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Nobel Prize in Medicines 1950



Edward Calvin Kendall **Tadeus Reichstein** **Philip Showalter Hench**

The Nobel Prize in Physiology or Medicine 1950 was awarded jointly to Edward Calvin Kendall, Tadeus Reichstein and Philip Showalter Hench "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects"

In the year 1563 the Italian anatomist, Eustachi, described how, at the upper poles of the kidneys in man, he had found two gland-like organs, which had been overlooked up to that time, but are now known as the adrenals. Somewhat later, central cavities filled with fluid were observed in them. Nothing was known about the function of these bodies for a long time, and, with the then limited development of the methods of experimental medicine, it was to be about three centuries before any clarity was reached. It marked no great advance when in 1716 the Bordeaux Academy of Science announced the prize subject: «What is the importance of the adrenals?» None of the papers sent in, which gave evidence rather of lively imagination than of scientific criticism, found favour in the eyes of the prizeawarding judge, the later so famous philosopher Montesquieu, who remarked: «Perhaps chance will at some time give us what all our efforts have not been able to achieve.»

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As late as in 1854 the German anatomist, Kölliker, was able to claim in a review of the subject that although the function of the adrenals was still unknown, yet in certain respects great advances had been made. For instance, they had been found in various groups of animals - actually they are met with throughout the whole series of vertebrates - and their more detailed structure had been elucidated. Two quite different parts were now distinguished, an outer part, a fairly firm cortex, and an inner, softer medulla, which in man readily disintegrates and is then the source of the fluid which had been observed earlier. Kölliker classified the adrenal cortices as ductless glands, which we now call the endocrine organs, assuming some co-operation with the nervous system for the medulla.

But now at last the «chance» of which Montesquieu had spoken was to present itself; all that was needed was a research worker who could seize the opportunity when it did present itself and understand its implication. Thomas Addison, the English doctor, observed a rare disease with a fatal course, which was characterized chiefly by anemia, general weakness and fatigue, disturbances in the digestive apparatus, enfeebled heart activity and a peculiar dark pigmentation of the skin. He was able to show that this morbid picture made its appearance in persons the greater part of whose adrenals was destroyed. Addison's work, characterized by himself as «a first and feeble step» which «doubtless both the physiologist and anatomist will be inclined to welcome and regard with indulgence», was published in 1855 and constitutes one of the basic contributions to our knowledge of the internal secretion in general and to the part played by the adrenals in particular.

In its turn it led to comprehensive experiments on animals, from which it emerged that removal of the adrenals led to speedy death, the symptoms recalling those known from Addison's disease.

The next step in the course of development was that attempts were made to obtain from the adrenals that active substance whose absence might be assumed to lead to the grave symptoms referred to. In 1894 Oliver and Schäfer proved that the injection of a watery extract from the adrenals had extremely pronounced effects. Within a few years adrenaline had been produced from the extract, its composition had been ascertained, and

its artificial production accomplished. The more detailed analysis showed effects of the same kind as those resulting on increased activity of the so-called sympathetic nervous system, which innervates internal organs such as the heart and vessels, the intestinal canal, etc. Since the adrenaline is produced by the medulla, there was thus a connection between this part and the nervous system, even though of a different nature from that apprehended by Kölliker. However, attempts to prevent by means of adrenaline the deficiency symptoms following on the removal of the adrenals failed completely. The explanation of this was given when Biedl and others showed that it is the cortex which is of vital importance, not the medulla. Thus the two parts are also different in respect of their functions in the body. It may be said that the medulla and cortex constitute independent bodies, which as a rule are combined in one organ.

Towards the end of the 1920's and the beginning of the 1930's, several American research groups announced that they had been successful in producing from the cortex a more or less pure extract, which when injected proved to prolong the life of animals from which the adrenals had been removed, and also had a favourable effect on patients suffering from Addison's disease. As long as efforts were confined chiefly to soaking out the active factor, or the cortin as it was called, with water, the results obtained were uneven and none too convincing. The demonstration of the fact that the active principle also passes into many organic solvents, such as alcohol, ether, benzene, etc., guided Swingle and Pfiffner to a method for producing the cortin, which yielded a product by means of which the experimental animals could easily be kept alive for months. With that the foundation was laid for further research, and it now seemed possible to produce the cortin in pure form and establish its nature.

The isolation of the cortin proved to be a difficult task, calling for the combined efforts of a number of research workers. Particularly important contributions were made in this field by Wintersteiner and Pfiffner, and also by Edward Kendall at the Mayo Clinic in Rochester, and Tadeus Reichstein in Basel, and their co-workers. As early as in 1934, Kendall and his group succeeded in preparing from cortex extract what was at first

assumed to be pure cortin in crystalline form. They found that it contained carbon, hydrogen, and oxygen, and indicated its empirical formula. But that was only a beginning. There was as yet no reason to suspect that the cortin was not homogeneous; further experiments proved clearly, however, that it was not. In reality Kendall and his co-workers had produced a mixture of different substances closely related to one another, and their work represents the early steps in the crystallization of a whole series of cortin substances. Even within the immediately succeeding years the number found totalled about twenty, and at the present time nearly thirty are known. The task of distinguishing between these chemically very closely related substances has been associated with immense difficulties, as they are found in the cortex in extremely small quantities and readily form mixed crystals. At least six of the substances have proved to have a more or less active effect on animals whose adrenals have been removed. Half of these were first isolated by Reichstein, closely followed by Kendall, the latter coming in first in the race to find a fourth. Still one more was first produced by Reichstein by a semisynthetic method from a derivative of bile acid and thus being readily available, it has been a valuable remedy in cases of Addison's disease and certain other cases of reduced function of the cortex. The latter was proved by Reichstein in the adrenal cortex also. There remains at least one active cortical substance - the best known of them all, first named Compound E and now called cortisone or cortone - which was isolated at four different laboratories, among them Kendall's and Reichstein's. The remaining inactive substances with very similar structures will probably be preliminary stages or conversion products of the active ones.

Side by side with the production in pure form of the cortin substances, their chemical structures were elucidated. Reichstein was able to convert one of them into a substance which biological tests proved to possess effects of the same nature as those of the male sex hormone, and he also established chemically the resemblance in structure to the latter. This acquires a special interest in view of numerous observations which showed that the cortex of the adrenals can materially affect the sex characters. Among other things it was known that the cortex is enlarged during pregnancy, and that tumours there can give

rise to abnormally early sexual development and a reversal to some extent of such development. As all the cortin substances are closely related to one another, Reichstein's finding implies that, like the sex hormones, they belong to the large and important group of steroids. The D vitamins and the bile acids, like our most important heart remedies, the active substances in Digitalis leaves and Strophanthus seeds, are also intimately associated with the steroids.

The six definitely active cortical hormones are characterized, inter alia, by a double bond in the steroid skeleton; if this double bond disappears, inactive substances are obtained. They differ very inconsiderably from each other chemically. They are built up of 21 carbon atoms, but the number of oxygen atoms in the molecule is three, four, or five. The position of the additional oxygen atoms in the molecule was first established by Reichstein and Kendall, and thus a way was opened for semisynthetic production e.g. from the more easily obtainable bile acids or material from a certain species of Strophanthus. This is of particular importance, since the yield from the adrenals is very poor, at most about 1:1,000,000.

It had gradually been realized that, in cases of Addison's disease, a number of symptoms make their appearance in addition to those which were known from the classic description, and corresponding changes had also been proved in animals after the adrenals had been removed. The most serious disturbances affect the metabolism and the function of the kidneys. The former manifest themselves in, inter alia, a reduced conversion of protein into sugar, and resultant difficulties in the storing of sugar, in the form of the starch-like glycogen, in the liver and muscles, in addition to which the sugar content of the blood may be reduced. Generally the combustion processes decline, muscular work is less satisfactorily performed, and the body temperature is apt to fall. The disturbances in the kidneys manifest themselves in the retention in the body of the nitrogenous waste products and also the potassium salts, while common salt is excreted in increased amounts. In this way the salt and fluid balance is disturbed. The more profound knowledge of the deficiency symptoms in the case of decreased internal secretion from the adrenals raised

the question whether the different active cortical steroids have the same effect. Not least thanks to the work of Kendall and his school, it has emerged that the comparatively inconsiderable dissimilarities in the matter of the structure of the cortical hormones are accompanied by material differences in respect of the effect. Thus some act especially strongly on the metabolism of sugar, others on the salt and fluid balances, and there are also several other differences. This was illustrated when Compound E was first tested. Pfiffner and Wintersteiner, like the Reichstein group, found that the substance had no, or extremely inconsiderable, life-prolonging effects on animals deprived of the adrenals. On the other hand, Ingle, Kendall's coworker, observed that it stimulated the muscular work of such animals very strongly.

With regard to the practical test of the cortical steroids on sick people it was of great importance that, for military purposes, large-scale experiments should be started in U.S.A. to produce some of them artificially from simpler compounds. In that connection the greatest interest attaches to Compound E, the structure of which was definitely known, thanks to Reichstein and Kendall. Many steps in the synthesis were extremely difficult, and in respect of a couple of them Kendall and his co-workers showed the way. Further, a distinguished contribution was also made by Sarett.

The testing which was now initiated was directed in the first place on chronic rheumatoid arthritis, and this was not a matter of chance. For a couple of decades, Philip Hench, now at the Mayo Clinic, had been studying the improvements in chronic troubles in the joints which made their appearance during pregnancy or in cases of jaundice. He conceived the possibility of some common factor in that connection and apprehended the morbid disturbances as an expression of changes in metabolism and not, as had been widely assumed earlier, as a result of infection. During pregnancy increased amounts of sex hormones are given off, while in jaundice the bile acids are retained in the body. As there is a relationship between the latter and the cortin substances, it appeared probable to him that the morbid changes might be connected with disturbances in the function of the adrenals. A similar line of thought had also been developed by Selye. In conjunction with

Kendall, Hench began to treat cases of chronic rheumatoid arthritis with cortin, but without success. Thus, when cortisone became available, it was natural that they should try their fortunes again. In the April of 1949, Hench, Kendall, Slocumb and Polley published their experiences in respect of the dramatic effects of cortisone in cases of chronic rheumatoid arthritis. A rapid improvement set in, pains and tenderness in the joints abated or disappeared, mobility increased, so that patients who had previously been complete invalids could walk about freely, and their general condition was also favourably affected. Similar results were obtained with a preparation from the anterior lobe of the pituitary, the so-called ACTH (Adreno-Cortico-Tropic Hormone), which, as the name indicates, stimulates the adrenal cortex to increased activity. Unfortunately if the improvement is to last, further supplies of the remedy are necessary, and during the process more or less serious secondary effects in the form of fullness of the face, the growth of hair on the face in women, nervous symptoms, etc., often develop in consequence of disturbances in the endocrine balance. Cortisone also has a good effect in cases of acute rheumatic fever, and this applies as well to some other illnesses, probably also to burns.

The reliability of the Mayo School's results has been confirmed from many quarters in the world. Even if it is still too early to judge what role cortisone and ACTH may play in the future as a remedy for cases of rheumatoid arthritis, it is already beyond all doubt that our knowledge of the nature of these illnesses and of the role of the cortical hormones has been materially advanced by the results of Hench and his co-workers. Perhaps we are even on the verge of a new epoch in the treatment of one of the groups of diseases which, from the social point of view, are among the most important and the most difficult to cure.

The value of a discovery lies not only in the immediate practical results, but equally much in the fact that it points out new lines of research. This is strikingly illustrated by the research during the last few decades into the cortical hormones, which has already led to unexpected and important new results within widely different spheres.

Dr. Hench, Professor Kendall, and Professor Reichstein. The Caroline Institute has decided to award this year's Nobel Prize in Physiology or Medicine to you jointly, for your

discoveries regarding the hormones of the adrenal cortex, their structure, and biological effects.

Your work is a splendid example of close co-operation between representatives for physiology, biochemistry, and clinical medicine, as well as between scientists belonging to different countries. Once again it emphasizes the international character of scientific research.

Professor Edward Kendall. You and your collaborators have greatly contributed to the isolation and identification of the cortical hormones, and you have facilitated the artificial production of some of these substances. You have shown conclusively that their biological actions differ all according to their chemical structure. By your work you have very considerably increased our knowledge in this field and also stimulated and enabled the practical application of the new discoveries.

Professor Tadeus Reichstein. To you and your co-workers we owe the first isolation of four active hormones from the adrenal cortex, the first synthesis of one of them, the proof of the steroid nature of said hormones, and numerous details on the structure and properties of these important bodies. In this way the wearisome road to synthesis was smoothed, and new medicaments created. Your discoveries in this field are of fundamental importance.

Doctor Philip Hench. Your brilliant investigations in respect of the beneficial effects of pregnancy and jaundice on rheumatoid arthritis have been the starting-point for the famous discovery during «the preceding year» that these diseases and some others are favourably influenced by hormones from the adrenal cortex. Thereby new therapeutic possibilities have been opened up, and a deeper insight into the nature of these conditions and the role of the adrenal cortex has been gained.

Gentlemen. It is well known that Alfred Nobel felt a personal interest in the study of the processes going on in the body in health and disease, as well as in the practical methods of healing. These two sides of medical research are intimately linked together in the discoveries that are honoured by this year's award.

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On behalf of the Caroline Institute I proffer you the hearty congratulations of your colleagues, and I express the hope that you will be able successfully to continue your work which has already resulted in such outstanding achievements.

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http://www.nobelprize.org/nobel_prizes/medicine/laureates/1950/press.html