efforts of Morgan's team was a great extension of the knowledge of genetics. Morgan's work and influence were acknowledged by the award of many honors, including foreign membership in the Royal Society. He died at the age of seventy-nine, on December 4, 1945.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"Mendel's paper was recovered in 1900. [In 1866 J. G. Mendel published an account of his experiments with garden peas, setting forth "Mendel's laws" of heredity. According to the first of these, two different hereditary characters, after being combined in one generation, will again be segregated in the next—i.e., in the new sex cells. The latter being fused with others, new and independent combinations can be formed; this is Mendel's second law, that of independent assortment. No notice was taken of his paper until 1900.] Four years later Bateson and Punnett reported observations that did not give the numerical results expected for two independent pairs of characters. For instance, when a sweet pea having purple flower-color and long pollen grains is crossed to one with red flowers and round pollen grains, the two types that go in together come out together more frequently than expected for independent assortment of purple-red and round-long. They spoke of these results as due to repulsion between the combinations purple and long and red and round, that came from opposite parents. Today these relations are called linkage. By linkage we mean that when certain characters enter a cross together, they tend to remain together in later generations, or, stated in a negative way, certain pairs of characters do not assort at random.

"It would seem, then, so far as linkage holds, that there are limits to the subdivision of the germinal material. For example in the vinegar fly [also called fruit fly], Drosophila melanogaster, there are known about 400 new mutant types that fall into only four linkage groups.

"One of these groups of characters of Drosophila is said to be sex-linked, because in inheritance the characters show certain relations to sex. There are about 150 of these sex-linked mutant characters. Several of them are modifications of the color of the eye, others relate to its shape or its size, or to the regularity of the distribution of its facets. Other characters involve the body color;

* T. H. Morgan, *The Theory of the Gene* (New Haven: Yale University Press, rev. ed., 1928), Silliman Lectures, pp. 10-14, 19-20.

others the shape of the wings, or the distribution of its veins; others the spines and hairs that cover the body.

"A second group of about 120 linked characters includes changes in all parts of the body. None of the effects are identical with those of the first group.

"A third group of about 130 characters also involves all parts of the body. None of these characters are the same as those of the other two groups.

"There is a small fourth group of only three characters; one involves the size of the eyes, leading in extreme cases to their total absence; one involves the mode of carriage of the wings; and the third relates to the reduction in size of the hairs.

"The method of inheritance of linked characters is given in the following example. A male Drosophila with four linked characters (belonging to the second group), black body color, purple eyes, vestigial wings, and a speck at the base of the wings, is crossed to a wild type female with the corresponding normal characters, that may be called gray body color, red eyes, long wings, and absence of speck. The offspring are wild type. If one of the sons is now crossed to a stock female having the four recessive characters (black, purple, vestigial, speck), the offspring are of two kinds only, half are like one grandparent with the four recessive characters, and the other half are wild type like the other grandparent.

"Two sets of contrasted (or allelomorphic) linked genes went into this cross. When the germ-cells in the male hybrid matured, one of these sets of linked genes went into half of the sperm-cells and the corresponding allelomorphic set into the wild type half of the sperm-cells. This was revealed, as described above, by crossing the hybrid (F_1) [first generation] male to a female pure for the four recessive genes. All of her mature eggs contain one set of four recessive genes. Any egg fertilized by a sperm with one set of the dominant wild type genes should give a wild type fly. Any egg fertilized by a sperm with the four recessive genes (which are the same as those in the female here used) should give a black, purple, vestigial, speck fly. These are two kinds of individuals obtained.

"The members of a linked group may not always be completely linked as in the case just given. In fact, in the F_1 female from the same cross, some of the recessive characters of one series may be

interchanged for wild type characters from the other series, but even then, since they remained united more often than they interchange, they are still said to be linked together. This interchange is called crossing-over, which means that, between two corresponding linked series, there may take place an orderly interchange involving great numbers of genes. . . .

"A study of crossing-over [in Drosophila] has shown that all possible percentages of crossing-over occur, up to nearly 50 per cent. If exactly 50 per cent of crossing-over took place, the numerical result would be the same as when free assortment occurs. That is, no linkage would be observed even though the characters involved are in the same linkage group. Their relation as members of the same group could, nevertheless, be shown by their common linkage to some third member of the series. If more than 50 per cent crossing-over should be found, a sort of inverted linkage would appear, since the cross-over combinations would then be more frequent than the grandparental types.

"The fact that crossing-over in the female of Drosophila is always less than 50 per cent, is due to another correlated phenomenon called double crossing-over. By double crossing-over is meant that interchange takes place twice between two pairs of genes involved in the cross. The result is to lower the *observed* cases of crossing-over, since a second crossing-over undoes the effect of a single crossing-over."

CONSEQUENCES IN THEORY AND PRACTICE

Professor Morgan began his career as a zoologist on strictly morphological lines—i.e., as a student of form and structure. He became, however, a distinguished experimentalist, particularly in genetics. Deeply interested in evolution, on which he wrote extensively, he was distrustful of Darwin's theory of natural selection and preferred the mutations theory of De Vries as an explanation of the origin of species. That is to say, he was inclined to think new species the consequence of spontaneous, inheritable changes due to aberrations of the chromosomes, threadlike intracellular structures which had been suggested as the carriers of hereditary char-

acters (genes). This suggestion, made at the beginning of the century by W. Sutton and T. Bovery, seemed to fit the scheme of Mendelian heredity. Prior to cell division each chromosome splits longitudinally into two daughter chromosomes; when cell division actually takes place, one of these becomes part of the structure of each new cell, which is thus endowed with the same combination of chromosomes as the original cell. Maturation division, however, which occurs in mature sex cells, is of a different kind: here the number of chromosomes is reduced by one half. When male and female sex cells come together and fuse, the original chromosome number is again restored, but now one half of each pair is derived from the male, the other half from the female, sex cell. If chromosomes were actually the carriers, as Sutton and Bovery suggested, of the hereditary elements, the genes, here was a mechanism to account for the Mendelian ratios in breeding experiments. But of this there was no proof.

It was about this time that Morgan began to work with Drosophila. The fruit fly of this name had already been shown by Lutz, Payne, and others to be amenable to culture in the laboratory. It is particularly well suited for studies in genetics because it breeds very rapidly (ten days from egg to egg) and because its cell nucleus contains only four chromosomes. Morgan found that Drosophila did not give rise to new species, in accord with the theory of De Vries, but rather provided valuable material for the study of Mendelian segregation.

As indicated in the quotation, Mendel's second law is subject to certain exceptions. These were accounted for by the doctrine of linkage. But linkage is not perfectly constant and factors are sometimes separated which usually occur together. Morgan's explanation was that chromosomes belonging to the same pair may exchange genes immediately before the maturation division. One or more breaks occur in each chromosome and the parts are then reunited crosswise. This is the mechanism of the crossing-over already described. The probability that a break will occur between genes when a chromosome is segmented in this way is increased by the distance separating the positions of two such genes; the more commonly such genes break off, the more commonly the factors they represent will be recombined in offspring.

All this assumes that the genes are arranged in straight lines, and not, for example, in circles. If this assumption is made, there is an exact correlation to be expected between the rate of occurrence of these recombinations and the relative distance between the genes in question in a chromosome. Charts of chromosomes have been established in this way, showing the positions of the genes. (Compare H. J. Muller's explanation of X-ray mutations; see below, pp. 239-241.)

Morgan's school of geneticists has been able to present convincing evidence that the chromosome is actually the carrier of the genes. This evidence is of several kinds. There are four chromosomes in Drosophila; there are also four linkage groups. But perhaps the most conclusive evidence is that which comes from the loss or from the addition of one of the small fourth chromosomes of Drosophila. Genetic indications can in this case be verified directly by the microscope.

The Morgan doctrines which are here sketched in outline were built up by the patient and comprehensive work of many years. They have been confirmed by other scientists in studies of both animals and plants. In the human being, too, it has been possible to identify linkage groups. It is now obvious that legal medicine owes a debt to genetic science. In the investigation of hereditary tendency to disease or physical defect it is likewise impossible to proceed without the aid of the basic contributions of laboratory geneticists. The study of mutations in genes and chromosomes is a promising part of current cancer research. Not only in medicine but also in agriculture and stock breeding the "theory of the genes," which owes so much to Morgan and his school, has shown itself to be a concept of great practical importance.

1934

GEORGE HOYT WHIPPLE

(1878–)

GEORGE RICHARDS MINOT

(1885–1950)

WILLIAM PARRY MURPHY

(1892–)

"For their discoveries concerning liver therapy against anemias."

BIOGRAPHICAL SKETCHES

WHIPPLE

GEORGE HOYT WHIPPLE WAS BORN IN ASHLAND, NEW HAMPshire, on August 28, 1878. He was educated at Andover Academy and Yale University (A.B., 1900) and received his M.D. degree from the Johns Hopkins University in 1905. With the exception of one year (1907-1908) as pathologist at the Ancon Hospital, Panama, Dr. Whipple was at the Johns Hopkins Medical School from 1905 to 1914, as assistant in pathology, instructor, associate, and associate professor. From 1914 to 1921 he was professor of research medicine at the University of California Medical School, and director of the Hooper Foundation for Medical Research, Uni-

versity of California. During the year 1920-1921 he was dean of the University of California Medical School. In 1921 Dr. Whipple became professor of pathology and dean of the School of Medicine and Dentistry of the University of Rochester. Much of his research, from the time when he was a junior in the Johns Hopkins Department of Pathology under Dr. William H. Welch, has dealt with normal and pathological liver function. Dr. Whipple has conducted penetrating studies of the origin, function, and fate of bile pigments and other body pigments in health and disease. He has made contributions of basic importance to our knowledge of the anemias. He has also studied plasma protein regeneration and iron metabolism. He became a Trustee of the Rockefeller Foundation in 1927, a member of the Board of Scientific Directors of the Rockefeller Institute in 1936, and a Trustee of the Institute in 1939.

MINOT

GEORGE RICHARDS MINOT WAS BORN IN BOSTON, ON DECEMBER 2, 1885. He attended Harvard University, receiving the A.B. in 1908, the M.D. in 1912, and the honorary degree of S.D. in 1928. After serving as medical interne at the Massachusetts General Hospital, he worked at the Johns Hopkins Hospital and Medical School under William S. Thayer and William H. Howell. In 1915 he returned to Boston, being appointed assistant in medicine at the Harvard Medical School and Massachusetts General Hospital. In 1922 he became physician in chief of the Collis P. Huntington Memorial Hospital of Harvard University; later he was appointed also to the staff of the Peter Bent Brigham Hospital. In 1928 he was made professor of medicine at Harvard and director of the Thorndike Memorial Laboratory, as well as visiting physician at Boston City Hospital. Although he published papers on a wide variety of subjects, including cancer, arthritis, and dietary deficiency (e.g., the role of dietary factors in "alcoholic" polyneuritis), his chief interest lay in disorders of the blood and the function and dysfunction of bone marrow. He contributed to knowledge concerning coagulation of the blood, the blood platelets, various hemorrhagic disorders, the blood picture in certain industrial poisonings,

leukemia, disorders of the lymphatic tissue and polycythemia, as well as the anemias. His most significant contributions were his studies of the anemias, and especially pernicious anemia.

MURPHY

WILLIAM PARRY MURPHY WAS BORN IN STOUGHTON, WISCONSIN, on February 6, 1892. His early education was received in the public schools of Wisconsin and Oregon. He received his A.B. from the University of Oregon in 1914 and then for two years taught physics and mathematics in Oregon high schools. After one year in the University of Oregon Medical School, Portland, and a summer session at the Rush Medical School, Chicago, he entered the Harvard Medical School and received the M.D. degree in 1922 as of 1920. After two years as house officer at the Rhode Island Hospital, he became assistant resident physician at the Peter Bent Brigham Hospital under Prof. Henry A. Christian for eighteen months, then junior associate, and later associate in medicine at the same institution. He was assistant in medicine at Harvard from 1923 to 1928, instructor from 1928 to 1935, and associate from 1935 to 1948. Since 1948 he has been lecturer. Dr. Murphy has been an active practitioner of medicine since 1923.

DESCRIPTION OF THE PRIZE-WINNING WORK

WHIPPLE *

"At the University of California (1914), Dr. [C. W.] Hooper and I took up a careful study of bile pigment metabolism by means of bile fistulas in dogs and investigated the effect of diet upon bile pigment output. As these studies were continued . . . it became apparent that we could not understand completely the story of bile pigment metabolism without more knowledge about the construction of blood hemoglobin in the body. Blood hemoglobin is a most important precursor of bile pigment and it was necessary to under-

* From G. H. Whipple, "Hemoglobin Regeneration as Influenced by Diet and Other Factors," *Les Prix Nobel en 1934.*

stand what factors influenced the building of new hemoglobin in the dog.

"For this reason we produced simple anemia in dogs by means of blood withdrawal and in short experiments followed the curve of hemoglobin regeneration back to normal. These experiments with Dr. Hooper were begun in 1917 and it was found at once that diet had a significant influence on this type of blood regeneration. Because of our interest in liver function and injury we soon began testing *liver* as one of the diet factors and could readily demonstrate that it had a powerful effect upon hemoglobin regeneration [1920]. These short anemia experiments were relatively crude and gave at best qualitative values for the various diet factors.

"After the transfer of the anemia colony of dogs from San Francisco to Rochester, New York (1923), Dr. Frieda Robscheit-Robbins and the writer began to use a different type of anemia. Dogs were bled by aspiration from the jugular vein and gradually reduced from a normal hemoglobin level of 140-150 per cent to about 1/3 normal, or 40-50 per cent, and this anemia level was maintained a constant for indefinite periods by suitable removal of new-formed hemoglobin. The potency of the diet factor was then accurately measured in terms of the grams hemoglobin removed to preserve the constant anemia level. The stimulus presumably was maximal and uniform, and the reaction of a given dog to a diet factor was shown to be uniform when repeated time after time.

"Much effort and time were spent in devising a basal ration adequate for health and maintenance during these long anemia periods lasting throughout the entire life of the dog (5-8 years). . . . [Such a diet] permits of minimal new hemoglobin regeneration and therefore gives a low base-line hemoglobin output from which to measure the increased output due to liver, kidney, gizzard or other favourable diet factor. . . .

"[From the results] it is obvious that liver . . . stands out as the most potent diet factor. . . . Gradually various diet factors were standardized and this information was placed at the disposal of physicians who were concerned with the therapeutic treatment of human anemias. Iron was found to be the most potent inorganic element.

"Pernicious anemia, examined from the point of view of the

pathologist, was described in 1921 [publication 1922] as a disease in which all pigment factors were present in the body in large excess but with a scarcity of stroma-building material or an abnormality of stroma-building cells." [The "stroma" is the framework, or structural basis, of an organ, tissue, or cell. In pernicious anemia the factors needed to form blood pigment are present, but the red blood cells, the necessary vehicle, do not form properly.]

MINOT *

"The idea that something in food might be of advantage to patients with pernicious anemia was in my mind in 1912, when I was a house officer at the Massachusetts General Hospital, as is noted in certain case records there. . . .

"The study of the patients' diets was begun in 1915 in an attempt to determine if some sort of dietary deficiency could be found. The similarity of certain symptoms and signs of pernicious anemia to those in pellagra, sprue and beriberi was appreciated, as was the fact that certain sorts of anemia were occasionally associated with a faulty diet. Elders, among others, suggested in 1922 that such a state of affairs existed in pernicious anemia. Furthermore, the almost constant occurrence of achlorhydria [absence of hydrochloric acid in the gastric juice] in pernicious anemia . . . led me to wonder if this disorder of the digestive system had something to do with the condition which might be in the nature of a dietary deficiency disease. Indeed, Fenwick, about 1880, suggested the primary role of the stomach, but it remained for Castle, in 1928, to demonstrate the part this organ plays in the causation of the disease. . . . [W. B. Castle showed that meat digested with normal gastric juice was almost as effective as liver, but found that meat by itself, or when digested with the aid of a synthetic gastric juice, failed to give any good effect. Normal gastric juice seems to contain an "intrinsic factor," which together with an "extrinsic factor" in meat forms the active substance causing red blood cells to mature. This active substance, called "erythrocyte maturing factor," or "EMF," is stored, among other places, in the liver. This

* From G. R. Minot, "The Development of Liver Therapy in Pernicious Anemia," *Les Prix Nobel en 1934.*

explanation was not forthcoming until Minot and Murphy had shown the value of liver therapy.]

"Although Pepper in 1875 and Cohnheim in 1876 recognized that the bone marrow was abnormal, there was a prevailing opinion in the early part of this century that abnormal blood-destruction played an important or primary role in the production of the disease. Nevertheless it was believed by many physicians, as I was taught, that the production of blood by the bone marrow was also deeply implicated. . . . [This] led me to believe firmly that something was needed to make the primitive red cells that crowd the bone marrow in relapse grow to normal cells. . . . In 1922 Whipple suggested that in pernicious anemia there might be a scarcity of material from which the stroma of the red blood cells was formed, or that there existed a disease of the stroma-forming cells of the bone marrow. This concept fitted with the idea that there was a deficiency of something in the body, and that dysfunction of pigment metabolism was resultant. . . .

"For centuries the concept that food bore a relationship to anemia had been vaguely expressed in the literature. It had been shown that liver and kidneys, rich in complete proteins, promoted the growth of animals, and that substances in liver could enhance cell-division. It was likewise recognized that liver-feeding could benefit patients with sprue (Manson 1883) and pellagra. These were among the reasons that led to the choice of liver as a substance likely to enhance blood-formation. Of invaluable importance was Whipple's fundamental and classical work on hemoglobin regeneration by means of liver and other foods in anemia due to blood-loss in dogs. . . .

"A few patients were fed relatively small amounts of liver during 1924 and early 1925. Although these patients did better than expected, the results permitted no more than speculations. Then Dr. Murphy joined in the work and we pursued the study of these and subsequent cases. Liver had been fed by Gibson and Howard and other individuals to pernicious anemia patients but without persistence or definite results. It seemed to us that to accomplish our object a large weighed amount of liver should be fed daily with regularity. Likewise to determine the effect it was considered essential that data should be obtained in a large number of cases

to be appropriately compared with controls. By May, 1926, we had fed liver intensively and daily to 45 patients. In many of these patients symptomatic improvement was obvious within about a week. Soon they craved food and color appeared in their faces. Tongue and digestive symptoms rapidly lessened. Within about 60 days the red blood cell counts had risen on the average from low levels to approximately normal. . . . An objective measure of the effects upon blood-production was the chief basis of our conclusions that by feeding liver significant improvement had been obtained. I refer especially to counts of new adult and young blood cells (reticulocytes) appearing, as Peabody's studies demonstrated later, as a result of the maturation of the immature cells crowding the bone marrow.

"The next step naturally was to attempt to determine the nature of the constituent in liver responsible for the effects and to learn if an extract for therapeutic use could be obtained. Dr. Edwin J. Cohn, . . . of the Harvard Medical School, soon made a potent extract suitable for oral use. . . . It remained for Gänsslen in Germany to produce the first practical extract for parenteral [injection] therapy."

MURPHY *

"Since the earliest use of liver in the treatment of pernicious anemia . . . new fields of observation have been made available both in the clinic and in the laboratory. We have been allowed the thrill of watching the patient through a few days of depression following the institution of liver therapy until remission occurs with its often sudden and almost unbelievable sense of well-being simultaneously with the maximum increase of the reticulocytes or new red blood cells. Then we have followed this remission through to completion, until the blood becomes normal. . . . Perhaps even more dramatic has been the improvement in the disturbances of locomotion resulting from nerve damage. . . .

"Observation of the patients at intervals in the office or hospital blood clinic and attention to the important details of treatment have made it possible for us to maintain our patients in a state of

* From W. P. Murphy, "Pernicious Anemia," *Les Prix Nobel en 1934.*

economic efficiency and with reasonably good health. Forty-two of the forty-five patients originally treated and discussed in our first paper [Minot and Murphy] in 1926 have been kept under observation. Of this number thirty-one, or approximately three fourths, are living and well [1934] after almost ten years of treatment. Eleven have died from various causes other than pernicious anemia."

CONSEQUENCES IN THEORY AND PRACTICE

The practical results of liver therapy in the treatment of pernicious anemia have already been indicated in quotations from the Nobel lectures of Dr. Minot and Dr. Murphy. Other agents have been introduced for the same purpose. "Ventriculin" is made from the stomach wall of the hog—desiccated, defatted, and powdered. Its effect is similar to that of liver. Of more recent innovations, vitamin B_{12} appears to be the most important. Folic acid, isolated from green leaves and from liver, and also synthesized, has a certain curative value in that it brings about the production of mature red blood cells; it is not satisfactory in the treatment of pernicious anemia because it does not stop the changes in the nervous system which often accompany this disease. Although obtainable from liver, it is quite distinct from the hematinic principle in liver extracts. Nothing has yet been introduced which has been capable of supplanting liver extracts in practice. In an insidious, chronic, debilitating disease, ultimately fatal before the introduction of liver therapy, it has become possible to suppress the symptoms and prolong life. Liver is not a "cure" but rather a symptomatic remedy; its use must be indefinitely continued. The initial effects of treatment are remarkable. Within a few days the number of reticulocytes (immature blood corpuscles) goes up, showing that the bone marrow, where the cells are formed, is increasingly active. The number of normal cells in the blood gradually increases, and the abnormal ones begin to disappear. Concurrently the patient feels better, looks better, and becomes stronger. Liver treatment is able to prevent the neurological symptoms which may otherwise appear, and can even cause a recession in established symptoms.

The two great innovations in the treatment of noninfectious disease during the first quarter of the present century were insulin for diabetes and liver for pernicious anemia. Both discoveries stimulated further research. Knowledge of the effect of liver gave a new direction to the study of hematopoiesis (the formation of blood) under both normal and pathological conditions. (For another aspect of research on pernicious anemia, see above, pp. 66-67.)

1935

HANS SPEMANN

(1869–1941)

"For his discovery of the organizer effect in embryonic development."

BIOGRAPHICAL SKETCH

HANS SPEMANN WAS BORN ON JUNE 27, 1869, IN STUTTGART, Germany, where he attended the humanistic Eberhard-Ludwig *Gymnasium*. After leaving school he spent a few years in his father's business and in the performance of his military service before beginning the study of medicine at the Universities of Heidelberg, Munich, and Würzburg. At Heidelberg he worked with the anatomist Carl Gegenbaur; at Munich, with August Pauly. He was graduated in 1895 in zoology, botany, and physics, under Theodor Bovery, Julius Sachs, and Wilhelm Röntgen, respectively. The years 1894-1908 were spent in the Zoological Institute at Würzburg. In the latter year he accepted the chair of zoology and comparative anatomy at Rostock. In 1914 he became director of the Kaiser Wilhelm Institute for Biology in Berlin-Dahlem. Finally, in 1919, he was called to the professorship at Freiburg-im-Breisgau, which he held until his retirement in 1935, the year in which he was awarded the Nobel Prize. He died at the end of 1941, in his seventy-third year.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"[My experiments] were all carried out on young amphibian embryos, mostly on those of the ordinary . . . *Triton teaeniatus* [species of newt]. In order to make the experiments understandable to nonspecialists, too, it becomes necessary first of all to picture the highlights of the normal development of these eggs.

"The development begins, in direct response to fertilization, with long-continued cell division . . . known as the segmentation process. Through the formation of a hollow space inside—the segmentation cavity—there arises the germinal vesicle or blastula. Its lower, vegetative half, the thick floor of the germinal vesicle, is composed of large, yolk-rich cells, whereas the upper, animal half, the thin roof, is composed of numerous small cells, poor in yolk substance. The junction between them is formed by the marginal zone, a ring of cells of medium size.

"There now sets in a very complicated process, in many respects mysterious, the so-called gastrulation. Its final result is that the whole material of the marginal zone and the vegetative half of the embryo are doubled into the interior, and are thus covered by the animal material. It is along the line of invagination, at the primitive orifice or blastopore, that the outer germinal layer, the ectoderm, changes to the two layers brought into the interior, the mesoderm, (originating in the marginal zone) and the entoderm (corresponding to the yolk-rich vegetative half of the embryo). . . .

"The anlage of the central nervous system [i.e., the primordial part in the embryo from which the adult structure is formed] arises in the ectoderm of the back . . . as a thickened, shield-shaped plate, broader in its anterior than in its posterior half. It is the medullary plate, the edges of which are thrust up into ridges, the medullary ridges. By the drawing together of the ridges, the plate is closed to form a tube, the medullary tube. This detaches itself from the epidermis and sinks deeper. Its thick anterior end, arising from the broad anterior part of the medullary plate, becomes the

* Translated from "Nobel-Vortrag von Hans Spemann," *Les Prix Nobel en 1935*.

brain; its thin posterior half the spinal cord. [Spemann then describes briefly the fate of the mesoderm, which forms the anlage of the vertebral column, etc., and the entoderm, which forms a groove, changing into the intestinal tube.]

"All these events . . . are essentially dependent not on a new formation of embryonic substance but on rearrangement of that already present. It is therefore to some extent possible . . . to mark out a topography of the later anlages of the organs in the blastula or early gastrula.

"In considering such a topographical map, the question recurs whether an actual difference in these parts corresponds to this pattern of presumptive anlages in the gastrula at the beginning; whether they are already more or less firmly ordained for their later fate, predestined [*determiniert*], or whether they are still indifferent and their destiny is first stamped upon them later.

"The first answer to this question was given by isolation experiments. That is to say, if one undertakes a division through the middle, not between the first two segmentation cells, but later, even in the stage of the blastula or the quite young gastrula, twins can still be produced by this means. This becomes especially clear if the division be made in such a way that the ventral half of the embryo is cut off from the dorsal. Then the latter also develops into an embryo of smaller size [but] of normal proportions. Here the new partition of materials is quite plain. The dorsal half, according to the topographical map, possesses almost all the material for the medullary plate, therefore much too much for a half-size embryo; on the other hand it lacks the whole presumptive epidermis. This latter must be made good from the material of the former.

"But now if presumptive medullary plate and presumptive epidermis can substitute for each other, then also they must allow themselves to be interchanged, one for the other, without prejudice to further normal development. Embryonal transplantation must thus in this early stage have another result than in the later stages. . . .

"The success of the new experiments rests on these ideas, and on the development of a method making it possible to manage the extraordinarily fragile young embryos and to operate on them.

"The first experiment now consists in the interchange of a piece

of presumptive epidermis and medullary plate between two embryos of the same age, in the beginning of gastrulation. Healing results so smoothly, and the further development goes on so normally, that the margins disappear without a trace, if the implant is not kept visible for a time by natural pigmentation or artificial vital staining. In this case it appears, as expected, that the pieces can interchange mutually, so that presumptive epidermis can become medullary plate, presumptive medullary plate epidermis.

"But from this follows not only the profound indifference of the cells in this early stage of development; rather, the result permits the much more important conclusion that in the new location influences of some sort must govern, which coerce the foreign piece to its fate. . ."

CONSEQUENCES IN THEORY AND PRACTICE

"In order [as Spemann wrote] to make the experiments understandable to nonspecialists," he felt it necessary to devote a large part of his Nobel lecture "to picture the highlights of the normal development of these eggs." The quotation given above terminates with the first indication of the general principle which was Spemann's chief contribution.

Spemann's most important forerunners were Roux and Driesch. W. Roux had obtained half-formations, etc. by destroying some of the cleavage cells in the frog's egg. His experiments led him to the view that up to a certain point something within each part of the embryo determines its fate; thereafter the general requirements of the organism and the need for certain cells determine their appearance and growth.

To illustrate the inductive effect which one embryonal area can exert on another, Spemann performed experiments on the developing eye. The retina grows out from the brain as a vesicle, later changed into a cuplike structure; the lens of the eye, on the other hand, is derived from the near-by epidermis. Spemann showed that the eyeball is able to bring about the formation of a lens from distant epidermis which does not normally develop in this way, in an area having nothing to do, under ordinary circumstances, with

lens production. The covering epidermis then begins to clear, as in the formation of the transparent cornea, despite its "foreign," noncorneal location.

Then came the experiments in division of the embryo described in the quotation above, and the transplants of pieces of presumptive medullary plate, showing how rearranged cells develop according to their new local environment. Spemann was also able to show that if a piece of the dorsal blastopore lip is implanted in another embryo, in an area of presumptive skin, the development of a second embryo is thereby induced. This upper blastopore lip he later showed to be the source of influences which determine the fate and cause the structural and functional differentiation of various parts, the medullary plate in particular; he therefore called the upper blastopore lip an "organization center." Other, secondary organization centers were also demonstrated, of which the eyecup may be considered one.

"[Spemann's] great achievement was to bring into fruitful coordination the two, in themselves inconclusive, lines of attack which had been opened up in the casual investigation of development. On one hand, the studies of Roux and Driesch on the developmental potentialities of the first-formed blastomeres of the egg, although they tackled the major problems of the formation of the animal as a whole, seemed to lead only to a sterile paradox. On the other hand, Roux's notion of dependent differentiation appeared to suggest a plausible causal mechanism for development, but the one known example of it, and that a somewhat doubtful one, was concerned with the development of a single organ, the lens of the eye. Spemann entered both these fields, with his famous constriction experiments on the early cleavage states of Triton, and his early grafting experiments on the optic rudiments of the same form. By 1918 he was able to bring forward his concept of the 'organization-centre' and demonstrate that the morphogenesis of the embryo, in its main outlines as well as in its details, is the result of the interactions between different regions of tissue. For the next fourteen years, Spemann was the leader of a school, which rapidly filled in the outlines of what had come to be called 'embryonic induction.' . . . In 1932 he participated in the next major step for-

ward, the beginning of the physico-chemical investigation of the process.

"Although his work was one of the most important influences in the final discredit of vitalism, Spemann was never one of those who hoped that the discovery of the organizer would rapidly enable us to reduce the problem of biological form to a few simple chemical statements. His attitude was, in fact, much more a biological than a physico-chemical one. The extreme caution with which he formed his conclusions, joined with intense concentration on a narrow field favourable for an attack on fundamental problems, enabled him to lay a foundation on which the science of experimental morphogenesis can be securely based." *

* Quoted from the obituary by C. H. Waddington in *Nature* (London), Vol. 149 (1942), p. 296.

1936

HENRY DALE

(1875–)

OTTO LOEWI

(1873–)

"For their discoveries relating to the chemical transmission of nerve impulses."

BIOGRAPHICAL SKETCHES

DALE

HENRY HALLETT DALE WAS BORN IN LONDON, ON JUNE 9, 1875. From Leys School, Cambridge, he proceeded to Trinity College, Cambridge, in 1894. This step in his education, like every subsequent stage, was marked by the winning of a scholarship. He was graduated through the Natural Science Tripos, Part II (Physiology and Zoology.) From 1898-1900 he worked in physiology at Cambridge under J. N. Langley. In the latter year he turned to clinical work at St. Bartholomew's Hospital. Cambridge granted him the B.Ch. in 1903 and the M.D. in 1909. For a time he worked in University College, London, with E. H. Starling; here he first met Otto Loewi. There followed four months with Paul Ehrlich at Frankfort on the Main. Dale then returned for a brief period to University College, but soon entered the Wellcome Physiological Research Laboratories as pharmacologist (1904). From 1906 to 1914 he was director of the Laboratories. It was during this period

that he undertook the work on the pharmacology of ergot which led to his later studies on tyramine, histamine, and acetylcholine. In 1914 he was elected Fellow of the Royal Society and in the same year was appointed director of the Department of Biochemistry and Physiology in the newly constituted National Institute for Medical Research. In 1928 he became director of the Institute. Dale has been the recipient of a very large number of honors and awards, has served on many official commissions, and has traveled widely. He is well known, also, through his graduate students in many parts of the world.

LOEWI

OTTO LOEWI WAS BORN IN FRANKFORT ON THE MAIN, ON JUNE 3, 1873. He studied in the *Gymnasium* there until 1891, when he undertook the study of medicine at Strasbourg. Later he took a part of his course in Munich but returned to Strasbourg for the degree Dr. med., which was granted in 1896. In 1896-1897 he studied chemistry in Frankfort with Martin Freund, then physiological chemistry with Franz Hofmeister in Strasbourg. In 1897-1898 he was assistant to Karl von Noordens in the City Hospital in Frankfort. He was then appointed assistant at the Pharmacological Institute in Marburg and became *Privatdozent* in 1900. He worked for some months in 1901-1902 with E. H. Starling in London, but remained at Marburg until 1905, when he was named associate professor in Vienna. For nearly thirty years (1909-1938) he was professor of pharmacology in Graz. He then went to England and later to the United States. Since 1940 he has been research professor at the College of Medicine of New York University.

DESCRIPTION OF THE PRIZE-WINNING WORK

DALE *

"My chemical collaborator [in 1914], Dr. Ewins, had isolated the substance responsible for a characteristic activity which I had

* H. H. Dale, "Some Recent Extensions of the Chemical Transmission of the Effects of Nerve Impulses," *Les Prix Nobel en 1936.*

detected in certain ergot extracts, and it had proved to be acetylcholine, the very intense activity of which had been observed by Reid Hunt already in 1906. Since we had found this substance in nature, and it was no longer a synthetic curiosity, it seemed to me of interest to explore its activity in greater detail. I was thus able to describe it as having two apparently distinct types of action. Through what I termed its 'muscarine' action, it reproduced at the periphery all the effects of parasympathetic nerves, with a fidelity which, as I indicated, was comparable to that with which adrenaline had been shown, some ten years earlier, to reproduce those of true sympathetic nerves. All these peripheral muscarine actions, these parasympathomimetic effects of acetylcholine, were very readily abolished by atropine. When they were thus suppressed, another type of action was revealed, which I termed the 'nicotine' action, because it closely resembled the action of that alkaloid in its intense stimulant effect on all autonomic ganglion cells, and, as later appeared, on voluntary muscle fibres. . . .

"Effects of acetylcholine, directly analogous to those which Loewi discovered in relation to the heart vagus, were covered by what I had termed the 'muscarine' action of acetylcholine, and were all very readily suppressed by atropine. But there remained, as yet without any corresponding physiological significance, the other type of action of acetylcholine, so similar in distribution to that of nicotine, which had come to my notice nearly twenty years earlier. . . .

"Although from the time when it first became clear that Loewi's Vagusstoff [see below, p. 192] was acetylcholine, I had begun to consider the possible significance of its 'nicotine' actions, it was long before the possibility of its intervention as transmitter at ganglionic synapses, or at voluntary motor nerve endings, seemed to be accessible to investigation. Experiments on the ganglion came first in order. Chang and Gaddum had found, confirming an earlier observation by Witanowski, that sympathetic ganglia were rich in acetylcholine. Feldberg . . . had observed . . . that the effects of splanchnic [visceral] nerve stimulation are transmitted to the cells of the suprarenal medulla by the release of acetylcholine in that tissue. Now these medullary cells are morphological analogues of sympathetic ganglion cells, and Feldberg, continuing this study

in my laboratory, found that this stimulating action of acetylcholine on the suprarenal medulla belonged to the 'nicotine' side of its actions. Clearly we had to extend these observations to the ganglion; and a method of perfusing the superior cervical ganglion of the cat, then recently described by Kibjakow, made the experiment possible. Feldberg and Gaddum . . . found that, when eserine [see below, p. 192] was added to the fluid perfusing the ganglion, stimulation of the preganglionic fibres regularly caused the appearance of acetylcholine in the venous effluent. It could be identified by its characteristic instability, and by the fact that its activity matched the same known concentration of acetylcholine in a series of different physiological tests, covering both 'muscarine' and 'nicotine' actions. It appeared in the venous fluid in relatively high concentrations, so strong indeed, that reinjection of the fluid into the arterial side of the perfusion caused, on occasion, a direct stimulation of the ganglion-cells. It was clear that, if the liberation took place actually at the synapses, the acetylcholine liberated by each preganglionic impulse, in small dose, indeed, but in much higher concentration than that in which it reached the venous effluent, *must* act as a stimulus to the corresponding ganglion cells. Feldberg and Vartiainen then showed that it was, in fact, only the arrival of preganglionic impulses at synapses which caused the acetylcholine to appear. They showed, further, that the ganglion cells might be paralysed by nicotine or curarine [the active principle of the arrow-poison, curare], so that they would no longer respond to preganglionic stimulation or to the injection of acetylcholine, but that such treatment did not, in the least, diminish the output of acetylcholine caused by the arrival of preganglionic impulses at the synapses. There was, in this respect, a complete analogy with the paralysing effect of atropine on the action of the heart vagus, which, as Loewi and Navratil had shown many years before, stops the action of acetylcholine on the heart, but does not affect its liberation by the vagus impulses.

"The difficulty facing us in the case of the voluntary muscle was largely a quantitative one. In a sympathetic ganglion, the synaptic junctions, at which the acetylcholine is released . . . , form a large part of the small amount of tissue perfused. In a voluntary muscle the bulk of tissue, supplied by a rich network of capillary blood

vessels, is enormous in relation to the motor nerve endings, of which only one is present in each muscle fibre. The volume of perfusion fluid necessary to maintain functional activity is, therefore, very large in relation to the amount of acetylcholine which the scattered motor nerve endings can be expected to yield when impulses reach them. With the skilled and patient cooperation of Dr. Feldberg and Miss Vogt, however, it was possible to overcome these difficulties, and to demonstrate that, when only the voluntary motor fibres to a muscle are stimulated, to the complete exclusion of the autonomic and sensory components of the mixed nerve, acetylcholine passes into the Locke's solution [chlorides of sodium, calcium, and potassium, with sodium bicarbonate, dextrose, and distilled water], containing a small proportion of eserine, with which the muscle is perfused. If, by calculation, we estimate the amount of acetylcholine thus obtained from the effect of a single motor impulse arriving at a single nerve ending, the quantity is of the same order as that similarly estimated for a single preganglionic impulse and a single ganglion cell. . . . We found that, if the muscle was denervated . . . , direct stimulation, although evoking vigorous contractions, produced no trace of acetylcholine. If, on the other hand, the muscle was completely paralysed to the effects of nerve impulses by curarine, stimulation of its motor nerve fibres caused the usual output of acetylcholine, although the muscle remained completely passive. Again there is a complete analogy with Loewi's observations on the heart vagus and atropine. . . ."

LOEWI *

"Natural or artificial stimulation of nerves induces in them an occurrence known as progressive excitation, which leads to a response in the organ activated by the nerves concerned.

"Up to the year 1921 it was unknown how excitation of a nerve influences its responsive organ to function—in other words, in what way the impulse of the nerve is transferred from the nerve ending to the responsive organ. For the most part it was supposed that there was a direct encroachment of the wave of excita-

* Translated from Otto Loewi, "Die chemische Übertragung der Nervenwirkung," *Les Prix Nobel en 1936.*

tion of the nerve fiber on the organ of response. But as a matter of fact, there were also those who had already formed the opinion that the transference takes place by chemical means, and had communicated [the results of their] researches. Thus W. H. Howell had formed the view on the ground of his own research that vagus stimulation liberates potassium in the heart, and that this occasions the result of stimulation. . . . [The vagus nerve has an inhibitory influence on the heart. In 1908, Howell, with W. W. Duke, reported an increase in the concentration of potassium in the fluid perfusing an isolated mammalian heart during vagal stimulation. Howell's work in this connection dates from 1906. Loewi also mentions the name of W. M. Bayliss, who had written in his famous textbook of physiology (ed. 1902, p. 344) that "the nerve may act by the production of the same chemical substance which excites directly, or the chemical excitant may act on the same terminal mechanism as the excitatory process in the nerve fibre does."]

"Although these data were known to me, I was first made aware a year after my discovery that earlier—i.e., in 1904—[T. R.] Elliott, at the conclusion of a short note, had already intimated the possibility that stimulation of sympathetic nerves works through the liberation of adrenalin, and that [W. E.] Dixon had already [1907], in a place difficult of access, brought out researches aimed at elucidation of the question whether a substance is set free on stimulating the vagus which induces the result. [Emil Du Bois-Reymond (1818-1896) hinted a similar explanation. It appears that none of these suggestions was supported by satisfactory proof.]

"In the year 1921 I succeeded for the first time in furnishing to this end the proof capable of only one interpretation, [by showing] that through stimulation of the nerves of a frog's heart [suspended in a glass vessel containing saline] substances are set free, part of which enter the perfusion fluid of the heart, and being transferred with this to [another] test heart, here work exactly like the stimulation of the corresponding nerves. It was thereby proved that the nerves do not act directly on the heart, but that the immediate result of nerve stimulation is the freeing of chemical substances, and that these first act directly in bringing about the

functional change in the heart which is characteristic of nerve action. . . .

[The autonomic, or involuntary, nervous system, controlling those functions that are largely independent of the will and of direct outside influences, has two divisions, called the sympathetic and the parasympathetic. The vagus nerve contains parasympathetic fibers; Loewi and his co-workers investigated the nature of the substance, which he called "Vagusstoff," released by their stimulation.] "We were able to establish that its action is suspended by atropine, and [in any case] disappears very quickly. In the search for a substance sharing both these peculiarities, I found that out of the series of known vagomimetic substances [i.e., chemicals with the physiological effects of "Vagusstoff"], muscarine, pilocarpine, choline, and acetylcholine, this held true only for the latter. It could then be directly established further, that the rapid cessation of the action of Vagusstoff and acetylcholine depends on the decomposition of these substances through the action of an esterase in the heart, already duly postulated by Dale. [An esterase is an enzyme, or ferment, which acts specifically on a certain ester; acetylcholine is numbered chemically among the esters.] I was able to show further that the action of this esterase is specifically retarded by minimal concentrations of eserine. [Eserine is a vegetable substance derived from the Calabar bean of western Africa; chemically it is an alkaloid and is known also as physostigmine. By showing that the breakdown of his "Vagusstoff" could be prevented in this way, Loewi made it relatively easy to enhance its effect and to detect its presence.] . . .

"Not only as regards its reaction with atropine and its destructibility by esterase, but also in respect of all other attributes, Vagusstoff behaves identically with acetylcholine. When, over and above this, acetylcholine could be directly demonstrated in the organs by Dale and Dudley, no doubt remained that Vagusstoff is acetylcholine."

CONSEQUENCES IN THEORY AND PRACTICE

For well over a century the study of the electric changes during nerve activity was the sole path toward knowledge of the mechanism of nervous function. Sherrington and Adrian, Erlanger and Gasser—all of them Nobel laureates—were electrophysiologists. But all cells, including nerve cells, require energy for their activity; in a living cell, chemical reactions form the source of energy. Only in the last thirty years, however, has evidence accumulated respecting the chemical side of nerve activity.

Loewi performed his perfusion experiments in 1921. In 1926 A. V. Hill and his associates were able to measure the heat production of the resting nerve and the increased heat production following stimulation. As in the case of Hill's studies of heat production in muscle, this biophysical approach pointed to chemical change from which the thermal change resulted. Gerard and Meyerhof, and at the same time (1927) Fenn, could confirm this by measurement of the extra oxygen uptake.

Loewi's work was limited to the autonomic nervous system. Dale and his associates, following the lead of Kibjakow, tried to extend this concept, suggesting that acetylcholine might transmit impulses across ganglionic synapses and at neuromuscular junctions. (It may be noted that an important part of Nobel Prize scientific study has centered in the nerve-muscle relationship.) The evidence, of which only an early indication is given in the excerpt from Sir Henry Dale's lecture, was chiefly based on (1) liberation of acetylcholine after stimulation of preganglionic fibers on motor nerves; (2) stimulation of the sympathetic ganglion and the striated muscle by injection of small amounts of acetylcholine; and (3) "potentiation" of the effects of nerve stimulation by the use of eserine. Dale and his group worked out ingenious techniques and contributed very extensively to the piling up of the evidence.

There were two principal difficulties. Neurons and striated muscle fibers act with lightning speed. Any chemical reaction involved must occur with the same speed. The question was whether or not the rate of acetylcholine metabolism was high enough to fit the

timetable of nervous mechanism. The second difficulty was the question whether the modes of conduction along nerve fiber and across synapses are fundamentally different. There seems to be reason to think that no basic difference exists.

In the last twenty-five years enzyme chemistry has assumed greater and greater importance. It seems probable that all "trace substances"—compounds active in minute amounts—are correlated to enzyme systems. Because of the high concentration of choline esterase it has been suggested that the rate of acetylcholine metabolism is high enough to parallel electrical events during nerve activity. It has also been pointed out that the choline esterase is localized at the neuron surface and that a parallel exists between the voltage associated with nerve impulse and the concentration of the enzyme. These findings in connection with other known facts have suggested that the release of acetylcholine is not limited to the nerve endings but occurs everywhere at the neuron surface. Acetylcholine appears to be an essential factor in generating the nerve action potential by its effect on the surface membrane of the nerve. Furthermore, although Loewi and Dale were once of the opinion that there is no acetylcholine present in sensory nerves, it has been detected more recently not only in the motor nerves but also in the sensory nerves, including the optic nerves. The range of action and the fundamental importance of the substance which began life, so to speak, as "Vagusstoff," have been shown to be vastly greater than was perceived some twenty to thirty years ago, when the pioneer experiments were performed.

Discoveries of this kind are contributions to basic knowledge. One should hardly expect any immediate practical results. (William Harvey's discovery of the circulation of the blood, announced in 1628, had little effect on practice for many years, yet this discovery is the foundation of all modern medicine.) In the case of Dale and Loewi, however, a sort of "premium" in the way of practical consequences was not long in appearing. The eserine which played so large a part in their experiments is also known as physostigmine. To put it briefly, this substance inhibits the esterase which inhibits acetylcholine, and therefore it "potentiates" the acetylcholine action. A disease called myasthenia gravis is known as a chronic and progressive muscular weakness, usually beginning

in the face and throat. On the assumption that physostigmine, exerting an inhibitory action on cholinesterase, might be of benefit in this disease, it was introduced as a new treatment by Mary Broadfoot Walker in 1934. Together with prostigmine, which is closely similar in action and which was introduced for the same purpose by L. Remen in 1932, physostigmine continues to hold a place in the management of myasthenia gravis.

REFERENCES

NACHMANSOHN, D. "The Role of Acetylcholine in the Mechanism of Nerve Activity," in R. S. Harris and K. V. Thimann, eds., *Vitamins and Hormones,* Vol. 3 (New York: Academic Press, 1945).

———. "Biochemical Approach," a symposium, in D. Nachmansohn, ed., *Nerve Impulse: Transactions of the First Conference, March 2-3, 1950* (New York: Josiah Macy, Jr. Foundation, 1951).

1937

ALBERT VON SZENT-GYÖRGYI

(1893–)

"For his discoveries in connection with the biological combustion processes, with especial reference to vitamin C and the catalysis of fumaric acid."

BIOGRAPHICAL SKETCH

ALBERT VON SZENT-GYÖRGYI [APPROXIMATE PRONUNCIATION, Saint Georgie] was born in Budapest, on September 16, 1893. Receiving his preliminary education in Budapest, he also studied medicine there, beginning in 1911. The professor of anatomy was Szent-Györgyi's uncle, in whose laboratory he began to do research as a first-year student; thereafter he published a series of histological studies. His education was interrupted by the First World War, in which he served on the Russian and Italian fronts. Having been wounded, he returned to the university and completed his course in 1917 He then went to Pozsony as assistant to the pharmacologist G. Mansfeld. Next he studied electrophysiology for a short time with A. von Tschermak in Prague. He also worked with L. Michaelis in Berlin. He spent two years in Hamburg in the study of physical chemistry, and two years in Leyden, Holland, as assistant in the Pharmacological Institute. After this he was assistant to H. J. Hamburger in the Physiological Institute of Groningen, Holland, where he discovered "hexuronic acid" in the adrenal cortex. At this time he was teaching biochemistry as *Privatdozent*. In 1927 he went to Cambridge as a Rockefeller Fellow. The fol-

lowing year he was in Rochester, Minnesota, at the Mayo Foundation, with E. C. Kendall. In 1929 he was back at Cambridge. Finally, in 1930, he returned to Hungary, as professor of medical chemistry at the University of Szeged.

World War II brought further changes, leading to the establishment, under Szent-Györgyi's direction, of the Institute for Muscle Research at Woods Hole, Massachusetts, financed by Armour and Company, the American Heart Association, the Association for the Aid of Crippled Children, and the Muscular Dystrophy Association. For approximately twelve years past, Szent-Györgyi has concentrated his energies on the study of the biochemistry of muscle.

A brilliant and original investigator, Szent-Györgyi is also an able writer, and the author of a number of books, some of which have appeared in English translation.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"I was led into the field of oxidations . . . by a false assumption. I was interested in the function of the adrenal cortex. If the function of this organ is suppressed, life, too, is suppressed (Addison's disease). But before life is extinguished, there appears in man a brown pigmentation, similar to that of certain fruits: apples, pears, bananas, etc., which, in withering, likewise assume a brown color. Through the investigations of the great Russian botanist, Palladin, it was known that this brown coloring of plants is connected with the damaged oxidation mechanism. Since I myself was convinced (and am still convinced) that in the basic functions, as represented, too, by oxidation, there exist no differences in principle between animal and plant, I undertook the study of the oxidation system of potatoes, browning of the plants depending on its damage. I did this in the hope of finding through these studies the key to the understanding of adrenal function.

"It was already known that those plants which turn brown as the result of damage—about half of all plants—contain a polyphenol, . . . besides this a ferment, the polyphenoloxidase, which,

* Translated from "Nobel-Vortrag von Albert Szent-Györgyi," *Les Prix Nobel en 1937*.

with the help of oxygen, oxidizes the polyphenol. There was a complicated interpretation of the working mechanism of this oxidase. It fell to me to show that it is simply a question of the oxidase, along with oxygen, oxidizing the polyphenol to quinone [compound which results when two opposite hydrogen atoms are replaced by oxygen]. In the intact plant the quinone is again reduced by the hydrogen mobilized from foodstuff. The phenol thus works as a hydrogen-transporter between oxygen and H-donator, and we are here confronted . . . with a system of successive hydrogen combustion. . . . In the damaged plant the reduction of the quinone cannot keep pace with the mounting oxidation of the phenol, and the quinones remain unreduced and form pigments.

"But the system gave me no information about adrenal function. So I turned to the plants which do not assume a brown color on withering, and which therefore must contain an oxidation system differently organized. As regards these plants, this much was known, that they contain a very active peroxidase. This peroxidase has the power to activate peroxide. In the presence of this ferment, peroxide is able to oxidize various aromatic substances to colored pigments. Without peroxidase this reaction does not take place. If, for example, benzidine is added to a peroxide in the presence of peroxidase, a deep blue color appears at once, produced by the oxidation of the benzidine. Without peroxidase this reaction, which also serves as a test for the ferment, does not occur.

"But when, in this reaction, I substituted for a purified peroxidase simply the juice squeezed from these plants, and added benzidine and peroxide, then the blue pigment appeared, but only after a slight delay of about a second. The analysis of this retardation showed that it was occasioned by the presence of a strong reducing substance, which again reduced the oxidized benzidine, until it was itself exhausted.

"It was a moment of great excitement, when, in my little cellar room in Groningen, I found that the adrenal cortex contains an analogous reducing substance in relatively large amount.

"My means and my chemical knowledge were both inadequate to investigate this substance more closely. But thanks to the invitation

of F. G. Hopkins and the help of the Rockefeller Foundation I was able ten years ago [i.e., in 1927] to transfer my laboratory to Cambridge, where for the first time I could devote myself to chemistry in earnest. Soon I was successful in isolating this fragile substance from adrenal glands and various plants and showing that it corresponded to the formula $C_6H_8O_6$ and was related to the carbohydrates. This latter circumstance induced me to turn to Prof. W. N. Haworth, who at once perceived the chemical interest of the substance and asked me for a larger amount for constitutional analysis. But unfortunately it turned out that adrenal glands were the only material suitable for large-scale preparation. All my efforts to find suitable vegetable material for a starting point remained ineffectual, and adrenal glands in large quantity were not available in England.

"Professor Krogh tried to help me by generously sending me adrenal glands by air from Copenhagen. But unfortunately the substance was spoiled in transit. The Mayo Foundation and Professor Kendall now came to my aid in a magnificent way and made it possible for me, regardless of expense, to work on the material from the great American slaughterhouses. The result of a year's work was 25 g. of a crystalline substance which received the name 'hexuronic acid.' This quantity of the substance I divided with Professor Haworth. He undertook to investigate the exact structural formula. I used the other half of my preparation to obtain a closer insight into the function of the substance. [It] could not take the place of the adrenal glands, but it overcame the pigmentation of Addison's disease to the point of disappearance.

"Unfortunately the amount of the substance proved insufficient for ascertaining the chemical constitution. The preparation could not be repeated for lack of means, and no cheaper material was found permitting extraction of the acid in larger amount.

"From the beginning I suspected the substance to be identical with vitamin C [discovered in 1907 by A. Holst and T. Frölich]. But my wandering life was unsuited for vitamin research, in which, also, I had no experience. In the year 1930, however, I gave up my nomad life, in that I settled down in my fatherland, at the University of Szeged. Also fortune soon sent me an excellent young American co-worker, J. L. Svirbely, who had experience

with vitamin research. . . . In the autumn of 1931 our first investigations were concluded and showed clearly that hexuronic acid has an antiscorbutic effect [preventing and counteracting scurvy] and that the antiscorbutic activity of the juices of plants corresponds with their hexuronic acid content. . . . [Szent-Györgyi here mentions related work of Tillman, King, and Waugh.]

"All at once the hexuronic acid that had been so long disregarded pressed into the foreground, and there was urgent need of larger amounts of this substance, in order on the one hand to continue the analysis of its constitution, and on the other to make sure of its vitamin nature. But we used the last remnant of our substance in our vitamin researches; it was impossible for us to undertake its preparation from adrenal glands; and, as I mentioned, every other material was inadequate for large-scale work.

"My city, Szeged, is the center of the Hungarian paprika industry. As this fruit is not transportable in good condition, I had had no earlier opportunity to test it. One evening the sight of this wholesome fruit inspired me with a last hope, and the same night investigation showed that this fruit offers an incredibly rich source of hexuronic acid, which Haworth and I rechristened ascorbic acid. Taking advantage of the last of the paprika season, which was nearing its end, it was possible, through the support given on a generous scale by the American Josiah Macy Jr. Foundation, to prepare more than half a kilogram, in the following year more than 3 kilograms, of crystalline ascorbic acid. I divided this substance among all the investigators who wished to work on it. I also had the privilege of furnishing both my fellow laureates, P. Karrer and W. N. Haworth, with plentiful material, and making possible their analysis of its constitution. I myself, together with Varga, prepared the mono-acetone derivative of ascorbic acid, forming splendid crystals, from which, after repeated recrystallizations, ascorbic acid, undiminished in activity, may again be split off. This was the first proof that ascorbic acid is identical with vitamin C and that the activity of the substance is not dependent on impurities. . . .

"To return to the oxidation processes, I now attempted further

analysis of the respiratory system of plants in which ascorbic acid and peroxidase play important roles. I had already found out, while in Rochester, that the peroxidase plants contain a ferment which reversibly oxidizes ascorbic acid, with two valences, in the presence of oxygen. Further analysis showed that here there was a respiratory system in which hydrogen is oxidized step by step. I should like to sum up briefly the result of this research carried out with St. Huszák.

"The ascorbic acid oxidase, with oxygen, reversibly oxidizes the acid to dehydroascorbic acid. The oxygen thereby combines with two labile H-atoms of the acid to form hydrogen peroxide. This peroxide reacts with peroxidase and oxidizes a second molecule of ascorbic acid. Both those molecules of dehydroascorbic acid, possibly by the mediation of SH-groups, now take up hydrogen again from foodstuffs.

"But the peroxidase does not oxidize the ascorbic acid directly. I succeeded in showing that between the two still another substance is inserted, which belongs to the large group of yellow, vegetable, water-soluble phenol-benzol-γ-pyran-dyestuffs (flavone, flavonole, flavanone). The peroxidase here oxidizes the phenol group to quinone, which then oxidizes the ascorbic acid directly by accepting both its H-atoms."

CONSEQUENCES IN THEORY AND PRACTICE*

Many scientists have contributed to present knowledge of the chemical events which are known in sum as "respiration." The contributions of Warburg and Keilin have been discussed in part above (see pp. 149-152). Cytochrome, however, is not a very powerful oxidizing agent and it was realized that what Szent-Györgyi calls the WK system (Warburg-Keilin) "could not oxidize such stable formations as the foodstuff molecules" without help. H. Wieland then showed that foodstuff is activated, and made

* The brief quotations in this section are from Albert von Szent-Györgyi, "Oxidation and Fermentation," in J. Needham and D. E. Green, eds., *Perspectives in Biochemistry* (Cambridge: The University Press, 1937), pp. 165-174.

ready for oxidation, by catalysts called dehydrogenases. These make the molecule give up its hydrogen more readily. The WK system then takes over.

This version of the story of respiration was further modified and supplemented by the work of Szent-Györgyi, who wrote:

"The theory is this: the C_4 dicarboxylic acids are a link in the respiratory chain between foodstuff and the WK system. Their function is to transfer the hydrogen of the foodstuff to cytochrome and to reduce by this hydrogen its trivalent iron again to the divalent form. Speaking more precisely, the cytochrome oxidizes off two hydrogen atoms from the succinic acid molecule. By the loss of two hydrogen atoms, the succinic acid is converted to fumaric acid. These two lost H atoms are replaced again by H coming from the foodstuff. The foodstuff, however, does not give its H immediately to fumaric acid. It gives its two H atoms to oxaloacetic acid, which is also a C_4 dicarboxylic acid. By taking up 2H, oxaloacetic turns into malic acid. Malic acid then gives its 2H to fumaric, and thus fumaric is converted to succinic acid. This can again be oxidized by cytochrome, while malic acid, after giving off its 2H, becomes oxaloacetic, which can take up H from the foodstuff again, and so the play goes on, H being transmitted all the time from the foodstuff *via* oxaloacetic-malic-fumaric-succinic to the WK system."

A catalytic system was demonstrated between the Wieland dehydrogenase system, on the one hand, and the WK system of ferrous enzymes, on the other.

Szent-Györgyi also described a respiratory system in which the hydrogen is oxidized by degrees through the agency of ascorbic acid. This discovery is the subject of the principal quotation given above. Although ascorbic acid, or rather the antiscorbutic substance, vitamin C, had been identified in the first decade of the century by Holst and Frölich, and had been shown to be the missing necessity in cases of scurvy and Barlow's disease (or infantile scurvy), it was through Szent-Györgyi and Svirbely that it could be proven identical with the highly reducing ascorbic acid obtained from adrenal glands and from certain vegetable materials. Thus the way was opened for clarifying the chemical composition of the

substance. Within two years of the Szent-Györgyi-Svirbely work, it became possible to produce a synthetic vitamin C. This result may be considered a by-product of basic research which had as its chief, although not its most directly useful, consequence added understanding of the mystery of respiration.

1938

CORNEILLE HEYMANS

(1892–)

"For his discovery of the role played by the sinus and aortic mechanisms in the regulation of respiration."

BIOGRAPHICAL SKETCH

CORNEILLE HEYMANS WAS BORN AT GAND, BELGIUM, ON MARCH 18, 1892. He is the son of Dr. J. F. Heymans, onetime professor of pharmacology and rector of the University of Gand, as well as founder of the J. F. Heymans Institute of Pharmacodynamics and Therapeutics at the same university. Heymans' father was his first and principal teacher and it was with him that the original experiments, leading to the award of the Nobel Prize, were begun. Corneille Heymans was educated at the local university, studied later in the laboratories of E. Gley in Paris, N. M. Arthus in Lausanne, H. H. Meyer in Vienna and E. H. Starling in London. In 1927-1928 he worked in the United States, chiefly in the laboratory of C. F. Wiggers at Western Reserve University, Cleveland. In 1922 he began to teach the course in pharmacodynamics at Gand, and in 1930 he succeeded his father there. He has traveled and lectured extensively and has been awarded many prizes and honorary degrees. He is probably the best known of Belgian workers in the biological sciences. Professor Heymans is now associated with the University of Ghent.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"It has long been known that . . . elevation of arterial pressure inhibits respiration; sudden and severe hypertension can even provoke [cessation of breathing]. It is equally well known that hypotension [low blood pressure] leads to [abnormally deep and rapid breathing]. These interactions . . . have generally been attributed to a direct action . . . on the activity of the respiratory center [the part of the brain which controls respiratory movements].

[Experiments to test this theory and to reveal the actual mechanism of these events were begun in 1924 by J. F. and C. Heymans, using crossed circulation in dogs. Two dogs, A and B, are anesthetized. The head of dog B is separated from its body, except for the vagus-aortic nerves, connecting with the respiratory center; these are left intact. Life is maintained in the body section by artificial respiration; circulation in the body continues. The isolated head is then linked to the body circulation of the other dog, A, by attaching from the latter the principal arteries for blood supply to the head, the two common carotids; these are anastomosed—i.e., joined end to end—with the corresponding parts of the nearly severed head of B. In the same way the external jugular veins of the two dogs are anastomosed. The severed head is thus completely isolated from its own body as regards circulation, but is connected by the aortic nerves. The effects which this head shows from whatever is done to its own body are mediated by the nerves; whatever is done to the body of the other dog can influence it only through the blood stream. Breathing movements due to the activity of the respiratory center may be seen in the head. A method is thus available for showing whether high and low pressure affect this center directly or by means of a nervous reflex.]

"We observed right away that arterial hypotension limited solely to the body circulation of the dog B brings about a stimulation of the activity of the respiratory center of the perfused head of B;

* Translated and paraphrased from Corneille Heymans, "Sur le rôle des presso —et des chimio—récepteurs vasculaires dans la régulation de la respiration," *Les Prix Nobel en 1940-44.*

augmentation of the arterial pressure in the trunk B, on the contrary, causes an inhibition of the activity of [this] respiratory center. . . . When one injects a hypertensive dose of adrenaline into the trunk B, one observes a total inhibition of the respiratory movements of the isolated and perfused head of B. . . ."

[This showed (1) that the effects once thought due to direct action of the blood pressure on the respiratory center are really brought about by a nervous reflex; and (2) that the path of this reflex lies through the aortic nerves. But what sense organ responds to the changes in pressure and starts the reflex? The carotid sinus (a slight enlargement of the common carotid artery at the point where it divides into the external and internal carotids) had previously been shown to play an important role in the regulation of heart rate and arterial blood pressure. Heymans was able to show that respiratory reflexes, as described in the quotation above, can also originate there. There exist in the wall of the sinus sensory organs which are called presso-receptors, because they are sensitive to pressure changes. Cross-circulation experiments of a rather different kind from those detailed above helped to show how they work. The sinus of one dog, B, was isolated from the general circulation and perfused with the blood of another animal, A, while the nerve supply of the sinus was left intact. With sinus B isolated, the arterial pressure of dog A was raised, whereupon that of dog B fell. Conversely, a reduction in blood pressure of dog A caused a rise in the blood pressure of dog B. Obviously the effect of a change in blood pressure upon these presso-receptors is to initiate reflexes which tend to reverse the pressure change. The effects of pressure on respiration are also mediated through reflexes beginning in presso-receptors.

[Close to the carotid sinus is a small structure looking like a gland, called the carotid body, or *glomus caroticum*. Heymans and his associates found this to be chemo-receptive, responding to changes in the chemical composition of the blood as the presso-receptors answer to changes in blood pressure. Variations in oxygen and carbon dioxide affect breathing by this means, although the increased respiration caused by an accumulation of carbon dioxide is partly the result of direct stimulation of the respiratory center. The aortic body (*glomus aorticum*) at the base of the aorta is also chemo-

receptive. It was found that certain drugs which stimulate respiration act directly on the respiratory center, but that others work only through the carotid and aortic bodies; still others have both a direct and a reflex action. Most of this information was worked out over a period of many years, with the help of many co-workers; it was accomplished in large part by means of ingenious isolation and cross-circulation experiments such as those described above.]

CONSEQUENCES IN THEORY AND PRACTICE

In an earlier section (see above, pp. 162-163) some account was given of the work of Sir Charles Sherrington on the integrative action of the nervous system. Sherrington revealed the role of the muscle spindle in initiating reflexes which have to do with posture. Other receptors were also studied by him as the initiators of special reflex action. It was the important contribution of Professor Heymans and his co-workers to show the part played by the sinus and aortic mechanisms in the regulation of respiration and blood pressure. The carotid sinus was demonstrated to be presso-receptive, the carotid and aortic bodies to be chemo-receptive. A later Nobel laureate, W. R. Hess (see below, pp. 260-264) has contributed to the proof that central control of blood pressure lies in groups of cells in the medulla and diencephalon; the peripheral mechanism is the set of reflexes described by Heymans. Hormonal factors, relating especially to the adrenal gland, are also involved. The heart, the kidneys, and the vascular system in general are primarily or secondarily concerned. Clinicians and laboratory scientists are therefore advancing from many directions in their assault on the still unsolved problems of blood-pressure abnormality. It is obvious that the Heymans contribution forms an essential part of the basic knowledge required.

There are, however, more immediate applications of this knowledge. The carotid sinus has nervous connections with the vagus. Among other effects which the latter nerve produces is inhibition of heart action. The sinus is also connected with the cervical sympathetic and the medulla. Now occasionally the sinus becomes hypersensitive and the consequence is a distinctive set of symptoms.

Patients have been observed who suffer from spontaneous attacks of dizziness, weakness, and unconsciousness, with or without convulsions, in whom mechanical stimulation over the division of one or the other carotid artery—i.e., pressure on the carotid sinus—will at once induce an attack. Three forms of this disturbance appear, corresponding to the threefold nervous communication mentioned above. In some cases cardiac inhibition, due to a vagal reflex, is marked; this can be abolished by the use of atropine. In others, vasodilatation, with a consequent fall in arterial blood pressure, is observed; this lowering of pressure and the symptoms which attend it can be prevented by ephedrine. The third, or cerebral variety, is associated with convulsions. Apparently it is best treated by denervation of the sinus—i.e., by cutting the nerve connections involved. Patients with spontaneous epileptic seizures induced by slight pressure on an irritable sinus have been relieved by this operation. Stripping of the nerve plexus from the carotid artery at the bifurcation (division into two parts) may affect a cure, or may give only temporary relief; division of the carotid sinus nerve is considered to give the best results.

It has long been known that pressure exerted on the carotid sinus area will often slow the heart and put a stop to attacks of the disturbance called "auricular paroxysmal tachycardia," a very rapid heartbeat which occurs in sudden paroxysms. This is a dangerous procedure which may stop the heart altogether. It should be performed only by a physician familiar with the proper technique and equipped with the drugs to meet an emergency. The effect was formerly attributed to pressure on the vagus; it is now known to be due to carotid sinus pressure.

1939

GERHARD DOMAGK

(1895–)

"For his discovery of the antibacterial effects of prontosil."

BIOGRAPHICAL SKETCH

GERHARD DOMAGK WAS BORN ON OCTOBER 30, 1895, IN LAGOW, Brunswick, Germany. He had just entered the University of Kiel when the First World War broke out, and in October 1914, he volunteered for the army, in which he served four years. At first he was in a grenadier regiment, but after being wounded in 1915 he was transferred to the medical corps for the remainder of the war. Returning to Kiel, he was graduated in medicine in 1921. In 1924 Domagk became *Privatdozent* at the University of Griefswald. The following year he received an appointment in the Pathological Institute at Münster, where in 1928 he became Extraordinary Professor of General Pathology and Pathological Anatomy. He then accepted a position with the I. G. Farbenindustrie and became director of the Laboratory for Experimental Pathology and Bacteriology at Wuppertal-Elberfeld. In a preconceived and systematic program, combining a search for new dyes with a search for new drugs, the I. G. Farbenindustrie postulated the preparation of a substance later to be called "prontosil" as early as 1920, but apparently nothing further was done about it until 1932. The synthesis of azo compounds had been entrusted to Drs. Fritz Mietzsch and Joseph Klarer, and it was one of Domagk's

duties to test the chemotherapeutic effects of the substances produced. It was in this way that the extraordinary powers of the sulfonamide drugs were first revealed in the trials of prontosil.

When notified in October 1939 that he had won the Nobel Prize, Domagk sent a letter of thanks to the rector of the Caroline Institute, but toward the end of November a second letter reached Stockholm in which Domagk declined the prize in accordance with Nazi law. In the interval he had been arrested by the Gestapo. The second letter was prepared by the Ministry of Education and Domagk signed it under duress. The year of grace permitted by the Nobel regulations had long expired, and the prize money had reverted to Nobel Foundation funds, before Domagk was able to speak freely. In 1947 he visited Stockholm, delivered his Nobel lecture, and received the gold medal and diploma; but it was then too late for the award of the prize money.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"Up to the present time [1935] it has been the general opinion that only protozoal infections were susceptible to chemotherapy. In the sphere of the protozoal infections we possess remedies which are operative against the cause—e.g., against trypanosome infections [sleeping sickness], suramin; against kala-azar, neostibosan; against malaria, plasmochin and atabrin; against spirochete infections, especially syphilis, salvarsan and its modifications.

"Chemotherapeutic agents operative to any extent against infections with cocci have been unknown up to the present. . . . [Cocci are bacteria of spherical shape, including the gonococci, which produce gonorrhea, the meningococci, of a kind of meningitis, the pneumococci, of pneumonia, and the staphylococci and streptococci, which cause a wide variety of infections. Domagk next reviews earlier attempts to find effective drugs for such diseases. These efforts had centered chiefly on a number of compounds of the

* Translated from Gerhard Domagk, "Ein Beitrag zur Chemotherapie der bakteriellen Infektionen," *Deutsche medizinische Wochenschrift,* Vol. 61 (1935), pp. 250-253.

metals, particularly gold. All had proved failures for one reason or another, many of the substances being too toxic for use.]

"Because of the disadvantages described, we turned our particular attention toward chemical compounds of other types, on a purely organic, metal-free basis, which in experiments with mice gave perceptible indication of being effective against streptococcal sepsis. Among azo and acridine compounds * we had become acquainted with a series of substances which showed a relatively good effect against streptococci in disinfection research *in vitro* [i.e., in the test tube]. But this effect, in part even an excellent one *in vitro,* was almost always completely lost on the injection of these substances into the animal body. . . . [Here follows an account of this research. One of the substances tested was an azo compound called chrysoidine. It was the addition to this compound (itself ineffective against streptococci) of a sulfonamide group (SO_2NH_2) which produced prontosil.]

"In the course of our investigations, however, we later hit upon a group of very innocuous azo compounds, which, to be sure, showed no substantial disinfective value against streptococci *in vitro,* but now in experiments with mice gave a clear and perceptible effect. To this group belongs *prontosil,* synthesized in 1932 by Mietzsch and Klarer. With prontosil we were able to establish the best chemotherapeutic effects observed at any time in *streptococcal infections in animal research.* It is the hydrochloride of 4′-sulfonamide-2, 4-diaminoazobenzene. . . .

"The harmlessness of the preparation is shown by the toxicological data. . . . [Large amounts, at least 500 mg. per kilo of body weight, were tolerated by mice and rabbits; larger doses were vomited. Similar data are given regarding subcutaneous and intravenous injections. So far as these tests showed, the drug appeared to be nontoxic.]

"Prontosil is . . . an extraordinarily inert compound pharmacologically . . . [i.e., it appeared to have little or no effect on the various functions of the healthy animal body].

"*Chemotherapeutically, prontosil shows an elective effect in*

* Azo compound: a substance derived from a hydrocarbon by replacement of part of the hydrogen by nitrogen. Acridine compound: a substance obtained from coal tar; usually a yellow or brown dye.

streptococcal sepsis in the mouse [i.e., it appears to act specifically on streptococci, as if by choice]. . . . All the animals alike were infected with 0.3 c.c. of a 24-hour streptococcal bouillon culture. Of the untreated control animals, none lived after 48 hours, so that no [further] comparisons could be made. . . . When the organs of untreated control animals are investigated, typical signs of severe general infection are found in the liver, spleen, kidneys, heart, and numerous other organs. . . .

"In the animals successfully treated with prontosil all these pathological tissue changes are lacking, when treatment is started promptly with adequate doses. In other cases one hinders the further extension of tissue damage already existing. . . .

"It is worth notice . . . that in research *in vitro,* [prontosil] shows no particular effect against either streptococci or staphylococci. *It works like a true chemotherapeutic agent only in the living organism. . . .*"

CONSEQUENCES IN THEORY AND PRACTICE

Accompanying this first report were three microphotographs of the blood of infected mice. The first, picturing blood from an untreated animal, showed innumerable cocci; the second, taken 24 hours after subcutaneous injection of prontosil, revealed active phagocytosis (the eating up of bacteria by white cells); and the third, taken 48 hours after the injection, displayed a later stage of the same healing process, with no free cocci whatever! These pictures demonstrated how prontosil "works like a true chemotherapeutic agent in the living organism," although not in the test tube.

The original protocol on the value of prontosil in the control of experimental streptococcal infections in mice is dated December 20, 1932. Experimental work on animals was continued. Meanwhile Domagk's young daughter developed a serious streptococcal infection following a needle prick. Ordinary treatment failed to check the spread of the infection. Domagk treated her with large doses of prontosil. She recovered.

Long before Domagk's original paper was published, reports appeared in the German medical literature. The drug was dis-

tributed for clinical trial early in 1933, and on May 17 Foerster read the first report before the Düsseldorf Dermatalogical Society.

Since chrysoidine was powerless to check streptococci, and since the only difference between chrysoidine and prontosil consisted in the sulfonamide group attached to the latter, it appeared that this group must be responsible for the chemotherapeutic effect. Assuming that prontosil is split up in the organism, releasing sulfanilamide (para-amino-benzene-sulfonamide), Mr. and Mrs. J. Trefouël, J. Nitti, and D. Bovet introduced the latter, which was given its clinical trials by P. H. Long and L. Colebrook. In the next few years a very large number of "sulfa drugs" appeared, with special advantages claimed for each, in reduced toxicity or in the type of organisms affected. Sulfapyridine, for example, introduced in 1937 by L. Whitby, was particularly effective in cases of pneumonia.

"In 1935," writes Professor Spink,* "there was no specific therapy for hemolytic streptococcic infections. Every clinician feared streptococcic bacteremia [the presence of living bacteria in the circulating blood], with its mortality rate approximating 75 per cent. Only a rare patient recovered from streptococcic meningitis. In midwinter, hospital beds were occupied with cases of erysipelas and mastoiditis, all caused by hemolytic streptococci. Sulfanilamide took the sting out of these debilitating and fatal streptococcic diseases. [The operation for mastoiditis has almost become a thing of the past since the advent of sulfatherapy.] The mortality rate of untreated pneumococcic meningitis was 100 per cent, but patients recovered following the use of sulfapyridine. Chronic cases of gonorrhea clogged up the out-patient services of hospitals, and its devastating complication, gonococcal arthritis, was the frequent cause of prolonged hospitalization. The sulfonamides soon offered a more hopeful outlook for these individuals. The sulfonamides proved to be highly effective in meningococcic bacteremia and meningitis. A new chapter, and a dramatic one, had been written in the therapy of human disease."

There were certain drawbacks. The "sulfa drugs" often provoked serious side effects, especially kidney failure. Many patients showed hypersensitivity to the drugs after one or more courses of

* Wesley W. Spink, "Present Status of Sulfonamide Therapy," *The Merck Report,* Apr. 1951, pp. 17-19.

treatment, in the form of skin eruptions and fever. Secondly, strains of bacteria, notably gonococci, soon appeared which were resistant to the sulfonamides. Thirdly, the sulfonamides had a relatively narrow range of activity; many of the causative agents of infectious disease were not susceptible to their action. The first of these difficulties, the toxicity of the "sulfas," was in part overcome by the development of newer and safer variants, such as sulfadiazine and sulfamerazine.

Although antibiotics, such as penicillin, streptomycin, and aureomycin, now occupy a more prominent place in the treatment of infectious diseases, because they are generally more efficient and less toxic and have a wider range, the sulfonamides, especially sulfadiazine and sulfamerazine, continue to be widely used. This is particularly true in parts of the world where the newer antibiotics are as yet unavailable. Ease of administration and low cost contribute to the enduring popularity of the sulfonamides. Moreover, they are undoubtedly effective, and in meningococcic infections they probably work as well as any of the antibiotics. There are likewise a number of diseases in which they have been given simultaneously with an antibiotic, although it is considered difficult to assess the merit of this practice. These drugs not only find a wide application in the treatment of disease but have also been used successfully in the prevention of such diseases as epidemic meningococcic meningitis.

The sulfonamides revolutionized the management of a considerable number of important infectious diseases. The knowledge acquired through the study of these drugs in laboratory and clinic has been put to further use in more recent work on the antibiotics.

REFERENCES

LONG, PERRIN H. "Award of the Nobel Prize in Physiology and Medicine to Dr. Gerhard Domagk," *Scientific Monthly,* Vol. 50 (1940), pp. 83-84.

1940–1942

No Award

1943

HENRIK DAM

(1895–)

"For his discovery of vitamin K."

EDWARD A. DOISY

(1893–)

"For his discovery of the chemical nature of vitamin K."

BIOGRAPHICAL SKETCHES

DAM

(Carl Peter) Henrik Dam was born in Copenhagen, on February 21, 1895. He was graduated in chemistry from the Polytechnic Institute there in 1920, and was awarded the degree Sc. Dr. in biochemistry by the University of Copenhagen in 1934. Meanwhile he had studied microchemistry with F. Pregl in Graz, Austria, in 1925, and metabolism of sterols in Rudolph Schoenheimer's laboratory in Freiburg, Germany, as a Rockefeller Fellow, in 1932-1933. He also worked with P. Karrer, in Zürich, in 1935 and later. Dam was appointed instructor in chemistry at the School of Agriculture and Veterinary Medicine in Copenhagen in 1920; instructor in biochemistry at the Physiological Laboratory, University of

Copenhagen, in 1923; and assistant professor at the Institute of Biochemistry of the same institution in 1928. He served as associate professor at the University from 1929 to 1941, and lectured in the United States and Canada in 1940-1941. This tour was planned before Denmark was occupied by German troops (April 1940). Dr. Dam carried out research in Woods Hole Marine Biological Laboratories in 1941; at the University of Rochester, New York, 1942-1945, as a senior research associate; and at the Rockefeller Institute for Medical Research, 1945, as an associate member. Despite his absence from Denmark he had meanwhile been appointed professor of biochemistry at the Polytechnic Institute, Copenhagen. His many papers, some published jointly and others alone, deal mainly with the biochemistry of sterols, fats, and the vitamins K and E.

DOISY

EDWARD A. DOISY WAS BORN IN HUME, ILLINOIS, ON NOVEMBER 13, 1893. From the University of Illinois he received his A.B. in 1914 and his M.S. in 1916; he was awarded a Harvard Ph.D. in 1920 and has since been granted honorary degrees by several universities, in addition to a large number of medals and prizes. He was assistant in biochemistry, Harvard Medical School, 1915-1917. From 1917 to 1919 he served in the U. S. Army. He then became, successively, instructor, associate, and associate professor in biochemistry, Washington University School of Medicine, 1919-1923; was appointed professor of biochemistry at the St. Louis University School of Medicine, in 1923; and was appointed director of the Department of Biochemistry, St. Mary's Hospital, in 1924. Dr. Doisy has been active in professional associations and has served on the League of Nations Committee on the Standardization of the Sex Hormones. His publications have dealt with various aspects of metabolism; insulin; blood buffers; isolation and chemical characterization of theilin, theelol, and dihydrotheelin; ovarian hormones and estrogenic substances; gonadotropic and thyrotropic principles, as well as various other aspects of endocrinology; isolation of vitamins K_1 and K_2; determination of constitution and synthesis of vitamin K_1; and antibiotic compounds.

DESCRIPTION OF THE PRIZE-WINNING WORK

DAM *

"The discovery of vitamin K arose from some studies on the cholesterol metabolism of chicks carried out during the years 1928-30 in the biochemical institute of the University of Copenhagen. [Cholesterol, which chemists classify as an alcohol, is found in bile, brain, blood cells, egg yolk, etc., and in varying amounts in animal tissues. It belongs among the sterols, solid alcohols closely related to steroids; the latter include a number of important hormones. Another sterol is ergosterol, which, when irradiated, forms vitamin D_2.] It was then already known that rats, mice and dogs can synthesize cholesterol but some experiments had been published which seemed to show that chicks could not thrive on a diet from which the sterols had been removed by extraction. When these experiments were published . . . in 1914, the role of fat-soluble vitamins was not very well recognized, and I therefore found it interesting to repeat them using artificial, practically sterolfree diets to which vitamins A and D were added in the form of sterol-free concentrates made from cod-liver oil, or of small amounts of cod-liver oil of known cholesterol content. Chicks were reared on such diets for different lengths of time from the day of hatching and the amount of cholesterol in their excretions and their body was determined and compared with the cholesterol content in newly hatched chicks from the same litter. It was thereby found that a considerable part of the cholesterol which the newly hatched chick has taken over from the egg yolk disappears during the first 2 or 3 weeks, whereafter cholesterol is formed in increasing amount as the body weight increases. Chicks therefore are able to synthesize cholesterol, just as well as are rats, mice and dogs, and they are also able to break it down.

"More interesting than this finding was, however, an unexpected symptom which showed up in some of the chicks which were kept

* From Henrik Dam, "The Discovery of Vitamin K, Its Biological Functions and Therapeutical Applications," *Les Prix Nobel en 1946*, pp. 205-220.

on the diet for more than 2 or 3 weeks. They got hemorrhages under the skin, in muscles or other organs, and blood occasionally taken out for examination showed delayed coagulation.

"The lack or low content of cholesterol in the diet could not be the cause of the hemorrhages, since the experiments showed that chicks can synthesize cholesterol. Further, the hemorrhages also appeared in chicks which received a daily supplement of cholesterol.

"The low amount of fat in the diet would, apparently, also be ruled out as a cause of the symptom since it was found that linseed oil and triolein could not prevent its appearance. . . . Other authors had already reported that chicks do not require vitamin C, and daily ingestion of lemon juice . . . also proved to be ineffective. . . . [When] pure vitamin C became available . . . I could easily show that . . . injections of ascorbic acid failed to prevent the disease. . . .

"The salt mixture could be varied considerably without influence on the disease, and wheat germ oil was without protective effect, whereas a high content of cereals and seeds in the diet prevented the symptom. It was therefore safe to announce that the new experimental disease was due to the lack of a hitherto unrecognized factor in the diet. This was done in 1934.

"Then a number of animal organs and plant material were examined for their ability to protect against the disease and it was found that green leaves and hog liver were among the most potent sources. It was also found that the factor was fat-soluble, and in 1935 it was characterized as a new fat-soluble vitamin and given the designation vitamin K. The letter K was the first one in the alphabet which had not, with more or less justification, been used to designate other vitamins, and it also happened to be the first letter in the word "koagulation" according to the Scandinavian and German spelling. . . .

"The hemorrhages in vitamin K deficiency develop in this way, that minute vascular lesions caused by minor mechanical trauma are not closed by rapid clotting, as is the case in normal animals. This causes oozing of blood from the impaired region.

"According to the accepted theory the process of blood coagulation may be separated into two stages.

"(1) Prothrombin + Thromboplastin + Ca → Thrombin

"(2) Fibrinogen + Thrombin → Fibrin . . .

"It is easy to show that it is *prothrombin* and no other component which is lacking when vitamin K has been withdrawn from the diet. . . .

"Vitamin K from green plants is called K_1. Chemically it differs slightly from vitamin K formed by putrefaction, which is called K_2 [discovered by Almquist and Stokstad, University of California]. . . . The preparation of pure vitamin K from green leaves was first reported by Dam, Karrer and co-workers, 1939. . . . The elucidation of its composition was accomplished by Doisy and co-workers, and by Fieser and co-workers. Doisy and co-workers also prepared pure vitamin K_2 from putrefied fishmeal [and established its chemical difference from K_1.] . . .

"Andrus, Lord and Moore, 1939, excised the liver in normal dogs and studied the prothrombin level with and without ingestion of vitamin K and bile salts. They found that the blood prothrombin decreased in both instances, indicating that the liver is necessary for the action of vitamin K. Several other observations also show that the liver is the organ concerned with prothrombin formation."

DOISY

[Doisy and his co-workers in the St. Louis University School of Medicine isolated vitamin K_1 from alfalfa (*Journal of Biological Chemistry,* Vol. 130 [1939], pp. 219-234). Partition among various solvents and crystallization from solvents proved unsuccessful, and the large amount of impurities in crude preparations made low-pressure distillations difficult and impractical; at the same time the inactivity of the vitamin toward many chemical reagents and its instability toward others eliminated chemical reactions as a means of isolation. After extraction, therefore, repeated adsorptions were used to obtain the vitamin. In a similar manner vitamin K_2 was isolated from purified fish meal (*Journal of Biological Chemistry,* Vol. 131 [1939], pp. 327-344). The constitution of vitamin K_1 was worked out and its synthesis accomplished by the same group in St. Louis. Almost simultaneously three other groups, Almquist and Klose, Fieser *et al.,* and Karrer *et al.,* reached the same goal. Doisy

and his co-workers summarized their findings on vitamin K_1 as follows.*]

"Vitamin K_1 was found to be a 2, 3-disubstituted α-naphthoquinone having an unsaturated side chain. By oxidation of the vitamin with chromic acid phthalic acid was formed, which demonstrated that the benzenoid ring of the vitamin carries no side chain. A second acid isolated from the oxidation products was identified as 2-methyl-1, 4-naphthoquinone-3-acetic acid, which showed that the quinone nucleus has a methyl group at the 2 position and that the side chain in the 3 position has an ethylenic linkage between the 2nd and 3rd carbon atoms from the quinone ring. These conclusions were confirmed by the products obtained by degradation of the diacetyl dihydro derivative of the vitamin. Oxidation with chromic acid formed the diacetyl dihydro derivative of the quinone acid, and a ketone $C_{18}H_{36}O$. This ketone was also formed by ozonolysis of the diacetyl dihydro vitamin and was identified as 2, 6, 10-trimethylpentadecanone-14 which proved the arrangement of the remaining carbon atoms of the unsaturated side chain.

"The constitution of vitamin K_1 as 2-methyl-3-phytyl-1, 4-naphthoquinone was confirmed by synthesis. Phytyl bromide was condensed with the monosodium salt of 2-methyl-1, 4-naphthohydroquinone, the vitamin being isolated in the pure condition as the diacetyl dihydro derivative. The synthetic compound was degraded by the same procedure as that used for the natural vitamin derivative and shown to give the same degradation products."

CONSEQUENCES IN THEORY AND PRACTICE

The first hemorrhagic disease in man to be recognized as due to a deficiency of vitamin K was the bleeding which accompanies obstructive jaundice. Bile is important for the proper absorption of vitamin K from the intestine,† and when the bile duct is blocked by gallstones or tumor a bleeding tendency is one of the consequences. This formerly constituted a real danger in operations for

* *Journal of Biological Chemistry*, Vol. 131 (1939), p. 369.

† Vitamin K is insoluble in water and its absorption and transportation depend on the presence of desoxycholic acid.

the relief of obstruction. But in 1938 three different groups, Dam and a colleague among them, independently reported that the bleeding tendency is due to vitamin K deficiency. As Dam observes: "Since then, the practical utilization of vitamin K in surgery has been tried by a large number of surgeons and its value has been fully established. It is possible by suitable vitamin K treatment, to eliminate completely the risk of bleeding in such patients, provided of course, that the case is not complicated by severe damage of the liver so that vitamin K cannot act."

Furthermore, "a bleeding tendency due to reduced absorption of vitamin K from the intestine can . . . be observed in certain intestinal diseases, where profuse diarrhoea occurs and the intestinal mucosa is damaged. This has been found in cases of sprue, for instance, where the absorption of fat is greatly diminished, or in ulcerative colitis." Here again vitamin K is useful in treatment.

Vitamin K deficiency is also seen in the newborn infant. The low prothrombin level which occurs in the first week after birth may be raised by treatment with vitamin K. Where bleeding actually is noted this is essential; the prothrombin may be raised to approximately normal values in 24 hours. Bleeding almost certainly occurs, however, in many cases where it is not easily detectable, and the administration of vitamin K to parturient women before delivery has reduced the death rate among the newborn.

Vitamin K is a napthoquinone compound having a phytyl side chain; vitamin K_2 contains a naphthoquinone ring with a much longer and more unsaturated side chain. It is now known that a number of synthetic 2-methyl-1, 4-naphthoquinone compounds possess vitamin K activity, as do several water-soluble substances—e.g., 4-amino-2-methyl-1-naphthol hydrochloride.

1944

JOSEPH ERLANGER

(1874–)

HERBERT SPENCER GASSER

(1888–)

"For their discoveries regarding the highly differentiated functions of single nerve fibers."

BIOGRAPHICAL SKETCHES

ERLANGER

JOSEPH ERLANGER WAS BORN IN SAN FRANCISCO, ON JANUARY 5, 1874. He received the B.S. degree in chemistry from the University of California, and in 1899 the M.D. degree from the Johns Hopkins University. After serving for one year as interne in the Johns Hopkins Hospital he was appointed assistant in the Department of Physiology at the Johns Hopkins University Medical School under Dr. William H. Howell, then served successively as instructor, associate, and associate professor at that school. He then went to the University of Wisconsin as the first professor of physiology in the newly organized medical school there, where one of his pupils was Herbert S. Gasser. In 1910 he was appointed professor of physiology and head of the department in the reorganized medical school of Washington University, St. Louis. Gasser later rejoined him there and their work together was carried out in St. Louis. Dr. Erlanger became emeritus professor in 1944.

GASSER

HERBERT SPENCER GASSER WAS BORN IN PLATTEVILLE, A SMALL town in Wisconsin, on July 5, 1888. He was educated in the State Normal School there, and afterward in the State University. He records that "the preclinical years of the Medical School had just started and classes were so small that the faculty became not only teachers but friends." His first course in physiology was with Dr. Joseph Erlanger. The clinical years were completed at the Johns Hopkins Medical School in 1915. Next there followed a year in pharmacology at Wisconsin. He then rejoined Dr. Erlanger, who had meantime become professor of physiology at Washington University, St. Louis. In 1921 Dr. Gasser was made professor of pharmacology at Washington University. Two years later, at the instigation of Dr. Abraham Flexner, of the Rockefeller Foundation, Gasser was granted leave of absence for two years of study in Europe. After his return to the United States he remained at Washington University until 1931, when he left to become professor of physiology at the Cornell Medical School in New York City. In 1935 he was appointed director of the Rockefeller Institute for Medical Research.

DESCRIPTION OF THE PRIZE-WINNING WORK*

[It has been mentioned earlier (p. 160) that Gasser was one of the pioneers in the use of amplifiers in physiology. Whereas Adrian combined the amplifier with the capillary electrometer, Erlanger and Gasser combined it with the cathode-ray oscillograph, invented by F. Braun in 1897. (Braun received the Nobel Prize in Physics in 1909.) A stream of electrons is given off from the negative electrode (cathode) in a Crookes tube; in Braun's cathode-ray tube, otherwise the same, these rays are narrowed into a threadlike beam which is subjected to the influence of external electric currents. It

* Joseph Erlanger and Herbert S. Gasser, "The Compound Nature of the Action Current of Nerve as Disclosed by the Cathode Ray Oscillograph," *American Journal of Physiology,* Vol. 70 (1924), p. 624.

is then focused on a screen so that the oscillations caused by these outside potentials may be recorded. Erlanger and Gasser, in their first publication on this subject (1922), pictured and discussed the changes which the action current in nerve was sometimes found to undergo in its course. The record of this potential close to its source was a triangular wave with a rounded peak. Later it exhibited one or more humps on the descending limb. In a subsequent paper, quoted below, Erlanger and Gasser presented a partial explanation, afterward greatly elaborated, of the nature of these waves.]

"Light upon the fundamental nature of the waves which the cathode ray oscillograph has disclosed in the amplified action current was first obtained in experiments designed to ascertain whether altering the distance the action current is propagated along the nerve affects the relative positions of the waves. In these experiments the nerve is mounted in a moist chamber and kept at a constant temperature. . . . The stimulus is delivered through pairs of platinum electrodes of which several, 3 to 5, range along the nerve at measured distances from the proximal lead into the oscillograph. By means of . . . switches situated outside the moist chamber any desired pair of electrodes can be connected with the inductorium. . . . At the longer conducting distances [in the sciatic nerve of the bullfrog] the action current is composed of three waves, though the third in some instances is not very distinct. These waves may be designated alpha, beta and gamma from before backwards in the action current. . . . [Figures derived from an analysis of the waves] give the very definite impression that the shift in the relative positions of the waves that occurs with the change in the conducting distance, is due to differences in the rates with which the waves move along the nerve. . . .

"Every observation we have made indicates that each wave represents a discrete action current started by the one stimulus, but travelling in different groups of nerve fibers. Thus each wave, or better, perhaps, each group of fibers . . . has its own conduction rate. . . . The positions of the starts of the slower waves can not be ascertained with even a reasonable degree of accuracy. We, therefore, have taken the times elapsing between the crests of alpha and of beta . . . [etc.] as the lags between these waves. This

is justifiable because . . . these crests at fairly long conducting distances are not materially displaced by summation and because . . . the times to maximum of all the waves are essentially alike. . . . [Each wave, or each group of fibers, was concluded to have not only its own conduction rate but also] its own threshold of stimulation and its own refractory period. . . . ["Threshold of stimulation" refers to the strength of stimulation required to produce an effect. It was found that different stimulation strengths produced different patterns; in one case, for instance, a completely developed action current appeared, while in another there was only an alpha wave, etc. Analysis of the patterns produced by graded action currents therefore contributed to the view that not one but several discrete action currents were being recorded. The "refractory period" is the time that must elapse after delivering an effective stimulus before another response to a second stimulus is obtainable from the same point. By applying stimulation at different intervals and studying the resultant wave patterns, the varying refractory periods of alpha, beta, etc. were revealed.]

"Of even greater . . . interest, however, is the experimental dissociation of the action current into the several processes of which it is composed, that is made possible through the fact that the alpha and beta (and gamma) processes have different stimulation thresholds as well as different refractory phases. If by properly selecting the strength of stimulation, an action current consisting solely of a maximal alpha process is started in a nerve, and if while the nerve still is absolutely refractory to this alpha process it is stimulated a second time through the same electrodes with a strong shock, one that ordinarily would elicit all of the processes, the action current started by the second stimulus will be without an alpha process."

CONSEQUENCES IN THEORY AND PRACTICE

The work described above, developed in further detail, led to the establishment of a theory of differentiated function. The evidence presented in the last paragraph above was a strong indication that the alpha process resulted from a separate action current in a separate division of the nerve—i.e., in a particular group of fibers.

It was concluded as the result of later studies that the thickest, or A-fibers, have the highest conduction velocity; that those of intermediate size, the B-fibers, have a lower rate; and that the lowest rate of all is in the slenderest, the C-fibers. Individual fibers, running in the same nerve, were thought to serve different purposes; for example, the lowest rate of conduction was found in fibers carrying pain impulses. A part of the work, pursued chiefly by Gasser, was concerned with the changes of excitability that occur at a nerve cross section at which impulses arrive. The arrival of one or several impulses to such a region was found to be followed by slow changes of excitability associated with slow changes of electrical potential. These changes of excitability enhance or depress succeeding impulses. It was shown that such "after-potentials" behaved in a different manner in the three main types of fiber, confirming the concept of a high degree of differentiation of the nerve fibers for their various tasks. Gasser, however, in his Nobel lecture, delivered in December 1945, observed in regard to pain, touch, temperature, etc., that "attempts to identify modalities with definite segments of the velocity spectrum have not been very successful. We are left faced with evidence for conduction of single modalities at very different velocities, and inclusion of a number of modalities within a narrow band of fibers. What then is the significance of the wide velocity range? Is it timing? Reflection on this, the most obvious interpretation of all, causes it to loom progressively larger. One need but consider the speed with which posture is controlled in preparation for the reception of oncoming detailed information and adjustment of fine movement; or again the mode of transmission of excitation through any central ganglion. . . . Differential axonal velocities must play their part in the mechanism. Be this their only contribution to integration, it is still a large one."

Adrian and others had studied responses from a single nerve fiber after teasing a nerve until only one fiber remained intact. In the work of Erlanger and Gasser, and especially in the later work of Erlanger and Blair, an intact nerve was selected, such as the frog's phalangeal nerve, likely to contain a fiber of particular excitability so that a threshold stimulus would excite that fiber only. Thus the investigation of a more nearly physiological condition became possible with the refined apparatus used. These studies have

been pursued, as Erlanger stated in his Nobel lecture, delivered in 1947, "because it is felt . . . that in the investigation of this comparatively simple structure, the nerve fiber, lies the hope of finding clues to an understanding of the much more complicated mechanisms that determine the activities of peripheral and central nervous mechanisms."

1945

ALEXANDER FLEMING
(1881–)

ERNST BORIS CHAIN
(1906–)

HOWARD WALTER FLOREY
(1898–)

"For the discovery of penicillin and its therapeutic effect for the cure of different infectious maladies."

BIOGRAPHICAL SKETCHES

FLEMING

ALEXANDER FLEMING WAS BORN ON AUGUST 6, 1881, AT LOCHfield, in Ayrshire, Scotland. He obtained his general education at Loudoun Moor School, Darvel School, Kilmarnock Academy, and the London Polytechnic. Before beginning the study of medicine he worked for four years in a shipping office. He then began his medical education at St. Mary's Hospital Medical School, University of London. He qualified in 1906 and immediately commenced work in Sir Almroth Wright's laboratory in St. Mary's Hospital. He has worked at St. Mary's ever since, latterly in the Wright-Fleming Institute. He has been professor of bacteriology since

1929. Fleming has published many articles on immunology, general bacteriology, and chemotherapy. His most important papers have dealt with antiseptics, lysozyme (an antibacterial substance discovered in 1922), and penicillin. He has consistently made use of variations of Wright's technique of the teat and the capillary tube (see lecture below) in his studies of human blood. He has been the recipient of many honorary degrees and prizes and was made Knight Bachelor in 1944.

CHAIN

SON OF DR. MICHAEL CHAIN, A CHEMIST AND INDUSTRIALIST, Ernst Boris Chain was born on June 19, 1906, in Berlin. Educated at the *Luisengymnasium,* Berlin, he early became interested in chemistry and in 1930 was graduated as a chemist from the Friedrich-Wilhelm University. After several years of research work on enzymes at the Pathological Institute of the Charité Hospital in Berlin he emigrated to England; this was early in 1933, soon after the access to power of the Nazi regime in Germany. He spent two years in the Cambridge School of Biochemistry, the domain of Sir Frederick Gowland Hopkins, whom he greatly admired. In 1935 he was invited to Oxford by H. W. Florey to develop a chemical section in the Department of Pathology. In 1938 he initiated jointly with Florey a systematic investigation of antibacterial substances produced by microorganisms. This work led to the reinvestigation of penicillin, described nine years earlier by Fleming, and to the discovery of its chemotherapeutic action.

FLOREY

HOWARD WALTER FLOREY WAS BORN ON SEPTEMBER 24, 1898, at Adelaide, South Australia. After attending local schools and Adelaide University (1916-1921), he went to Magdalen College, Oxford, in 1922, as a Rhodes Scholar. He later studied at Cambridge and at the London Hospital, and was Rockefeller Travelling Fellow in the United States, 1925-1926. He became Huddersfield Lecturer in Special Pathology, Cambridge, 1927; professor of pathology, University of Sheffield, 1931; and professor of pathol-

ogy, Oxford, 1935. In 1935 he invited Chain to join him at Oxford. In 1941 he was elected Fellow of the Royal Society and in 1944 was made Knight Bachelor. He has received many prizes and honorary degrees. In 1944 he was Nuffield Visiting Professor to Australia and New Zealand. The subjects of his research have included inflammation, capillary blood circulation, and the functions of the lymphocyte. His work on lysozyme led to a general study of antibiotics, in association with Chain; this in turn led to the discovery of the chemotherapeutic value of penicillin.

DESCRIPTION OF THE PRIZE-WINNING WORK

FLEMING *

"The origin of penicillin was the contamination of a culture plate of staphylococci by a mould. [Staphylococci are among the common pus-forming bacteria. A culture plate is a flat, shallow glass dish containing a gelatinous solid, commonly agar, on the surface of which the bacteria are grown.] It was noticed that for some distance around the mould colony the staphylococcal colonies had become translucent and evidently lysis [solvent action] was going on. This was an extraordinary appearance and seemed to demand investigation so the mould was isolated in pure culture and some of its properties were determined.

"The mould was found to belong to the genus penicillium and it was eventually identified as penicillium notatum. . . .

"Having got the mould in pure culture I planted it on another culture plate and after it had grown at room temperature for 4 or 5 days I streaked different microbes radially across the plate. Some of them grew right up to the mould—others were inhibited for a distance of several centimetres. This showed that the mould produced an antibacterial substance which affected some microbes and not others. . . .

"Then the mould was grown on fluid medium to see whether the antiseptic substance occurred in the fluid. After some days the

* From Alexander Fleming, "Nobel Lecture on Penicillin," *Les Prix Nobel en 1945*, pp. 155-164.

fluid on which the mould had grown was tested . . . by placing it in a gutter in a culture plate and then streaking different microbes across the plate. The result [indicated] that the microbes which were most powerfully inhibited were some of those responsible for our most common infections. . . .

"All the experiments I have cited showed that [penicillin] was bacteriostatic, that is, it inhibits the growth of microbes. But I showed also that it was bactericidal—that it actually killed them. Then the very first observation . . . showed that it induced lytic changes in the bacteria. Thus it was bacteriostatic, bactericidal and bacteriolytic. . . .

"I had since the war of 1914/18 been interested in antiseptics and in 1924 I described what I think is probably the best experiment I ever did. This showed up in a dramatic fashion the relative activity of a chemical on bacteria and on human leucocytes [white blood cells].

"Normal human blood has a strong bactericidal power on the ordinary cocci . . . but this power is completely lost if the leucocytes are removed from the blood. If defibrinated blood is infected with a small number of staphylococci . . . and incubated in a capillary space [e.g., a fine glass tube with a hairlike bore] the cocci which survive grow out into colonies which can easily be enumerated. But only about 5 per cent grow out. If however, phenol [carbolic acid] is added to a concentration of 1 in 600 all the cocci grow out freely. Here the phenol in a concentration which does not interfere with bacterial growth has destroyed the leucocytes which constitute one of our most powerful defenses against infection.

"I had tested all the chemicals which were used as antibacterial agents and they all behaved in the same way—in some concentration they destroyed leucocytes and allowed bacteria to grow. When I tested penicillin in the same way on staphylococcus it was quite a different story. The crude penicillin would completely inhibit the growth of staphylococci in a dilution of up to 1 in 1000 when tested in human blood [phenol loses its inhibitory power when diluted more than 300 times] but it had no more toxic effect on the leucocytes than the original culture medium in which the mould

had been grown. I also injected it into animals and it had apparently no toxicity.

"A few tentative trials [on hospital patients] gave favourable results but nothing miraculous and I was convinced that . . . it would have to be concentrated. . . .

"We tried to concentrate penicillin but we discovered . . . that penicillin is easily destroyed . . . and our relatively simple procedures were unavailing. . . .

"In 1929 I published the results which I have briefly given."

CHAIN AND FLOREY *

"It was first established that penicillin was an acid . . . [which, extracted from the culture fluid with ether and shaken up with dilute aqueous alkali, formed stable salts]. In addition to ether, a number of organic solvents . . . could be used to extract the free acid form of penicillin. The salts of penicillin were much more soluble in water than in the organic solvents, and therefore penicillin was removed from the organic solvent by about 1/5 to 1/10 the volume of alkali solution. A concentration of penicillin was thereby achieved, and by repeating the extraction several times with different solvents and at a suitable pH, a considerable purification of penicillin and simultaneous reduction of the bulk of liquid was obtained. . . . [By drying at low temperature and pressure] a preparation of a salt of penicillin was obtained, in powder form, which kept its antibacterial activity unchanged for a long time.

"Chemically, however, the preparation was far from pure, containing, as is now known, not more than a small percentage of pure penicillin. The isolation of penicillin in the pure state from this mixture proved a difficult problem because of its instability towards many reagents and the unfavourable solubilities of the free acid and its salts. . . . [By distribution between different solvents and water, by adsorption methods, and by a variety of other means, later much elaborated, it became possible] to produce penicillin preparations from which crystalline salts could be made. The purest material obtained at Oxford [1945] has an activity of about 1,000

* From Ernst Chain and H. W. Florey, "The Discovery of the Chemotherapeutic Properties of Penicillin," *Caribbean Medical Journal*, Vol. 7 (1945), pp. 151-155.

Oxford units per mg., and is capable of inhibiting the growth of certain bacteria at a dilution of about 1:50,000,000. . . . [The Oxford unit, also called Florey unit, was an arbitrary amount determined by comparison with a standard preparation.]

"For the first biological experiments very crude preparations were used. . . . So great was the antibacterial power of even the crudest extracts that at that time—not realizing the extraordinary potency of penicillin—we believed them to be fairly pure. In actual fact we know now that they contained about 1 per cent of pure penicillin. . . .

"It was shown that the extracts were remarkably non-toxic to mice. . . . Not only were the extracts relatively innocuous to the whole animal, but leucocytes and tissue cultures withstood many hundreds of times the concentration needed to inhibit such organisms as the streptococcus. In light of present knowledge of the gross impurity of the original extracts, one can only be thankful that the mass of impurities, as well as the penicillin, were so little toxic.

"Penicillin was readily absorbed in animals after intramuscular or subcutaneous injection, and from the small intestine. It could not of course be given by mouth because the acid of the gastric juice destroyed it, nor by rectum as the bacteria there inactivated it. It was largely excreted, still in an active form, in the urine . . . and to a certain extent in the bile and saliva. . . . Though penicillin was readily soluble and diffusible, it did not pass in detectable quantities from the blood into the cerebro-spinal fluid.

"In agreement with Fleming's observations it was found that the action of penicillin was bacteriostatic, in that it merely inhibited the growth of organisms and did not kill them quickly, as did poisonous antiseptics. . . . Most antibacterial substances such as ordinary antiseptics and the sulphonamides are . . . not active in the presence of pus, and hence their therapeutic efficacy is severely limited. It was therefore a particularly fortunate property of penicillin that pus, tissue autolysates [products of the self-digestion of cells, called autolysis], blood and serum had no inhibitory effect on its activity. It was found too that the number of organisms present had little effect on its inhibitory power—again a contrast with the sulphonamides. . . .

"In terms of the labour involved it was . . . a big step from experiments on mice to making observations on the human subject, for the mould produces very little of the active substance. Months elapsed before enough material could be accumulated to try the first injection on man.

"Injection in the human subject disclosed that some substance was present in the crude penicillin preparations which caused a rigor and sharp rise of temperature. This had not been suspected from observations on animals. By good fortune the pyrogenic effect was not due to the penicillin but to an impurity which could be removed.

"Insufficient material had been accumulated for the first 2 cases treated, and although both patients, who were seriously ill, did well for a time, they relapsed and further treatment could not be carried out for lack of material. In the course of some months enough was accumulated . . . to treat by parenteral injection a further 18 patients. . . . Toxic reactions, apart from pyrogen, were not observed and some striking recoveries of patients infected with staphylococci were obtained. Suitable dosage was worked out and the principles of treatment were formulated. At the same time penicillin was shown to be valuable for local application in various septic conditions. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

Chain and his colleagues at Oxford began the long and difficult task of elucidating the structure of penicillin; this problem was subsequently taken up elsewhere, chiefly in the United States. Meanwhile the job of producing penicillin in quantity from the mold was undertaken by a number of American pharmaceutical houses, at first independently, later under the aegis of the War Production Board. The manifold production problems were solved in a surprisingly short time.

Penicillin could be used on many cases in which sulfonamides would be ruled out, as on patients with kidney damage and those reacting allergically to the "sulfa" drugs. Its effectiveness was at first hard to evaluate, for insufficient supplies and insufficient ex-

perience often resulted in inadequate dosage. It proved effective against pneumonia and other diseases due to staphylococci and largely beyond the reach of the "sulfas" or any other form of treatment. It showed itself a powerful weapon against streptococci and the bacilli of gas gangrene. It cured gonorrhea rapidly and without the sometimes unpleasant reactions due to "sulfa" therapy. It transformed the treatment of syphilis. It cured a large percentage of cases of bacterial endocarditis, a disease previously regarded as almost 100 per cent fatal. Although powerless against tuberculosis, typhoid fever, and such nonbacterial diseases as malaria and infantile paralysis, it was shown to have a wide "bacterial spectrum" and to be the most powerful microbe-killer yet discovered.

Penicillin nevertheless has its limitations. It is primarily active against gram-positive organisms—those which take a blue or deep violet stain when treated by Gram's differential staining method. It has little activity against the gram-negatives—the red-staining organisms which cause cholera, typhoid, dysentery, and other diseases. Many of these have since proved susceptible to streptomycin and other new agents. Penicillin has acted as a spur to the search for these newer antibiotics, of which about half a dozen are now in fairly general use, most of them the products of soil bacteria. It is now quite common, although still expensive, to give penicillin orally, means having been found to prevent its destruction before it can act. It was at first supposed that penicillin was quite innocuous and that all bad effects would vanish as soon as a pure product had been obtained. Although it is true that penicillin is remarkably nontoxic for a drug of such potency, it is nevertheless not entirely free of noxious side effects; these are seldom so serious, however, as those which sometimes complicate the use of the sulfonamides. A not uncommon, and certainly highly unpleasant, allergic symptom is a severe urticaria (a reaction in the nature of hives) which may persist for days, or even for weeks, after the discontinuance of penicillin therapy. Bad reactions to penicillin are annoying, and sometimes dangerous, but they are neither frequent enough nor serious enough to constitute any considerable limitation on the use of the drug. As in the case of the sulfonamides, bacterial generations may arise which are penicillin-resistant.

Despite its various limitations and drawbacks, penicillin remains the most important of antibiotic drugs.

REFERENCES

RATCLIFF, J. D. *Yellow Magic: The Story of Penicillin* (New York: Random House, 1945).

1946

HERMANN JOSEPH MULLER

(1890–)

"For his discovery of the production of mutations by means of X-ray irradiation."

BIOGRAPHICAL SKETCH

HERMANN JOSEPH MULLER WAS BORN IN NEW YORK CITY, ON December 21, 1890. He attended a public primary school in Harlem and the Morris High School in the Bronx. In 1907 he won a scholarship for entry into Columbia College, where he became interested in biology. He attributes his particular interest in genetics to reading a book on this subject by R. H. Lock. In 1909 he founded a students' biology club, in which Altenburg, Bridges, and Sturtevant participated, all destined to be distinguished geneticists. After graduation he held first a scholarship, then a teaching fellowship, in physiology, the latter at Cornell Medical College; he then taught zoology at Columbia, 1912-1915. From 1910 on he was a member of Morgan's research group (see above, p. 165) and in 1912 he began to do original research in genetics. From 1915 to 1918 he was an instructor in the Rice Institute, Houston, under Julian Huxley. During this time and the two years following, when he instructed at Columbia, he elaborated methods for quantitative mutation study. In 1920 he went to the University of Texas as associate professor, becoming professor in 1925. His first evidence of mutations produced by X rays was obtained in 1926 and published in 1927. In 1932 he was awarded a Guggenheim Fellowship

for a year in Oscar Vogt's institute in Berlin, in Timoféeff's Department of Genetics. He then spent more than three years as Senior Geneticist at the Institute of Genetics of the Academy of Sciences of the U.S.S.R., first in Leningrad, later in Moscow. Then followed work in the Institute of Animal Genetics, University of Edinburgh (1937-1940), Amherst College (1940-1945) and Indiana University, where he accepted a professorship in the Zoology Department in 1945.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"If . . . mutations were really non-teleological, with no relation between type of environment and type of change, and above all no adaptive relation, and if they were of as numerous types as the theory of natural selection would demand, then the great majority of the changes should be harmful in their effects, just as any alterations made blindly in a complicated apparatus are usually detrimental to its proper functioning, and many of the larger changes should even be totally incompatible with the functioning of the whole, or, as we say, lethal. . . .

"To get exact evidence . . . required the elaboration of special genetic methods, adapted to the recognition of mutations that ordinarily escape detection—(1) lethals, (2) changes with but small visible effects, and (3) changes without any externally visible effects but influencing the viability more or less unfavourably. . . .

"It was possible in the first mutation experiments, which [Edgar] Altenburg and the writer conducted, partly in collaboration, in 1918-19, to get definite evidence in *Drosophila* that the lethal mutations greatly outnumbered those with visible effects, and that among the latter the types having an obscure manifestation were more numerous than the definite conspicuous ones used in ordinary genetic work. Visible or not, the great majority had lowered viability. Tests of their genetic basis . . . showed them to be most varied in their locus in the chromosomes, and it could be calculated . . . that there must be at least hundreds, and probably

* From H. J. Muller, "The Production of Mutations," *Les Prix Nobel en 1946*, pp. 257-274.

thousands, of different kinds arising in the course of spontaneous mutation. . . .

"Objectivity of recognition, combined with [their greater number] . . . made it feasible for lethals to be used as an index of mutation frequency. . . . In the earliest published work, we . . . attempted not only to find a quantitative value for the 'normal' mutation frequency, but also to determine whether [temperature] . . . affected the mutation frequency. . . . The results . . . indicated that a rise of temperature, within limits normal to the organism, produced an increase of mutation frequency of about the amount to be expected if mutations were, in essentials, orthodox chemical reactions.

". . . Mutations, when taken collectively, should be subject to the statistical laws applying to mass reactions, but the individual mutation . . . should be subject to the vicissitudes of ultramicroscopic or atomic events. . . . This is a principle which gives the clue to the fact . . . that differences in external conditions . . . do not appear to affect the occurrence of mutations, while on the other hand, even in a normal and sensibly constant environment, mutations of varied kinds do occur. It is also in harmony with our finding, of about the same time, that when a mutation takes place in a given gene, the other gene of identical type present nearby in the same cell usually remains unaffected, though it must of course have been subjected to the same macroscopic physicochemical conditions. On this conception, then, the mutations ordinarily result from submicroscopic accidents, that is, from caprices of thermal agitation, that occur on a molecular and submolecular scale. . . .

"Now this inference . . . led naturally to the expectation that some of the 'point effects' brought about by high-energy radiation like X-rays would also work to produce alterations in the hereditary material. For if even the relatively mild events of thermal agitation can . . . have such consequences, surely the energetically far more potent point changes caused by powerful radiation should succeed. And, as a matter of fact, our trials of X-rays . . . proved that such radiation is extremely effective, and inordinately more so than a mere temperature rise, since by this method it was possible to obtain, by a half hour's treatment, over a hundred times as many

mutations . . . as would have occurred . . . spontaneously in the course of a whole generation. These mutations too were found ordinarily to occur pointwise and randomly, in one gene at a time, without affecting an identical gene that might be present nearby in a homologous chromosome.

"In addition to the individual gene changes, radiation also produced rearrangements of parts of chromosomes. As our later work . . . has shown, these latter were caused in the first place by breakages of the chromosomes, followed afterwards by attachments occurring between the adhesive broken ends, that joined them in a different order than before. The two or more breaks involved . . . may be far apart, caused by independent hits, and thus result in what we call *gross* structural change. . . . By the rejoining, in a new order, of broken ends resulting from two . . . nearby breaks, a *minute* change of sequence of the genes is brought about."

CONSEQUENCES IN THEORY AND PRACTICE

Possibly the most obvious lesson of Muller's important discovery is that "the great majority of mutations being undesirable . . . their further random production in ourselves should so far as possible be rigorously avoided." It thus "becomes an obligation for radiologists . . . to insist that the simple precautions are taken which are necessary for shielding the gonads. . . . And, with the coming increasing use of atomic energy, even for peacetime purposes, the problem will become very important of insuring that the human germ plasm . . . is effectively protected from this additional and potent source of permanent contamination."

Other agents were soon found to produce mutations—alpha rays, neutrons, ultraviolet and infrared light, mustard gas and related chemical compounds. The latter were investigated by J. M. Robson and C. Auerbach, because Robson had noticed a similarity between the effects of mustard gas on the body and those produced by X ray and radium. Muller had already inferred that "a large proportion . . . of the somatic effects of irradiation . . . arise secondarily as consequences of genetic effects produced in the somatic cells. The

usefulness of this interpretation has been shown in recent studies . . . dealing with improved methods of irradiation of mammalian carcinoma." Dr. Muller is also of the opinion that studies in this field are "helping to clear the way for an understanding of the mechanism by which radiation acts in inhibiting growth, in causing sterilization, in producing necrosis [local death of tissue] and burns, in causing recession of malignant tissue, and perhaps also, on occasion at least, in inducing the initiation of such tissue."

The importance of the discovery in aiding scientists to understand the mechanism of evolution has been hinted in the principal quotation. Its importance for further studies in genetics is suggested by Muller's assertion that "every natural mutation, when searched for long enough, is found to be producible also by radiation." The abundant, if random, production of mutations has enormously extended the materials of the geneticist's work. For instance, "position effect" (implying that the function of a gene is to a certain extent dependent upon what other genes are near by) had been observed previously, but it was not known to what extent the effect might be a special one until numerous rearrangements could be studied; this was made possible by irradiation, and there is now evidence that "position effect" is a general principle. This is one instance only of the way in which Muller's discovery has affected genetics. Analysis of the properties of the chromosomes and their parts has gained a great deal from studies in which parts have been removed, added, or rearranged. Mutations are produced at random, but they are so numerous that it is possible to pick out those best suited for successive steps in analysis, and the method has been applied not only to "pure" genetics but also to studies in the biochemical synthesis of amino acids, vitamins, purines, etc. By means of induced mutations it has been possible to develop strains of fungi which have lost the power to synthesize certain substances. Such studies promise to shed more light on synthetic processes in the organism and to improve our understanding of certain hereditary metabolic disturbances. Hereditary diseases in general are ultimately due to mutations. Mutations also determine the development of new properties in bacteria, such as resistance to particular drugs.

The possibility of applying any influence which will change individual genes to order seems very remote, but there has been evidence that induced mutations may at times be used for selection in artificial breeding.

1947

BERNARDO ALBERTO HOUSSAY

(1887–)

"For his discovery of the part played by the hormone of the anterior pituitary lobe in the metabolism of sugar."

(The award for 1947 was shared with C. F. and G. T. Cori; see below, pp. 248-254.)

BIOGRAPHICAL SKETCH

BERNARDO ALBERTO HOUSSAY WAS BORN IN BUENOS AIRES, ON April 10, 1887. His early studies were in a private academy. In 1901 he was admitted to the School of Pharmacy of the University of Buenos Aires, where he was graduated in 1904. He had already commenced his work at the medical school, from which he obtained his M.D. in 1911 for his thesis on the hypophysis, or pituitary body. Before he had completed his medical studies he was appointed professor of physiology in the University of Buenos Aires School of Veterinary Medicine. In 1919 he resigned this position to occupy the chair of physiology in the medical school, as the first full-time professor in an Argentine university; he remained as professor and director of the Institute of Physiology until 1943. Since 1944 Professor Houssay has carried on his research at the Institute of Experimental Biology and Medicine, organized with the support of private funds. He has worked in almost every field of physiology, but has given particular attention to problems of endocrinology. From first to last he has never ceased to study the functions of the hypophysis.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The production and consumption of glucose and hence the blood sugar level are controlled by a functional endocrine equilibrium. [The endocrine glands are ductless glands secreting hormones into the bloodstream.] This mechanism acts on the liver—the organ which produces and stores glucose—and on the tissues which are the consumers of glucose, by means of hormones which play a part in the chemical processes of carbohydrate metabolism.

"The secretion of each endocrine organ is controlled by a physiological mechanism. For instance, the pancreas secretes insulin in adequate quantities so as to maintain a normal blood sugar level and the blood sugar level regulates the amount of insulin secreted. Thus hyperglycemia [high blood sugar] increases the secretion of insulin [which lowers the blood sugar], and hypoglycemia [low blood sugar] diminishes or completely inhibits it. . . . The extrinsic innervation of the pancreas is not necessary for the regulation of insulin secretion [i.e., cutting the nerves has little effect on the control of the endocrine part of the gland].

"Not only is the secretion of each gland regulated according to the organic needs of each moment, but there is also an equilibrium between the secretions of the different glands [e.g., those which raise blood sugar and those which lower it]. . . .

"In 1907, when I was a medical student, I was attracted to the study of the hypophysis because the microscopic picture showed glandular activity and its lesions were accompanied by serious organic disturbances, such as acromegaly, dwarfism, etc. [The hypophysis, or pituitary body, is a small two-lobed body at the base of the brain. Both parts produce hormones. Those of the anterior lobe control the thyroid, the sex glands and cortex of the suprarenal glands, regulate the formation of milk and the growth of the whole body; Houssay has shown that this anterior lobe also has a part in the conversion of sugar. Disordered function in the secretion of the growth hormone causes acromegaly, a disease described

* B. A. Houssay, "The Rôle of the Hypophysis in Carbohydrate Metabolism and in Diabetes," *Les Prix Nobel en 1947*, pp. 129-136.

by Pierre Marie in 1886, in which there is progressive enlargement of the head and face, the hands, feet, and thorax.]

"The frequency of glycosuria [sugar in the urine] or diabetes in acromegaly has been reported many times. . . . Moreover extracts of the posterior lobe of the hyphosis produce . . . a transitory hyperglycemia. Therefore it was commonly accepted that if the hypophysis played a part in carbohydrate metabolism, it would be due to the activity of its posterior lobe.

"One year after the discovery of insulin a systematic study of the influence of endocrine glands on its activity was organized in my laboratory. [When the hypophysis had been removed from dogs, a difficult surgical procedure, they were found to be excessively sensitive to the action of insulin; this was also found in a large kind of toad, plentiful in Argentina, which Houssay used in many of his experiments. Later he found that administration of extract of anterior lobe prevented or corrected this hypersensitiveness to insulin.] The next step consisted in the removal of the pancreas in hypophysectomized dogs and toads. . . . [A dog without a pancreas is diabetic; but removal of the hypophysis or its anterior lobe] produced a considerable attenuation of the severity of pancreatic diabetes. The injection or implantation of anterior hypophyseal lobe reestablished or even increased the usual severity of diabetes. . . .

"Later the diabetogenic [diabetes-producing] effect was also demonstrated in dogs with a surgically reduced pancreas or [by other workers] with an intact pancreas. A permanent diabetes was produced by prolonged treatment with the extract of anterior lobe. . . . [This was shown to be due to the damage caused to the β cells, or insulin-secreting cells, of the pancreas.] If after a few days the anterohypophyseal treatment is discontinued the diabetic condition disappears, the blood sugar returns to a normal level, and later the β cells regain their normal aspect. If daily injections . . are continued for several weeks . . . the animals remain permanently diabetic."

CONSEQUENCES IN THEORY AND PRACTICE

The far-reaching importance in animal metabolism of the tiny hypophysis has been realized only in the present century. Its relation to body growth was first clearly appreciated during the first decade of the century, but not until 1944 did H. M. Evans and C. H. Li produce the growth hormone in pure form. In the same way the influence of the pituitary body on sex functions, although perceived about fifty years ago, was not worked out in detail until much later. The effect of the hypophysis on the pancreas, although surmised, was little investigated or understood before the work of Houssay. Beginning in 1924, Houssay demonstrated that an animal deprived of its pituitary is abnormally sensitive to insulin; that a pituitary extract will offset this effect, showing an anti-insulin property; that this influence emanates from the anterior lobe of the pituitary; that diabetes caused by removal of the pancreas is distinctly relieved by removal of the pituitary body too; and that the diabetogenic (diabetes-producing) capacity of the anterior lobe is so great that sufficient quantities of extract injected into a test animal will evoke the symptoms of diabetes.

In 1930 P. E. Smith discovered that the anterior lobe of this vital organ also has an adrenocorticotropic function—i.e., that it produces a hormone which stimulates the functional activity of the adrenal cortex. This hormone was later isolated and is known as ACTH (see below, p. 282). One of its effects, and doubtless the principal one, is to cause the adrenal cortex to secrete cortisone. A number of workers investigating the latter substance have reported that it possesses a diabetogenic capacity. One might therefore suppose that the ability of a pituitary extract to influence carbohydrate metabolism is actually nothing more than its ability to enlist the force of the adrenal cortex. There seems to be evidence, however, that this is not the whole story; and among other points it is particularly relevant to note here that C. F. and G. T. Cori, who received the other half of the 1947 Prize, could show a direct influence of pituitary extract on an important step in the body chemistry of carbohydrate—an influence reinforced by an extract of the

adrenal cortex and blocked by insulin. (See below, p. 254.) Houssay had already shown that, whatever the mechanism concerned, the diabetes which results from pituitary injections is due to destruction of the insulin-producing cells of the pancreas.

Carbohydrate metabolism is of such enormous importance to the body's economy that whatever serves to throw light upon it is a useful contribution. Hope of determining the basic cause of diabetes must depend upon increasing knowledge of this exceedingly complex mechanism. Houssay has demonstrated a link in the cycle. He has also helped to attract further attention to the importance of the anterior pituitary, a subject of ever-increasing interest.

CARL F. CORI

(1896–)

GERTY T. CORI

(1896–)

"For their discovery of how glycogen is catalytically converted."

(The award for 1947 was shared with B. A. Houssay; see above, pp. 244-248.)

BIOGRAPHICAL SKETCHES

CARL F. CORI

CARL FERDINAND CORI WAS BORN IN PRAGUE, THEN PART OF Austria-Hungary, on December 5, 1896. His father was director of the Marine Biological Station in Trieste, and his maternal

grandfather, Ferdinand Lippich, professor of theoretical physics at the German University of Prague, so that he was early subjected to influences deriving from both the physical and the biological sciences. He attended the *Gymnasium* at Trieste and studied medicine at Prague, where he was graduated in 1920. His wartime studies were interrupted by service as a lieutenant in the Sanitary Corps of the Austrian Army on the Italian front. His collaborative scientific work with Gerty Theresa Cori (née Radnitz) began when they were classmates, with a publication on the complement of human serum. They were married in 1920. At the Universities of Vienna and Graz, Cori devoted the next two years chiefly to pharmacology. In 1922 he moved to the United States, becoming an American citizen in 1928. From 1922 to 1931 he served as biochemist at the State Institute for the Study of Malignant Diseases in Buffalo, New York. He then joined the faculty of Washington University Medical School in St. Louis, first as professor of pharmacology and later as professor of biochemistry. His work has been centered on enzymes and hormones, particularly in relation to carbohydrate metabolism.

GERTY T. CORI

GERTY THERESA CORI (NÉE RADNITZ) WAS BORN IN PRAGUE, on August 15, 1896. She was privately tutored until the age of ten, when she entered a school for girls. In 1914 she enrolled in the medical school of the German University of Prague, and in 1920 she received her doctorate. In the same year she married her classmate, Carl F. Cori, with whom she had already published an immunological study. After two years at the Carolinen Children's Hospital in Vienna she joined her husband at the State Institute for the Study of Malignant Diseases in Buffalo, New York; in 1931 she accompanied him to the Washington University School of Medicine as research associate, and in 1947 she was appointed professor of biochemistry. Their joint work has dealt with the catalytic and hormonal metabolism of the carbohydrates.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The discovery of polysaccharide phosphorylase and glucose-1-phosphate [Cori ester] can be traced to systematic work on the formation of hexose-6-phosphate in muscle. Of particular importance was the fact that the method used for the determination of hexose-6-phosphate consisted of two independent measurements, one based on the reducing power of the compound and the other on its phosphate content, and that there was generally good agreement between these two measurements. In this manner it was found that a number of procedures led to an increase in the hexose-6-phosphate content of muscle, among which may be listed anaerobiosis, injection of epinephrine in intact animals, incubation of isolated frog muscle in Ringer's solution containing epinephrine, and gastric stimulation of mammalian or frog muscle.

"Balance experiments during aerobic recovery of previously stimulated and isolated frog muscle indicated that the hexose-6-phosphate which disappeared was in large part reconverted to glycogen; hence it was made probable that the reaction, glycogen → glucose-6-phosphate, was reversible. The next step was the finding that the increase in hexose-6-phosphate in isolated frog muscle incubated anaerobically with epinephrine was accompanied by a corresponding decrease in inorganic phosphate. . . . Phosphocreatine and adenosine triphosphate (ATP) remained unchanged, suggesting that they were not involved in the formation of hexose-6-phosphate, but since their regeneration through lactic acid formation was not excluded, the experiments were repeated with muscles poisoned with iodoacetate. The results were the same as with unpoisoned muscle and it was therefore concluded that hexose-6-phosphate was formed from glycogen by esterification with inorganic phosphate. . . .

"The following experiments led to the detection and isolation of glucose-1-phosphate. Minced frog muscle was extracted 3 times

* From Carl F. Cori and Gerty T. Cori, "Polysaccharide Phosphorylase," *Les Prix Nobel en 1947*, pp. 216-235. The first quotation is from Part I, by Carl F. Cori; the second is from Part II, by Gerty T. Cori.

with 20 volumes of cold distilled water, a procedure which removed most of the acid-soluble phosphates normally present in muscle, but did not remove glycogen. When the washed residue was incubated anaerobically at 20° in isotonic phosphate buffer at pH 7.2, some hexosemonophosphate was formed. On addition of a catalytic amount of muscle adenylic acid, the formation of hexosemonophosphate was very markedly increased. When phosphate was replaced by isotonic KCl, no ester formation occurred. The glucose part of the ester could have come only from glycogen, and the phosphate part only from the added inorganic phosphate, thus confirming the reaction postulated for intact muscle.

"After short periods of incubation there was much more organic phosphate present in the hexosemonophosphate fraction than corresponded to the reducing power of hexose-6-phosphate. Such a discrepancy had not been encountered before in analyses of the hexosemonophosphate fraction, and since the discrepancy became smaller or disappeared completely after longer periods of incubation, the formation of a precursor of glucose-6-phosphate was suspected. Short hydrolysis in NH_2SO_4 at 100° (conditions under which hexose-6-phosphate is not hydrolyzed) revealed the presence of a compound which yielded equivalent amounts of fermentable sugar and inorganic phosphate. . . .

"The new phosphate ester was isolated as the crystalline brucine salt in a large-scale experiment . . . and identified as glucose-1-phosphate.

"When glucose-1-phosphate was added to a cell-free frog or rabbit muscle extract, it was converted rapidly to glucose-6-phosphate by an enzyme which was named phosphoglucomutase. It was due to the leaching out of the mutase that glucose-1-phosphate accumulated in minced frog muscle. Mutase is greatly enhanced in its activity by magnesium ions. In order to demonstrate the formation of glucose-1-phosphate from glycogen and inorganic phosphate in muscle extract, it was necessary to remove magnesium ions by dialysis. . . . [The chemical properties of the isolated ester were determined and it was later synthesized.]

"The first clue for a possible reversibility of the reaction, glycogen + phosphate → glucose-1-phosphate, came from the observation that addition of glucose-1-phosphate to a reaction mixture con-

taining enzyme, glycogen and phosphate was strongly inhibitory, while glucose-6-phosphate had only a weak inhibitory effect on the formation of glucose-1-phosphate. Further investigation showed that conditions for reversibility were unfavourable because the concentration of glucose-1-phosphate could not be maintained, owing to the activity of phosphoglucomutase. . . . It became clear that a separation of the two enzymes was necessary in order to investigate reversibility. A partial separation was first achieved by adsorption of phosphorylase on aluminium hydroxide, followed by elution with disodium phosphate and dialysis to remove inorganic phosphate. When glucose-1-phosphate was added to this enzyme preparation, inorganic phosphate was set free and a polysaccharide was formed in equivalent amounts, showing the reversibility of the reaction. . . . Reversibility could also be demonstrated with phosphorylase preparations of heart and brain [and liver]. . . ."

* * *

"The protein fraction of a muscle extract, precipitated by less than 0.5 saturation with $(NH_4)_2SO_4$, showed a marked rise in phosphorylase activity per unit of protein over the unfractionated starting material. This was however the case only when the enzyme was catalyzing the reaction toward the right:

Glycogen + inorganic phosphate $\rightleftarrows$ glucose-1-phosphate

"When enzyme activity was tested in the opposite direction a puzzling difficulty was encountered. Activity set in only after a lag period; refractionation of the enzyme increased this lag period from minutes to hours and in some preparations completely abolished the activity toward polysaccharide formation. . . .

"Liver phosphorylase, upon salt fractionation, was found to retain activity toward polysaccharide synthesis. Such preparations always contained traces of glycogen, while the purified muscle enzyme was free of glycogen. This observation offered a clue. Addition of glycogen to the reaction mixture in as low a concentration as 10 mg. per cent led to immediate activity of muscle phosphorylase preparations, seemingly inactive when tested without glycogen addition. . . . From these observations it followed that glycogen was needed for the activity of the enzyme in both directions. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

The chemical changes involved in the contraction and relaxation of muscle have long been subjected to careful study (cf. the work of Meyerhof, pp. 106-108 above). It seemed probable that cyclical changes also occur during periods of rest, a conversion of energy taking place in the same way but with less intensity. Ever since the discovery of glycogen, or animal starch, by Claude Bernard, much effort has also been devoted to the study of carbohydrate metabolism. In the work of the Coris these two avenues of research, already merging, were brought together. The discoveries of these workers helped to elucidate specific details of what happens when glycogen is changed into sugar and vice versa. Tissues such as muscle and liver contain enzyme systems which bring about the phosphorylation of both glycogen and glucose. To an understanding of the phosphorylation of glucose, Meyerhof (1927) was the pioneer contributor with his discovery of "hexokinase," which later turned out to consist of two enzymes, both present in muscle. The phosphorylation of glycogen was explained by the Coris on the basis of a somewhat different mechanism.

As indicated above, they were able to produce from muscle an ester of hexose-phosphoric acid in which the phosphoric acid was linked to the sugar near carbon atom 1. In the presence of muscle extract this changed to the 6-ester, the process requiring the presence of magnesium and of a special enzyme, phosphoglucomutase. When the latter had been destroyed in the presence of phosphorylase, which causes phosphoric acid to be split off, they were able to build up glycogen from Cori ester, thus reversing the process; but, as shown in the brief quotation from Gerty T. Cori's Nobel lecture, small quantities of glycogen had to be present in order to bring about the synthesis. The reaction between the Cori ester and the 6-ester was also shown to be reversible. Two of the Coris' associates succeeded in converting glucose into a glucose-6-phosphoric acid.

The Coris further showed that addition of pituitary gland extract retarded the synthesis of hexose-6-phosphate ester, an action

strengthened by an extract of the adrenal cortex but blocked by insulin. In this way they were able to throw light on the chemical mechanism by which the hormones concerned in carbohydrate metabolism do their work.

1948

PAUL MÜLLER

(1899–)

"For his discovery of the high efficacy of DDT as a contact poison against several arthropods."

BIOGRAPHICAL SKETCH

PAUL MÜLLER WAS BORN IN OLTEN, SOLOTHURN CANTON, Switzerland, on January 12, 1899, but lived from the age of four or five in Basel. There he went to school and, during 1916-1917, worked in industrial chemical laboratories, an experience which he considers to have been of great practical value. In 1918 he returned to secondary school, completing the course in 1919. He then began the academic study of chemistry at the University, obtaining his doctorate in 1925, with chemistry as major and physical chemistry and botany as minors. In the same year he accepted a position as managing chemist with the dye works of the J. R. Geigy Company of Basel. There he has worked not only on dyes and insecticides but also on disinfectants and tanning agents. DDT was synthesized and its effects discovered in the autumn of 1939, but the first commercial DDT insecticides did not appear until 1942. During the Second World War and since, such insecticides have found world-wide use for a broad range of agricultural and hygienic purposes.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"The composition of important vitamins and hormones, as well as bacteriostatic substances such as penicillin, streptomycin, etc., . . . has been made clear, and some have since been synthesized. But despite all these successes, we are still far from knowing how to predict, with any degree of reliability, what physiological effect to anticipate from a given composition. . . .

"The relationships are still more difficult in the field of artificial, and particularly synthetic, insecticides. . . .

"When I began, about 1935, on behalf of my firm, the J. R. Geigy Company of Basel, to work in the field of insecticides and especially the insecticides important for agriculture, the situation looked hopeless. There already existed an immense literature in this field, and a flood of patents had been taken out. But of the many patent insecticides there were practically none on the market, and special experiments indicated that they were not equal in value to . . . arsenicals, pyrethrum [etc.].

"That gave me the courage to work on. But just the same the chances were very bad, for only an exceptionally cheap or unusually effective insecticide could have any prospect of finding application in agriculture, yet the demands which must be made on an insecticide for agriculture are especially severe. . . . I reflected about what my ideal insecticide must be like and what characteristics it should have. I soon perceived that a contact insecticide would have a far better chance than a food poison. The characteristics of this ideal insecticide must be as follows:

"1. Great toxicity for insects,

"2. Rapid commencement of toxic effect,

"3. Little or no toxicity for warm-blooded animals and plants,

"4. No irritant effect and no smell, or a faint and at any rate not unpleasant one,

"5. The range of effectiveness should be the greatest possible, and extend to the largest possible number of arthropods [joint-

* Translated from Paul Müller, "Dichlordiphenyltrichloräthan und neuere Insektizide," *Les Prix Nobel en 1948,* pp. 122-132.

footed invertebrate animals, including crustaceans, insects, centipedes, and arachnoids—spiders, scorpions, mites, and ticks],

"6. Long duration of effect—i.e., great chemical stability,

"7. Low price = economic use. . . .

"To begin with, at all events, it was a question of finding a substance with great effect as a contact insecticide. . . . My biological tests were carried out in a large glass case . . . into which I shot a fine spray of the substance to be tested in a nonpoisonous solvent. . . .

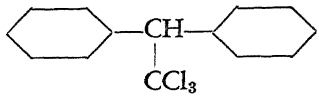
"After the fruitless testing of hundreds of different substances, I realized that it is not easy to find a good contact insecticide. In the field of science one attains something only through obstinacy and steadfast work. . . .

"It was known to me from earlier research that compounds with the group $—CH_2Cl$ . . . often show definite effectiveness. From work on moth repellents carried out in our firm at this time by Dr. H. Martin and his co-workers, in which I myself had no share, it was known to me that compounds with the general formula:

$$Cl—X—Cl,\ X = SO_2,\ SO,\ S,\ O,\ \text{etc.}$$

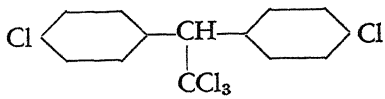
often showed quite considerable effect as food poison for moths.

"In studying the literature I came across an article by Chattaway and Muir . . . in which the formation of diphenyltrichloroethane is described:



I recollected my old research with substances containing the $—CH_2Cl$ group . . . and I was curious as to what possible influence the $=CCl_3$ group would have on the contact-insecticide effect.

"The substance was produced in September 1939 and the test gave a very considerable contact-insecticide effect on flies. I began to make derivatives of this basic formula, and, influenced I daresay by the results of the work on moth repellents, I synthesized the p,p′-dichlor-compound:



[DDT]

"This compound, which had already been brought forward by an Austrian student in the course of his dissertation in 1873, had now such a strong contact-insecticide effect as I had never observed in any substance thus far. After a short time my fly chamber was so much poisoned that after it had apparently been carefully cleansed, new flies perished from contact with the walls without spraying of the substance. . . . [This effect persisted for about a month.]

"Other insects were tested later. . . . The new compound was everywhere effective, although often death first occurred after some hours or even days. . . . [DDT was found to fulfill all but the second of Müller's seven desiderata of the ideal insecticide: its action, although very powerful, is not immediate, and it is therefore often combined with a "knockdown" such as pyrethrum.]

"Finally the laboratory results were confirmed by field research . . . and it was found that the effect against Colorado beetles lasts four to six weeks. . . .

"The DDT insecticides have now been introduced into all possible spheres of insect control, for example in hygiene, in the safeguarding of textiles and provisions, and in the protection of plants."

CONSEQUENCES IN THEORY AND PRACTICE

It is hardly necessary to expatiate on the significance of Dr. Müller's discovery. As shown above, the primary aim was to find a good agricultural insecticide; this aspect of the success attained is not without importance, from the nutritional point of view, for world health. Effectual control of flies has had a more direct bearing on medicine in the reduction of fly-borne diseases. Most dramatic of the triumphs of DDT has been its success against typhus. In October 1943 a typhus epidemic broke out in Naples under conditions which made control seem impossible. In January 1944, when sixty new cases were appearing daily, use of DDT was begun on a large scale for delousing the population. In three weeks 1,300,000 persons were deloused and the outbreak was stopped. Never before in history had it been possible to check a winter epidemic of typhus. This experience was repeated in Japan three

months after the occupation. Müller thus provided a corollary of the greatest importance to the work of the 1928 Nobel laureate, Charles Nicolle, who discovered that typhus is conveyed by lice (see above, pp. 130-133). DDT has similarly proved of great value in preventing malaria and other diseases spread by arthropods. The discovery has also been a stimulus for further work in synthesizing chemical compounds to control plant and animal parasites and to destroy the vectors of disease.

REFERENCES

WEST, T. F., AND CAMPBELL, G. A. *D.D.T. and Newer Persistent Insecticides* (London, 2nd ed., 1950).

1949

WALTER RUDOLF HESS

(1881–)

"For his discovery of the functional organization of the interbrain as a coordinator of the activities of the internal organs."

(The award for 1949 was shared with Egas Moniz; see below, pp. 264-271.)

BIOGRAPHICAL SKETCH

WALTER RUDOLF HESS WAS BORN ON MARCH 17, 1881, IN Frauenfeld, a town in eastern Switzerland. He was fortunate in his early training, which combined expeditions into the woods and fields with elementary instruction in physical science by his father, who permitted him great freedom in the use of scientific apparatus. He matriculated in 1900 at the *Gymnasium* of his native town, thereupon beginning the study of medicine, which he pursued in Lausanne, Berne, Berlin, Kiel, and Zurich; his medical doctorate was granted by the latter university in 1906. Although attracted to physiology early in his medical course, he turned to ophthalmology on graduation and practiced his specialty until 1912. In that year, although already the father of a family, he gave up a successful practice to devote himself to the study of physiology, principally in Bonn. In 1917 he was appointed director of the Physiological Institute in Zurich. Further advanced study, postponed by the First World War, took him to England, where he came under the influence of Langley, the great pioneer in the study of the autonomic

nervous system, Sherrington, Starling, Hopkins, and Dale. His research was at first directed to hemodynamics (study of the blood pressure), then to the regulation of breathing, and finally to the central control of the internal organs in general through the vegetative, or autonomic, nervous system. He worked out a technique for applying pin-point electrical stimulation to specific areas in the brain, using fine electrodes (0.2 mm. in diameter), insulated except at their very tips. He could thus produce strictly localized stimulation and also localized destruction of brain tissue. His investigations in this field were rewarded by the discoveries for which he was given the Nobel Prize. In addition to the work under review, Hess made early contributions to the study of blood viscosity (1907-1920) and squint (Hess screen, 1911).

DESCRIPTION OF THE PRIZE-WINNING WORK*

"In contrast with the very extensive . . . investigation of the vegetative [i.e., involuntary or autonomic] nervous system, there existed relatively limited knowledge of the central organization of the whole regulating apparatus. . . . It had nevertheless become clear that . . . the parts of the brain joined from above directly to the spinal marrow—the medulla oblongata and *the portion lying immediately under the cerebrum, the so-called interbrain*—exert a decisive influence on the vegetative regulations. . . . [Something was known in this connection of the function of a group of nuclei at the base of the brain referred to collectively as the hypothalamus.] But up to the time the special investigations were started, what still lay in the dark was the relation of particular functions to definite morphological substrata. . . . To achieve clarity on this point, so far as possible, was the problem I duly set myself. . . .

"[The autonomic nervous system is divided into two parts: the sympathetic, arising from cells in the thoracic and upper lumbar region of the spinal cord; and the parasympathetic, arising from cells in the midbrain, the medulla oblongata, and the lower, or

* Translated from W. R. Hess, "Die zentrale Regulation der tätigkeit innerer Organe," *Les Prix Nobel en 1949*, pp. 115-123.

sacral, region of the spinal cord. There is also evidence that the sympathetic has a control center in the hypothalamus. The two divisions of the system have different, and usually opposite, effects on the organs and vessels they innervate.] Those functions which are mediated by the sympathetic division of the vegetative nervous system are related to a part, extending from posterior to middle . . . of the hypothalamus. This is therefore to be considered the central 'source,' so to speak, of the sympathetic. To give complete physiological meaning to this discovery calls for further explanation. . . . The question has . . . arisen whether a circumscribed effect is associated with the classical sympathetic, defined primarily by the limitation of its root zone to the thoracic spinal marrow. . . . . Where the sympathetic takes effect, it sustains the efficiency of the body and helps the organism to better success through coming to terms with its environment. It is functional insofar as it comprises an *ergotropic or dynamogenic* [i.e., energizing or work-producing] *system.* But with this knowledge further experiences fit in, of particular interest to the psychiatrist, but also to anyone who is aware that behind the diversity of phenomena stands the unity of the organism. Stimulations in a *circumscribed area* of the ergotropic (dynamogenic) zone regularly induce a distinct *change of mood.* Thus a previously good-natured cat becomes angry; she begins to mew and spit, and on someone's approach she turns to a well-directed attack. While the pupils widen markedly, and at the same time the hair stands on end, a picture develops such as the cat shows when she is attacked by a dog and is unable to elude him. The widening of the pupils and bristling of the hair are quite comprehensible as sympathetic effects; but the same does not hold good for the change in psychic attitude. . . .

[Space does not permit listing all the various effects produced by the pin-point electrical stimulation of different centers. When the electrode is placed a little farther forward than in the experiment just described, a general relaxation of skeletal muscles ensues. Not far away is another center which when stimulated soon brings on what appears to be a perfectly natural sleep. From various sharply limited areas it is possible to influence blood circulation and breathing, salivation and heat regulation, etc.]

"In each case *collective symptoms* appear. [Several activities are

initiated at the same time, as in the case of the angry cat, to bring about a coordinated response.] *Groups of organs* are called into action, and in such a way that the separate effects are combined. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

Professor Hess is one of the group of modern investigators (students of the nervous system and the endocrine glands) who have contributed to present knowledge of the integrated action of the body—of the way in which the organism mobilizes its force and reacts, as a whole, to routine demands made upon it, and especially to emergencies. The mechanism of the body's reactions, both nervous and hormonal, to unusual stress is today one of the most actively cultivated and most promising fields of research.

Since the internal organs, such as the blood vessels, heart, lungs, and digestive tract, are chiefly controlled by the autonomic nervous system, it is obviously of prime importance to know as much about this system as possible. Dr. Hess has greatly extended the knowledge of the subject contributed by W. H. Gaskell, J. N. Langley, and others. It is such knowledge which underlies modern surgery in this field. Sympathectomies (eradications of parts of the system) have been used in the treatment of angina pectoris, essential hypertension, certain forms of disease in the blood vessels of the extremities, and a variety of other conditions. The regulation of blood pressure to meet the varying demands of the body occasioned by changes in external and internal environment is dependent in large part on sympathetic regulation, and it is known that injuries, encephalitis, and tumors which damage the central control areas occasionally cause profound blood-pressure changes. Other sympathetic effects have also been attributed to such causes.

Current teaching of the functions of the hypothalamus is based largely on American and British work. The distinctive feature of Hess's approach to the problem is his use of the intact, unnarcotized animal. His method is to place steel-needle electrodes in the brain under anesthesia, and to fasten them in place by fixing them to a frame, which in turn is attached to the skull itself. The actual ex-

periments in stimulation of brain centers are performed later without anesthesia. In this way the effects both of anesthesia and of operative trauma are eliminated and the experiments approach more nearly the ideal physiological condition.

It is likely that these experiments, constituting basic research in physiology, will assume greater significance as more is learned of further nerve communications, especially with the higher brain centers, and as the mechanism of integrated action and the response to stress are made clearer. Hess himself looks to electroencephalography (the study of "brain waves") and to biochemistry to answer the "where" and "how," remarking that it is characteristic of work of this kind to raise new questions.

REFERENCES

McDONALD, D. A. "W. R. Hess: The Control of the Autonomic Nervous System by the Hypothalamus," *The Lancet,* Mar. 17, 1951, pp. 627-629.

EGAS MONIZ

(1874–)

"For his discovery of the therapeutic value of prefrontal leucotomy in certain psychoses."
(The award for 1949 was shared with W. R. Hess; see above, pp. 260-264.)

BIOGRAPHICAL SKETCH

EGAS MONIZ (ANTÔNIO CAETANO DE ABREU FREIRE) WAS BORN at Avança, Portugal, on November 29, 1874. A student of the medical faculty of Coimbra, he continued his work there, becom-

ing professor in 1902. In 1911 he became the first occupant of the new chair of neurology in Lisbon. For many years, partly in collaboration with Almeida Lima, he devoted himself to angiography, the visualization of blood vessels, especially those of the brain, after the injection into an artery of a substance opaque to X rays. In this field he was a pioneer, for he obtained the first "arteriograph" in man. In 1931 he published a large volume on the diagnosis of cerebral tumors by this method. In 1936 appeared the first memoir on prefrontal leucotomy. He is also the author of several other volumes on various aspects of medicine, including clinical neurology, sexual physiology and pathology, and medical history, and has produced literary and political writings. Dr. Moniz has taken an active part in the political life of Portugal. He was deputy in several legislatures from 1903 to 1917, Portuguese Minister in Madrid in 1917, Minister of Foreign Affairs, 1917-1918, and president of the Portuguese delegation to the Paris Peace Conference, 1918.

DESCRIPTION OF THE PRIZE-WINNING WORK*

"It was no sudden inspiration which caused me to work out the surgical operation which I named 'prefrontal leucotomy.' I already laid stress on this fact in my first publication in 1936 and also in my first monograph, which I published in Turin in 1937.

"As an adherent of the doctrine of Ramón y Cajal [see above, pp. 36-37] and on the basis of the theory regarding the connections of the nerve cells, I turned my attention to the origin of normal and pathological psychic activity and its dependence on the neurons. The impulses course along the fibrils through the neurons. Changes are brought about at the synapses which influence many other cells.

"I pondered, along with the activity of the brain in normal psychic life, the changes which are displayed in most psychoses and which heretofore still had no anatomico-pathological explanation. I was particularly struck by the fact that the psychic life in some

* Translated from Egas Moniz, "Mein Weg zur Leukotomie," *Deutsche medizinische Wochenschrift*, Vol. 73 (1948), pp. 581-583.

mental diseases—here I thought especially of the compulsive psychoses and melancholia—is constricted to a very small circle of thoughts, which master all others, recurring again and again in the sick brain, and I sought to find an explanation for this.

"[A section on the general anatomy of the nervous system follows.] Starting from [the] anatomical facts I came to the conclusion that synapses, which are found in millions of instances, are the organic foundations of thought. [A synapse is the close approximation or contact of processes of different nerve cells; it is the point of functional linkage between one nerve cell and another.]

"The normal psychic life depends on good synaptic function, and psychic disturbances arise as consequences of synaptic disturbances. . . .

"If the fibrils become sick or the in-between substance suffers a change . . . the passage of the impulses is more difficult as a result of the more or less complete interruption of coherence. In other cases the [terminations] adhere to the cells with abnormal firmness and the impulses then always take their course along the same paths and always find their expression in the same psychic manifestations. I explain in this way the perseverance of the same morbid thoughts, which constantly reinvade the diseased psyche. . . ."

[The author next discusses the nature of the nerve impulse and the factors determining the course it takes. He gives a brief account of Pavlov's work on the conditioned reflex to indicate that new association pathways may be set up. He also discusses the anatomy of the prefrontal lobe, defining it for his own purposes as the region lying in front of the motor area. He points out that its functions are not definitely localized, as are those of the motor area.]

"The prefrontal region is closely associated with the psychic phenomena and has a less autonomous function than the so-called brain centers. Its activity depends on the enormous number of synapses of innumerable neurons which are concerned in the formation of the psychic phenomena.

"The functions of the prefrontal lobe can be established in the higher mammals experimentally and in man through clinical findings.

"The classical experiments of Bechterew and Luzaro are worthy of mention. They found that after removal of the prefrontal lobe in dogs the dogs became aggressive, irritable, and impulsive. Their capacity for adaptation was diminished. These findings were confirmed by the experiments of other authors.

"Very valuable are the experiments of Fulton and Jacobsen with chimpanzees previously trained. They found that a unilateral excision of the prefrontal areas produced no important change. Bilateral removal of this region, however, always produced an alteration in the behavior of the animal. After extensive destruction it became impossible to elicit from the animals the performances of their old training. . . .

"These facts are in accord with what has been established in humans. Clinical experience has yielded valuable results for the solution of this important problem. . . . [Evidence is derived from injuries, tumors, and surgical removals.]

"A whole frontal lobe, as is well known, can be removed without considerable consequences for the psychic life. This can at most bring about for the first few days a disorientation for space and time, which, however, gradually disappears again (Penfield).

"Richard Brickner's case is extremely important. This author made a detailed psychiatric investigation in a patient from whom Dandy had to take out important parts of both anterior lobes in order to remove an extensive meningeoma [a tumor of the membranous envelope of the brain].

"At first there occurred a loss of knowledge earlier acquired. But the patient little by little adapted himself again to his environment, despite clearly existing difficulties: character changes, diminished intelligence, etc. According to Brickner the patient later recovered the same personality as before the operation and retained his 'personality type.'

"Prefrontal leucotomy gave still more exact findings regarding the function of the frontal brain. But that is already history and I should like to speak now of the time before the operation which concerns us here was carried out. I should like, so to speak, standing on this side of the bank, to give an account of the reasons which induced me to cross the river.

"People who suffer from melancholia and are tormented by unhappy compulsive ideas, and for whom a medical treatment, a shock treatment or psychotherapy, is of no use, live in everlasting anguish on account of a thought, perpetually present, which overtops all the cares of daily life.

". . . These morbid ideas are deeply rooted in the synaptic complex which regulates matters of knowledge in the consciousness, stirs these up, and keeps them in constant activity.

"All these considerations led me to the following conclusion: It is necessary to alter the synaptic arrangements and thus the paths which are selected by the impulses in their continual course; thereby the corresponding thoughts are altered and forced into other channels.

"On these grounds, after two years' deliberation, I determined to sever the connecting fibers of the neurons in question. In the conviction that the prefrontal lobes are very important for the psychic life, I chose this region for my experiment. . . . Through complete alteration of the existing fiber arrangements, and organization of other synaptic fiber groups, I believed that I could transform the synaptic reactions and thereby cure the patient.

"Since my plan was to do away with a large number of associations, I preferred to attack the cell-connecting fibers of the anterior parts of both lobes of the frontal brain 'en masse,' in order to obtain positive results. At first alcohol injections were used for the destruction, later I performed incisions with the leucotome, a small apparatus designed for this purpose. The white matter of the brain has only a limited blood supply and the operation ought on that account to be free from danger. Everything was done with the greatest care in order to protect the patient's life.

"Permit me to reproduce here a short paragraph from my book *Tentatives opératoires,* which is a cornerstone of my work.

" 'On the eve of my first experiment I had to begin with a justified anxiety. But all fears were put aside by the hope of obtaining favorable results. If we were able to do away with certain psychic symptom-complexes through destruction of the cell-connecting groups, then we would demonstrate conclusively that the psychic functions and the regions of the brain which contribute to their

manifestation are in close relation to one another. That would be a great step forward and a fundamental fact for building the investigation of the psychic functions on an organic basis.'

"And this page concluded thus:

" 'We are sure that this operation will produce a strong discussion in medical, psychiatric, philosophic, and other fields. We expect that, but at the same time we hope that this discussion will serve the progress of science, and above all that it will be of use to mentally ill patients.'

"So we went to work with our outstanding co-worker, Almeida Lima, whom we are obliged to thank for a large part of the pioneer work. The first alcohol injection into the white matter of the prefrontal lobe was made on November 12, 1935, and the first operation with the leucotome was carried out on December 27 of the same year. We obtained cure and improvement, but no mischance which would have compelled us to give up our work."

CONSEQUENCES IN THEORY AND PRACTICE

As the founder of modern psychosurgery, Egas Moniz opened a new chapter in the surgery of the brain. Sir Victor Horsley (1857-1916), famous for his work on cerebral localization, had devised an operation for resecting an area of brain cortex to relieve convulsive movements of the arm. There had been other operations of like nature, but concerned, as was Horsley's, with the motor part of the brain. Aside from these, the great brain surgeons, such as Harvey Cushing, had been chiefly occupied in operations to minimize the damage of brain injuries, or to remove brain tumors. Interference with the parts of the brain controlling psychic functions had never been attempted in a rational manner before 1935, except when these parts were affected by injury or tumor.

Psychosurgery has since undergone great technical evolution. There are at least six types of operation on the frontal lobe currently in use for the treatment of mental disorders. These are all, however, variations on the basic method of Egas Moniz, for the common feature in all such procedures is the interruption of frontal lobe fibers.

Dr. Walter Freeman and Dr. James Watts, having performed a large number of these operations by the lateral approach through the temple, devised a somewhat simpler procedure, the transorbital lobotomy, so called because the instrument is inserted through the eye socket. "Open" operations have also been worked out, involving greater exposure and aiming at better control through a direct view of the field; these require removal of a piece of the skull rather than the mere drilling of a hole. "Selective cortical undercutting," developed by Dr. William B. Scoville, of Yale, implies a selective local cut where the grey matter of the brain joins the major white fibers. This is supposed to work as well as the more radical division of the latter, but to cause fewer side effects.

When psychosurgery is used in a long-standing and badly degenerated case of schizophrenia, the side effects may hardly be noticed. In less severe cases they are of great importance and constitute psychosurgery's principal drawback. Compulsive worries, morbid thoughts, and terrible anxieties may be abolished or greatly weakened. It appears that the inevitable price for this relief, at least when the more radical measures are used, is a certain blunting of personality. This effect, as Dr. Edward K. Wilk observes, "reveals itself in the higher realms of creative imagination, foresight, ambition and social sensitivity." It is for this reason that psychosurgery remains a last resort in mental cases, to be employed only when all other treatments have failed.

The results reported for the different operations vary considerably; results also vary in different examples of the same operation. Broadly speaking it may be said that about one third of psychosurgery patients improve sufficiently to go home, one third are improved but have to be kept in a hospital, and one third show no improvement.

REFERENCES

FULTON, J. F. *Frontal Lobotomy and Affective Behaviour, A Neurophysiological Analysis* (New York: Norton, 1951).

———, "Surgery of Mental Disorder," *McGill Medical Journal,* Vol. 17 (1948), pp. 1-13.

GREENBLATT, M., R. ARNOT, AND H. C. SOLOMON, eds. *Studies in Lobotomy* (New York: Grune and Stratton, 1950).

"Symposium: A Psychiatric Evaluation of Psychosurgery," *Surgery, Gynecology and Obstetrics,* Vol. 92 (1951), pp. 601-617. (A popular abstract appeared in *Time,* May 28, 1951, pp. 38-40.)

1950

EDWARD CALVIN KENDALL

(1886–)

PHILIP SHOWALTER HENCH

(1896–)

TADEUS REICHSTEIN

(1897–)

"For their discoveries concerning the suprarenal cortex hormones, their structure and biological effects."

BIOGRAPHICAL SKETCHES

KENDALL

EDWARD CALVIN KENDALL WAS BORN IN SOUTH NORWALK, Connecticut, on March 8, 1886. His advanced education was pursued at Columbia University, where he received the B.S. degree in 1908 and the M.S. the following year. He was Goldschmidt Fellow in 1909-1910, and obtained his Ph.D. in chemistry in 1910. For a short time (1910-1911) he was research chemist with Parke, Davis and Company in Detroit. From 1911 to 1914 he worked in St. Luke's Hospital, New York City. Since 1914 he has been professor of physiological chemistry and head of the Section

of Biochemistry in the Graduate School at the Mayo Foundation, Rochester, Minnesota.

In 1914 Kendall was able to isolate the active constituent of the thyroid hormone, a substance he called thyroxin. Its structure was determined partly by Kendall, partly by C. R. Harrington; Harrington and G. Barger were responsible for its definitive synthesis in 1926. Apart from his work in this field, Kendall has been occupied chiefly with studies of oxidation in the animal organism, glutathione,* and the isolation and synthesis of hormones of the adrenal cortex.

HENCH

PHILIP SHOWALTER HENCH WAS BORN IN PITTSBURGH, February 28, 1896. He was graduated (A.B.) from Lafayette College in 1916 and took the M.D. in 1920. From 1921 to 1924 he was fellow at the University of Minnesota. He received the M.S. degree in 1931. In 1928-1929 he worked in Freiburg and in von Müller's Clinic in Munich. At the Mayo Clinic he was first assistant in medicine from 1923 to 1925, associate from 1925 to 1926, consultant and head of the Section for Rheumatic Diseases from 1926 on. At the Graduate School of the Mayo Foundation he was instructor in medicine from 1928 to 1932, assistant professor from 1932 to 1935, and associate professor from 1935 to 1947. He has been professor since 1947. Dr. Hench has devoted the greater part of his career to the study of rheumatic diseases.

REICHSTEIN

TADEUS REICHSTEIN WAS BORN ON JULY 20, 1897, IN WŁOCŁAWEK, Poland. He passed most of his early childhood at Kiev, where his father worked as an engineer. In 1905 the family moved to Berlin and later to Zurich, where they settled permanently and acquired Swiss citizenship in 1914. After private tutoring, Reichstein entered the Zurich Oberrealschule (technical school of junior college grade) and then the Eidgenössische Technische

* An important substance in oxidation-reduction, discovered by another Nobel laureate, F. G. Hopkins. See above, p. 136.

Hochschule (state technical college), where he obtained his first degree, in chemical engineering, in 1920. After a year in industry he returned to E.T.H., receiving the doctor's degree in organic chemistry in 1922. He then worked for some years on an industrial project, a study of the aromatic substances of roasted coffee. In 1930 he became a part-time instructor at E.T.H., and in 1931 was appointed Leopold Ruzicka's assistant. His later appointments in the Department of Organic Chemistry at E.T.H.—assistant professor, 1934, and associate professor, 1937—were followed by his selection in 1938 as head of the Department of Pharmacology and director of the Pharmaceutical Institute, University of Basel. Since 1946 he has been head of the Organic Division in the same university and director of its organic laboratories. Independently of Sir Norman Haworth and his associates in Birmingham, Reichstein succeeded in synthesizing ascorbic acid (vitamin C) in 1933. This was his best-known work prior to his Nobel Prize investigations in the chemistry of adrenal cortical hormones.

DESCRIPTION OF THE PRIZE-WINNING WORK

KENDALL *

"Of the several ductless glands, the adrenal cortex is the last to yield its secrets to the investigator. The essential work on the pancreas was done in a matter of months, and insulin was made available to clinical medicine within less than a year. It required only a few years to complete the work on the parathyroid, adrenal medulla, and the male and female sex hormones, but eighteen years passed from the time the physiologic activity of the adrenal cortex was first demonstrated until cortisone was available for use in clinical medicine. This is a measure of the unprecedented difficulties which had to be surmounted.

"Investigations of the adrenal cortex carried out during the decade 1930-1940 by Wintersteiner and Pfiffner, Reichstein and

* E. C. Kendall, "Cortisone—Its Historic Development and Certain Chemical and Biochemical Aspects," *The Merck Report,* Vol. 59, No. 4 (Oct. 1950), pp. 4-8.

his associates, and in my laboratory, resulted in the isolation of no less than 28 crystalline compounds. Of these only four showed significant physiologic activity when tested in small animals. These compounds were designated in my laboratory by the letters A, B, E, and F. . . .

"No sharp qualitative difference was found between the physiologic activity of these four compounds on adrenalectomized animals [animals with the adrenal glands removed], and it was assumed that any one of them could be used in substitution therapy for patients with Addison's disease [adrenal insufficiency, usually due to tuberculosis of the glands]. Unfortunately, the supply of these four hormones was so limited that it was impossible to carry out an investigation on the human being. For example, the amount of compound A which could be isolated from half a ton of adrenal glands of cattle was equivalent to only one small tablet. The supply of adrenal glands was necessarily limited to the number of cattle slaughtered, and the amounts of compounds A, B, E, and F which could be obtained in the laboratory were, therefore, insignificantly small.

"The most significant physiologic properties of these compounds were their strong effect on the metabolism of carbohydrate and protein, and their rather mild influence on the metabolism of water and electrolytes. These two types of physiologic activity were clearly recognized, and were associated with the chemical structure of these hormones some time before 1940.

"There was speculation that compounds A, B, E, and F would be of value for substitution or replacement therapy in Addison's disease, and there was hope that they would be useful in the treatment of shock, traumatic injuries, burns, and some types of infection; but beyond this there was no projected place for any product of the adrenal cortex in clinical medicine. The prospect that the hormones of the adrenal cortex would have but limited application against disease offered no encouragement toward making these compounds available in quantity for study in clinical medicine.

"However, World War II provided a great impetus to efforts to synthesize and produce these hormones on a large scale. Shortly before the entry of the United States into World War II, it was thought that adrenal cortical hormones might be valuable in avia-

tion medicine and in the treatment of shock and battle fatigue. There were rumors that Germany was buying the adrenal gland output of Argentine slaughterhouses, extracting these glands, and administering the extracts to *Luftwaffe* pilots. According to these rumors, the adrenal extracts enabled the pilots to fly and fight at altitudes of forty thousand feet without difficulty. Though untrue, the rumors persisted and provided a real stimulus to attempts to synthesize adrenal cortical hormones.

"In 1941, the National Research Council placed three subjects at the top of its war agenda, in this order: (1) hormones of the adrenal cortex, (2) penicillin, and (3) antimalarial agents. And on December 20, 1941, the National Research Council called a conference in Washington, D. C., inviting scientific representatives of the Mayo Clinic, certain universities, and a few industrial organizations . . . to survey possible production of adrenal cortical hormones.

"It was decided first to attempt to make compound A, 11-dehydrocorticosterone. This was accomplished in my laboratory in 1944, and in 1945 Merck & Co., Inc., prepared a large sample by our method.

"In the first months of 1946 the synthesized product was tested on laboratory animals and was found to behave exactly as did compound A isolated from the adrenal cortex. It was found to be of value in protecting them against certain poisons and exposure to cold, but when given to patients who had Addison's disease it was found to be of little value. This was a great disappointment and interest in the hormones of the adrenal cortex sank to a very low level.

"There was no conclusive evidence that compound E (which we later named *cortisone* to avoid confusion with vitamin E) would be qualitatively different from compound A, and there was, therefore, no assurance that large-scale production of compound E, or cortisone, would be worth while. Nevertheless, Merck & Co., Inc., had in the meantime decided to go ahead in an attempt to synthesize this compound. This was ultimately accomplished by Dr. L. H. Sarett, who, working in the research laboratory of Merck & Co., Inc., succeeded in preparing a few milligrams of the compound.

The yield was so small, however, that the method used by Dr. Sarett could not be applied to large-scale production.

"During the following eighteen months important improvements of some of the steps in the preparation of compound A were devised in my laboratory, and Dr. Sarett discovered an entirely new procedure to convert a product closely related to compound A, to compound E, or cortisone. . . . The final yield of cortisone was thereby raised almost a hundredfold. Further important practical improvements were introduced, and several new, more productive steps were devised through the continuing work in my laboratory and by the staff of development chemists at Merck, under the leadership of Drs. Max Tishler and Jacob van de Kamp. . . . [But in April, 1948, when a group of clinicians met to consider the question] it was feared that compound E would take a place among discarded drugs, right beside compound A."

HENCH AND KENDALL *

"Since 1929 one of us (P. S. H.) has studied the beneficial effects of pregnancy and jaundice on rheumatoid arthritis. Results of these and other studies led us to the following conclusions. Even though the pathologic anatomy of rheumatoid arthritis is more or less irreversible, the pathologic physiology of the disease is potentially reversible, sometimes dramatically so. Within every rheumatoid patient corrective forces lie dormant, awaiting proper stimulation. Therefore, the disease is not necessarily a relentless condition for which no satisfactory method of control should be expected. The inherent reversibility of rheumatoid arthritis is activated more effectively by the intercurrence of jaundice or pregnancy than by any other condition or agent thus known. Regardless of the supposed 'validity' of the microbic theory [i.e., the theory that arthritis is caused by microbes] rheumatoid arthritis can be profoundly influenced by phenomena which are primarily biochemical.

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* Philip S. Hench, Edward C. Kendall, Charles H. Slocumb, and Howard F. Polley, "The Effect of a Hormone of the Adrenal Cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis," *Proceedings of the Staff Meetings of the Mayo Clinic,* Vol. 24 (1949), pp. 181-197. This is the original "preliminary report."

"It became increasingly difficult to harmonize the microbic theory of the origin of rheumatoid arthritis with the phenomenon of relief of the disease by jaundice or pregnancy. It became easier, rather, to consider that rheumatoid arthritis may represent, not a microbic disease, but some basic biochemical disturbance which is transiently corrected by some incidental biologic change common to a number of apparently unrelated events. It seemed logical to suppose that what causes relief of rheumatoid arthritis in pregnancy is closely related to, if not identical with, that which relieves the same disease in jaundice; if so, it could be neither hyperbilirubinemia [the presence in the blood of an excessive amount of bilirubin, a reddish bile pigment found in large amount during jaundice] nor a unisexual (female) hormone since neither of these is common to both pregnancy and jaundice. It was believed that the discovery of some biochemical denominator common to various agents or states beneficial in rheumatoid arthritis, but common especially to jaundice and pregnancy, would provide us with an improved treatment or control of the disease.

"Finally, it was conjectured that the hypothetic common denominator or 'antirheumatic substance X' was not a disintegration product from a damaged liver, but probably was a biologic compound specific in nature and function, a compound which was normal to the human organism. But if this was true, we had no certain clue as to its chemical nature or the organ of its origin. . . . [There follows an account of the attempts to relieve arthritis with female hormones, biliary products associated with jaundice, etc.]

"In time we conjectured that the antirheumatic substance X might be an adrenal hormone. This conjecture was strengthened by the knowledge that temporary remissions of rheumatoid arthritis are frequently induced by procedures which are now known to be capable of stimulating the adrenal cortices, such as general anesthesia or surgical operation. In 1938 we administered to several rheumatoid volunteers lecithin [one of a group of compounds containing two fatty acid molecules and a molecule each of glycerophosphoric acid and choline] separated from the adrenal gland, not as an adrenal product per se, but in an attempt to induce hyperlipemia [an excessive degree of lipemia, or fat droplets in the blood] such

as may occur in association with pregnancy and jaundice. In January, 1941, we recorded our interest in adrenal cortical fractions in general and in Kendall's compound E in particular, and we used briefly Kendall's cortical extract. But compound E was not available to us until September, 1948. . . .

"Since the fall of 1948 [this report is dated April 13, 1949] we have given compound E more or less continuously to 5 rheumatoid patients, and for periods of eight to sixty-one days to 9 other patients; a total of 14 patients. None had mild or moderate disease. All had 'moderately severe' or 'severe' chronic polyarticular rheumatoid arthritis of four and a half months to five years' duration. . . .

"To provide adequate controls, the intragluteal injection of compound E [i.e., injection into the buttocks] was in some cases preceded, and in other cases replaced, by the injection of a fine aqueous suspension of cholesterol . . . indistinguishable in appearance from compound E. The times when the control solution and the adrenal hormone were interchanged were unknown to the patients and were, for five weeks, unknown even to the three clinical authors who were evaluating the results. . . . [The dosage was more or less guesswork at first but fortunately turned out to be about right from the beginning. Progress was checked not only by appearance and symptoms but by the sedimentation rate of the red blood cells and other objective tests.]

"In each of the 14 patients the initial results were as follows. Within a few days there was marked reduction of stiffness of muscles and joints, lessening of articular aching or pain on motion and tenderness, and significant improvement of articular and muscular function. . . . Articular swellings generally diminished, sometimes fairly rapidly and completely. . . . [Some flexion deformities disappeared.]

"Those who found the following maneuvers difficult or impossible often were able within a few days to do them much more easily or even 'normally': getting in or out of bed unassisted, rising from chairs or toilets, shaving, washing the hair or back of the neck, opening doors with one hand, lifting a cup or book with one hand, and climbing stairs.

"The appetite often was rapidly improved. Several patients

gained weight on routine general diets. . . . Improved strength was frequently noted. Several patients stressed the loss of the 'toxicity' of the disease and experienced a marked sense of well-being. . . .

"[On discontinuance of injections] the arthritis returned slowly in most cases, and rapidly in two . . . and again improved strikingly after use of the hormone was resumed."

REICHSTEIN *

"Research on the hormones of the adrenal cortex is based on the following facts:

"*a.* The adrenals are vital organs; in nearly all animals complete bilateral adrenalectomy leads to death in a few days. Numerous post-operational insufficiency symptoms have been observed, but there is as yet no agreement as to which constitutes the primary cause of death.

"*b.* The vital function is connected with the adrenal cortex, and appears to operate principally by delivery into the blood of a mixture of substances, since by injection of suitable cortical extracts adrenalectomized animals can be kept alive and the numerous insufficiency symptoms prevented or cured.

"*c.* Investigation of active cortical extracts shows that the activity can be concentrated in those fractions which contain principally a mixture of relatively heavily oxygen-substituted steroids. A considerable number (twenty-eight in all . . .) of such steroids have been isolated as pure crystalline compounds; the structure and configuration of most of these are known in detail, while some have been prepared by partial synthesis. Some six or seven compounds have been found to be more or less active according to various methods of assay, in that they either prolong life in adrenalectomized animals or are able to prevent or cure single insufficiency symptoms. . . .

[Reichstein and Shoppee then discuss the evaluation of these methods of assay and the chemical methods of isolation of the com-

* T. Reichstein and C. W. Shoppee, "The Hormones of the Adrenal Cortex," in R. S. Harris and K. V. Thimann, eds., *Vitamins and Hormones,* Vol. 1 (New York: Academic Press, 1943).

pounds. There follows a list of the steroids isolated from the adrenal gland, with the structural formula and the physical, chemical, and biological properties of each, so far as then known. Of the twenty-eight substances mentioned, Reichstein, alone or with his associates in Basel, isolated twenty-six, and it was one of his colleagues who isolated the twenty-seventh. Many of these substances were also isolated by other scientists working independently elsewhere, many of them by Kendall and his group. This is true of the eighth substance on this list, 17-hydroxy-dehydrocorticosterone, later to be called cortisone.]

"Isolated and described as 'Compound F' by Wintersteiner and Pfiffner [1936], isolated and called 'Compound E' by Kendall *et al.* [1936], isolated and named 'Substance Fa' by Reichstein [1936], also isolated by Kuizenga and Cartland [1939]. [Then follows an account of the physical properties of cortisone, such as melting point, nature of the crystals, etc., and of the more important chemical characteristics. The constitution and configuration had by this time been worked out, chiefly by Reichstein himself.] The compound is little active in the test with dogs. . . . It also possesses only slight activity in the survival test in rats. . . . On the other hand it possesses high activity in those methods of assay which are related to carbohydrate metabolism. [Half a dozen workers] demonstrated its diabetogenic [diabetes-producing] activity . . . in rats and Grattan and Jansen its anti-insulin effect in mice. Big doses produce glycosuria [sugar in the urine] even in normal rats. As shown by Thorn *et al.*, in normal dogs it *increases* the excretion of sodium and chloride. . . ."

CONSEQUENCES IN THEORY AND PRACTICE

As stated by Kendall at the beginning of the first quotation above, the adrenal cortex long resisted all efforts to probe its secrets. "Addison's disease," a chronic insufficiency resulting from any one of several adrenal lesions but chiefly from tuberculosis, was first described by Thomas Addison in 1849. Toward the end of the century and early in the present one, a series of investigations resulted in the isolation of adrenaline, product of the adrenal

medulla; W. B. Cannon then demonstrated the "emergency function" of this hormone. But no relevance to Addison's disease was shown and efforts to obtain active extracts from the cortex were at first unsuccessful. The work of Hartman, Swingle, and Pfiffner led to the production of "cortin," which was used in the treatment of Addison patients. This was only the beginning. The extensive work of Reichstein, Kendall, and many others had by 1943 reached the point described by the former in his lengthy review, a brief excerpt from which is given above. Meanwhile the clinical observations and speculations of Hench had suggested that the cortical hormones might be of more than theoretical interest. The wartime speed-up carried the work forward, although progress was still relatively slow because of the complexity of the chemical problems involved.

In the preliminary report on the treatment of rheumatoid arthritis, Hench and his colleagues had already recorded their experience not only with cortisone but also with ACTH, or "adrenocorticotropic hormone." This is a product of the anterior lobe of the so-called "master gland," the pituitary body or hypophysis, situated at the base of the brain. (This important organ was the chief object of study of the 1947 Nobel laureate in medicine, B.A. Houssay. See above, pp. 244-248.) ACTH was found to produce effects which are in general quite similar to those of cortisone. It acts on the adrenal cortex, stimulating it to action, and the consequences are therefore indirect. While Merck and Company were busy with the production of cortisone, chemists of Armour and Company were occupied in the extraction of ACTH, following the pioneer work of Smith, Collip, and others, and likewise stimulated by wartime pressure.

It is not too much to say that a revolution in medicine was in preparation. As other scientists and clinicians took up the study of these compounds, it was found that both agents not only influenced a few relatively rare endocrine conditions, but might profoundly alter many diseases which appeared to be nonhormonal and to have no connection with the pituitary or adrenal gland. Both were shown to be antirheumatic, first in rheumatoid arthritis and then in acute rheumatic fever. Beyond this they possess marked anti-allergic activity and have limited influence on certain blood dyscrasias—

i.e., diseased states of the blood with abnormal cells. A variety of skin conditions, inflammatory diseases of the eye, intestinal diseases such as ulcerative colitis, and even respiratory infections are greatly improved by the use of these extraordinary drugs. But although the symptoms of many diseases may be partly suppressed or temporarily abolished altogether, the diseases are not "cured." In pneumonia and tuberculosis, for example, the causative organisms persist. To describe what is known of the way in which the hormones work, Dr. Hench has borrowed the Churchillian expression "a riddle wrapped in a mystery inside an enigma." Hench has also remarked that these agents do not extinguish the fire, but they provide an asbestos suit in which the patient, like Shadrach, Meshach, and Abednego, walks unscathed in the furnace. If the protection is not discarded until the end of the natural duration of the "fire" the patient remains well. This may almost be taken literally, as well as figuratively, for a severely burned patient, beyond the help of older methods, may sometimes by this means be kept alive and even reasonably comfortable until the worst danger is over.

Another comparison which has been suggested in describing the effects of these hormones is that between disease and an iceberg, each seven-eighths submerged. Cortisone or ACTH melts away the visible portion, i.e., the characteristic symptoms of a given disease which represent a specialized response to a specific form of stress; the submerged seven-eighths is left unchanged. This concept of a basic pathologic process underlying disease in general—a general response to stress as distinguished from more obvious special responses—is an attempt to explain the wide-ranging action of these hormones and their function in the organism. It is a subject to encourage speculation. More important, it encourages further careful work in clinic and laboratory, and it is probable that cortisone and ACTH will find their greatest long-term value as tools of research.

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