firmed experimentally. This and similar successes of group theory have so impressed physicists that any day now we shall hear them say, "The world is just made up of irreducible representations of groups."

Conclusion

Let me emphasize the point I have been trying to make. The mathematician's playing with the roots of equations, a play which had no practical motivations and almost no possibilities of practical application, led to the recognition of the importance of symmetry and groups. The study of theory of groups led to mathematical discoveries in geometry and differential equations, and finally to prediction of the existence of a new elementary particle. Surely a surprising outcome for the ivory-tower speculations of an impractical mathematician!

Despite my professional bias, I must acknowledge that the importance of symmetry was recognized before mathematicians invented the theory of groups. In 1794 William Blake wrote:

> Tiger, Tiger, burning bright
> In the forests of the night,
> What immortal hand or eye
> Could frame thy fearful symmetry?

However, to the mathematicians must be given the credit of recognizing that, to understand symmetry, you must study the theory of groups. I can now answer my original question, What are mathematicians doing? They are trying to make precise the intuitions of poets.

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NEWS AND COMMENT

1966 Nobel Laureates in Medicine or Physiology

Two eminent scientists, Peyton Rous and Charles Huggins, were named last week to share the 1966 Nobel prize in medicine or physiology for their work on cancer. Rous is Member Emeritus of Rockefeller University; Huggins is director of the Ben May Laboratory for Cancer Research at the University of Chicago. The following are descriptions and appreciations of their work by W. Ray Bryan and by Paul Talalay and Guy Williams-Ashman.

Charles Huggins

The ravages of cancer present medicine with one of its most difficult and challenging problems. Cancer research must be concerned not only with understanding of the nature and causes of malignant transformations but also with the development of effective measures to combat the tragic consequences of this disease in man. The award of the 1966 Nobel prize for medicine or physiology jointly to Charles Huggins and Peyton Rous honors two scientists whose investigations have revolutionized both our comprehension of the cancerous process and approaches to the treatment of human cancer, and have served to inspire many aspects of contemporary cancer research.

The Nobel prizes over the past 65 years have served as chronicles of human achievement. With the single exception of a prize given in 1926 for a rather restricted contribution to carcinogenesis, no Nobel award has been made hitherto for work on cancer, a fact which only serves to emphasize the importance of this year's Nobel prizes, and of the researches of Huggins and Rous.

Charles Huggins is director of the Ben May Laboratory for Cancer Research at the University of Chicago. Born in Halifax, Nova Scotia, in 1901, the year of the very first Nobel awards, he was educated at Acadia University, Nova Scotia, and the Harvard Medical School. Following a surgical apprenticeship under Frederick A. Coller at the University of Michigan, he became in 1927 a member of the original faculty of the School of Medicine at the University of Chicago, where he has worked and taught for 40 years. With the encouragement and guidance of his distinguished surgical chief, Dallas B. Phemister, Charles Huggins entered the field of urology, and he headed the urological division of the department of surgery for 25 years. Sent to Europe by Phemister in 1930 for training in clinical urology, Huggins spent several months in the laboratory of Sir Robert Robison at the Lister Institute. Here he became acquainted with the phosphate esters and the phosphatases, which came to play a prominent part in his later work on induction of bone formation and the treatment of prostatic cancer. In that year he also met Otto Warburg, an experience which made a strong impression on Huggins, and which later matured into a long and interesting friendship.

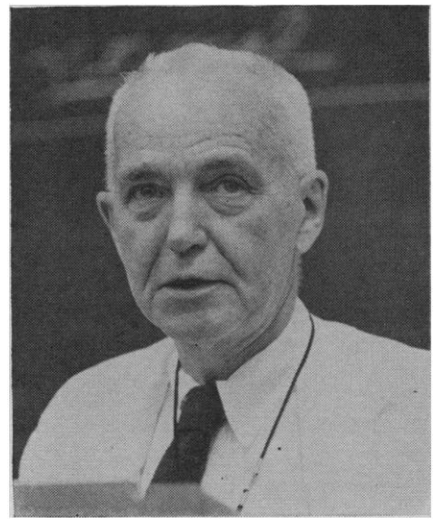
Professional identification with urology gave Huggins an opportunity to concern himself with problems in the physiology and diseases of the male genitourinary system. After several years of novel and important work on the induction, by bladder epithelium, of the transformation of connective tissue elements into bone, he turned his attention to the chemistry and hormonal control of the secretions of male accessory glands of reproduction. It was these studies that formed the basis for Huggins's work on carcinoma of the prostate which has been honored by the Nobel prize. By an ingenious surgical procedure introduced in 1939,

he isolated the prostate gland of dogs from the urinary tract, and was able thereby to study the output and biochemistry of canine prostatic secretion with quantitative methods. These experiments laid the groundwork for our present understanding of the androgenic control of prostatic growth and function, and of the remarkable inhibition of these processes by estrogenic hormones.

In a series of three papers published in 1941, Charles Huggins, in collaboration with his pupils Clarence V. Hodges and William Wallace Scott, described the effects of orchiectomy, and of the administration of androgens and estrogens, on metastatic carcinoma of the prostate in man. Huggins found that androgens can stimulate prostatic cancer, whereas castration or injection of estrogens frequently has the opposite effect. In these researches, determinations of the circulating levels of acid and alkaline phosphatases (previously shown by Alexander and Ethel Gutman to be elevated in some patients with prostatic cancer) provided an invaluable index of the status of the disease and its metastases. Huggins discovered that, by reducing the amount or activity of circulating androgenic hormones, dramatic and objective amelioration was achieved in a substantial proportion of patients with advanced cancer of the prostate. Thus there emerged a rational therapy for a previously hopeless and tragic disease, providing much benefit and relief from suffering to many elderly men, who were returned to active and useful lives, often for many years. The effectiveness of antiandrogenic treatment of prostatic cancer was soon confirmed in other clinics and adopted all over the world.

As a result of Huggins's investigations, estrogens were the first nontoxic agents of known chemical composition to be recognized as ameliorators of widespread carcinomatosis in man. The principal estrogenic substance used in treatment of carcinoma of the prostate has been diethylstibestrol, originally synthesized by Sir Charles Dodds and his colleagues in London—an inexpensive form of these hormones which is highly effective when taken by mouth.

These pioneering studies provided, over and above their remarkable clinical benefits, an immense stimulus for many subsequent developments in cancer chemotherapy. The fact that health could be restored to certain patients by modification of their hormonal status led Huggins to propose two new principles of medicine: that cancers are not always autonomous and self-perpetuating, and that they may be sustained by hormonal secretions that are apparently normal in kind and rate. This marked the birth of the concept of the hormonal dependence and responsiveness of certain cancers, which afterward was found applicable to several other tumors in man and experimental animals.



Charles Huggins

Studies on the urinary excretion of steroids in patients with prostatic cancer revealed that the levels of androgen metabolites were comparable with those observed in normal men of similar age. Following orchiectomy, the output of these steroids usually diminished to very low levels, only to undergo, in many instances, a secondary rise to higher than preoperative levels. Huggins correctly ascribed this compensatory increase to enhanced adrenocortical function, and suggested that the limited value of antiandrogenic therapy in some cases might reflect production by the adrenal cortex of sufficient quantities of growth-promoting steroids to maintain the prostatic cancers in the absence of the testes. Bilateral adrenalectomy was first performed in man by Huggins (1944) with some cursory benefit, even prior to the availability of cortisone for replacement therapy. These clinical observations proved to be decisive in his later work on carcinoma of the breast.

Antoine Lacassagne was the first to provide evidence, in an experiment described in 1932, for a causal relationship between estrogen administration and mammary tumors in mice. But even much earlier, in 1896, Sir George Beatson had reported that ovariectomy had a beneficial effect on the course of cancer of the breast in a few women. In 1951 Huggins turned his attention to the breast cancer problem. In conjunction with his pupils D. M. Bergenstal and Thomas Dao, he demonstrated that bilateral adrenalectomy could be performed with safety in the human when adequate replacement therapy with cortisone was available. It was shown that this operation, together with ovariectomy, provided a considerable measure of relief and objective improvement in some 30 to 40 percent of patients with advanced metastatic cancer of the mammary gland. In some instances the beneficial effects of adrenalectomy were both prolonged and profound. Once again, development of these procedures stemmed from theoretical and laboratory considerations which were clear to Huggins at a much earlier date.

Over the last decade, Huggins has again moved from the clinic to the laboratory, becoming deeply involved with experimental models for human mammary cancers. The long delay involved in the induction of many mammary tumors in animals, and the relative insusceptibility of these neoplasms to hormonal influences, thwarted many early investigations on experimental mammary cancer. Following a lead provided by the late Harry Shay of Philadelphia, Huggins found that single doses of certain polycyclic aromatic hydrocarbons, notably 7,12-dimethylbenz(a)anthracene (DMBA), constantly and speedily induce mammary tumors in selected strains of female rats. Many of these tumors, like some of their counterparts in humans, are hormone-dependent. Such tumors grow or shrivel in response to alterations in the endocrine status of the hosts. A by-product of these studies was the important finding that DMBA rather specifically causes massive hemorrhagic necrosis of the adrenals in rats. The Huggins rat mammary tumors are currently the object of intensive experimentation in many different laboratories.

Only one other surgeon—Emil Theodor Kocher—has ever received a Nobel prize (1909). Huggins, throughout his

life's work, has demonstrated a unique ability to practice the art of discovery both at the bedside and in the laboratory. Besides his numerous contributions in the field of hormone-dependent tumors, Huggins has made many notable discoveries in chemical physiology. These include pioneer studies on the chemistry and function of substances in seminal plasma, the introduction of chromogenic substrates for determination of a variety of hydrolytic enzymes, and the delineation (together with E. V. Jensen) of sulfhydryl-disulfide interchange reactions in proteins.

Charles Huggins married Margaret Wellman in 1927. They have a son and a daughter, and six grandchildren. A man of wide culture and simple habits, Huggins is devoted to his family and to Mozart and Bach. The extraordinary breadth of his scientific interests and achievements, his great courage in the clinic and at the laboratory bench, and his utter dedication to the cancer problem have excited world-wide admiration. The award of a Nobel prize to one who has done so much for the human cancer patient is richly deserved.

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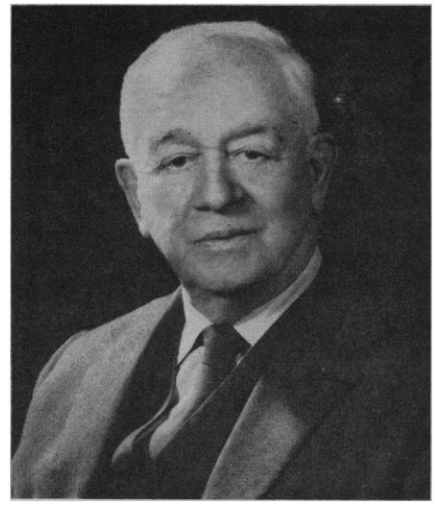
Peyton Rous

The award of the Nobel prize for medicine to Peyton Rous crowns a career of almost 60 years as outstanding pioneer investigator, intellectual leader, and leading statesman in cancer research. Rous's outstanding potential was recognized by Simon Flexner, who lured him to the Rockefeller Institute (now Rockefeller University) at the time of his search for great future talent. At the threshold of his research career, back in 1909, Rous initiated studies of a tumor on the breast of a domestic chicken which a local farmer had brought to this famed institute for medical research. Peyton Rous succeeded in establishing a serially transplantable tumor in closely related fowls from the same flock, which the farmer had enthusiastically supplied. Transplants to more distant relatives, or to fowls from another flock of the same breed, failed to grow. This success, reported in 1910, represented a notable achievement for its time, since only a few cancer investigators throughout the world had succeeded in transplanting



Peyton Rous

tumors of any animal species. Rous's success demonstrated the importance of genetic factors and led to the introduction of genetic homogeneity of experimental animals into research on the transplantation of cancer and other tissues.

A year later, in 1911, he successfully transmitted his malignant tumor (a sarcoma that now bears his name) to other related chickens by means of cell-free filtrates, demonstrating for the first time that a virus was etiologically related to a malignant tumor. Leukemia of domestic fowls had previously been shown to be caused by a virus, but avian leukemia was then looked upon as an infectious disease, not as a disease belonging in the category of cancer.

A brief wave of expectancy that the cause of cancer had been discovered by Rous gave way to disparagement, and then ostracism of the viral approach to cancer, when the technique used by him failed to bring to light any virus associated with any mammalian cancer. The Rous sarcoma, as well as other chicken tumors that had been found also to be associated with viral etiological agents, came to be looked upon as extreme viral hyperplasias differing fundamentally from "true" cancers of mammals and having no relevance to the human cancer problem. During the several decades which elapsed before the Rous sarcoma gradually regained acceptance as a tumor in the category of cancer, Rous and his associates introduced new techniques which were to pave the way for further development of the burgeoning scientific discipline of virology. Among the most notable of these were the propagation of virus on chorioallantoic membranes of embryonated eggs and the dispersion of tissue cells for uniform quantitative suspension by trypsinization. They also made many outstanding contributions which established not only the Rous sarcoma as a "true" neoplasm but also a virus-caused benign lesion of rabbits, Shope papilloma, which, they discovered, progresses to malignant cancer. The ability of carcinogenic chemicals to hasten the transition to cancer and to activate quiescent subclinical infections by the benign papilloma virus was also demonstrated.

During these trying years, when few laboratories were engaged in cancer-virus research and most scientists in the cancer field considered viruses to be of importance only in certain exceptional cases, Peyton Rous kept the viral approach alive and attracted many new workers to the field by his insight into the problem and his numerous logical analytical discussions presented at scientific meetings and published in leading journals.

Rous and other early workers who attempted to carry out systematic studies of the Rous sarcoma virus faced many difficulties. Infectious virus was not always recoverable from transplanted or virus-induced tumors, and would sometimes "disappear" for several transplant generations before "reappearing" without explanation. Many of the experiments were therefore failures, due to the absence of infectious virus in the starting material. Virus sent to various laboratories throughout the world and maintained at these different locations failed to give comparable results in similar experiments, and experiments were sometimes not reproducible even in the same laboratory. Years later, several strains of the virus maintained in different locations proved to differ even in antigenicity, raising the question whether the original virus of Rous had been lost and other viruses of different antigenicity, coming from spontaneous tumors appearing by chance in the transmission experiments, had taken its place.

The work of numerous investigators has contributed to the reproducibility of experiments with the Rous sarcoma virus and to an understanding of the reasons for the former difficulties and dilemmas.

Host responses to this RNA tumor virus were shown to be dose-dependent and to vary all the way from extremely malignant virus-disseminated

systemic disease, through non-virus-producing and metastasizing cancerous lesions of the classical type, to regressing near-neoplastic lesions and (with the help of an adjuvant at subliminal doses) immunoproliferative reactions. Work which contributed to reproducibility had inadvertently selected for what proved to be a more rapidly acting "helper" virus, with which astute investigators were able to show that the Rous sarcoma virus genome is itself defective, and entirely dependent upon the genome of a "helper" for maturation to infectious form. It was found that any of the avian leukemia viruses could act as a "helper" and that the outer protective envelope of the defective sarcoma virus took on the properties of the "helper" agent. This accounted for the deviations in antigenicity encountered by chance in earlier investigations and made possible the fabrication in the laboratory of "pseudotype" strains of Rous sarcoma virus with predetermined antigenic specificity. The protein envelope was found also to determine the infectivity of the virus for specific genetic types of chickens. Moreover, helper-coded envelopes have been picked up by chance, as well as introduced in the laboratory, which enable the Rous sarcoma virus to cross species and induce malignant sarcomas in mammals, including monkeys.

The new insight into virus-host interactions, particularly the two-hit kinetics associated with the requirement of dual infection by related avian RNA viruses for the induction of virus-producing tumors, has brought new approaches to cancer-virus research and the search for similar viruses in other animal systems, including man. Already the story is repeating itself in viral-induced murine leukemias and sarcomas, once they had been brought to light by the use of immunologically tolerant test animals.

The virus discovered in 1911 still leads the way in research on the RNA tumor viruses. For his initial discovery and numerous fundamental contributions to the understanding of viral carcinogenesis, Peyton Rous has received six previous outstanding awards, including the National Medal of Science presented by President Johnson, and honorary doctoral degrees from seven leading universities throughout the world.

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British Medicine: (I) Doctors Carry On but Show New Militancy

London. The current pay freeze in Britain, instituted by the government to curb inflation and improve the balance of payments, has had anything but a cooling effect on the tempers of junior hospital medical staff. Unrest has been expressed most overtly so far in a rising rate of emigration, particularly among doctors in the hospital service. To the British, this loss of expensively trained medical manpower is a particularly galling aspect of the brain drain.

Britain's junior hospital doctors are the counterparts of interns and residents in the United States. And there are striking transatlantic similarities in complaints about long hours, excessive patient loads, low pay, inadequate supervision by seniors, and haphazard training programs in many hospitals. As in the United States, hospital service in Britain has come to depend on foreign-trained doctors. In Britain a lot of these foreign-trained physicians are from less-developed Commonwealth countries. Many of these doctors never go home, and, in terms of manpower, for both the U.S. and Britain it is a case of robbing the poor to care for the rich.

There are, however, very significant differences between the hospital service in Britain and in the U.S. Existence of the National Health Service in Britain accounts, of course, for some of these differences, but the systems of postgraduate medical education in the two countries are distinct variants.

Discontent among junior hospital medical staff members in Britain was brought to a head by postponement of a raise granted them after negotiations last spring. The increase was due to start 1 April, but some points were still being negotiated in July when the government issued its pay "standstill" order. Because the raise had not actually gone into effect, the first payment at the new scale for the hospital doctors was deferred to 31 December. A few weeks ago the government announced that on that date the doctors would also get, retroactively, their increase for 3 months. The reaction of the young doctors, however, has generally been to regard government officials as Indian givers.

While pay was the precipitant, everyone involved in the case of the hospital doctors makes it clear that the trouble runs much deeper, involving the structure of British medicine and a history of underinvestment in medical services which goes back much farther than the two decades of the National Health Service's life.

The problem can only be discussed, however, in the context of the NHS. The government owns and operates the hospitals and employs all doctors who work in them. These doctors fall into two main categories: consultants (specialists) and junior medical staff. The juniors are divided into two groups, house officers and registrars, with each of these groups in turn divided into junior and senior grades. The housemen are roughly equivalent to American interns, and the registrars, to residents. All British medical school graduates spend at least two 6-month terms as junior house officers before they can be certified to practice, and most, including those going into general practice, serve in three or four of the 6-month posts.

The process of specialization in Britain differs sharply from that in the United States. In the U.S. the would-be specialist seeks appointment as a resident on a hospital staff and works under the direction of a chief of service. Posts are created according to the resources of the particular hospital or medical center and the wishes of the senior medical staff. After prescribed periods of service, candidates take examinations set by appropriate specialty boards. The successful examinee is free to set up in practice as a specialist.