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Nobel Prize in Medicines 1945

Sir Alexander Fleming

Ernst Boris Chain

Sir Howard Walter Florey

The Nobel Prize in Physiology or Medicine 1945 was awarded jointly to Sir Alexander Fleming, Ernst Boris Chain and Sir Howard Walter Florey "for the discovery of penicillin and its curative effect in various infectious diseases"

Attempts have been made to reach the goal of medical art - the prevention and cure of disease - by many different paths. New and reliable ones have become practicable as our knowledge of the nature of the different diseases has widened. Thus the successful combating of certain disturbances in the activities of the organs of internal secretion, as also of the deficiency diseases, or avitaminoses, has been a direct result of the increase in our knowledge of the nature of these afflictions. When, thanks to the research work of Louis Pasteur and Robert Koch, the nature of the infectious diseases was laid bare, and the connection between them and the invasion of the body by bacteria and other micro-organisms was elucidated, fully a generation ago, this was an enormous advance, both for the prevention and the treatment of this important group of diseases. This was so much the more important as the group included a number of the worst scourges of humanity, which had slain whole peoples, and at times had laid waste wide areas. But now possibilities were revealed which have not yet been by any means fully utilized. In rapid succession, different forms of vaccination were evolved, and subsequently also serum treatment, for the introduction of which the first Nobel Prize for Physiology or Medicine was given 44 years ago today. In these cases advantage was taken of the capacity of the human and animal bodies themselves to produce protective substances in the fight against the invaders, and to do so in great abundance. But it is by no means the higher organisms only that are able to produce such substances. In cooperation with Joubert (1877), Pasteur himself observed that anthrax bacilli cultivated outside the body were destroyed if bacteria from the air were admitted, and with prophetic acumen he realized that it was justifiable to attach great hopes to this observation in the treatment of infectious diseases. Nevertheless more than two decades passed before an attempt was made to profit by the struggle for existence which goes on between different species of micro-organisms. Experiments carried out by Emmerich and Loew (1899) did not give such favourable results, however, that any great interest was aroused, nor did success attend the later efforts of Gratia and Dath and others. It was reserved to this year's Nobel Prize winners to realize Pasteur's idea.

The observation made by Professor Alexander Fleming which led to the discovery of penicillin, is now almost classical. In 1928, in the course of experiments with pyogenic bacteria of the staphylococcus group, he noticed that, around a spot of mould which had chanced to contaminate one of his cultures, the colonies of bacteria had been killed and had dissolved away

Fleming had earlier made a study of different substances which prevent the growth of bacteria and, inter alia, had come upon one in lacrimal fluid and saliva, the so-called lysozyme. As he points out himself, he was therefore always on the look-out for fresh substances which checked bacteria, and he became sufficiently interested in his latest find to make a closer investigation of the phenomenon. The mould was therefore cultivated and subsequently transferred to broth, where it grew on the surface in the form of a felted green mass. When the latter was filtered off a week later, it was found that the broth had such a strongly checking effect on bacteria that even when diluted 500-800 times it completely prevented the growth of staphylococci; consequently an extremely active substance had passed to the broth from the mould. This proved to belong to the Penicillium group or brush moulds, and therefore first the broth, and later the substance itself, was called «penicillin». It was soon realized that most of the species of Penicillium did not form it at all, and a closer scrutiny showed that the species which polluted Fleming's culture was Penicillium notatum. It had been described for the first time by Richard Westling, in the thesis which he defended in the autumn of 1911 at the University of Stockholm for the degree of Doctor of Philosophy - an illustration of the international nature of science, but also of the suddenly increased importance which sometimes accrues to sound work as a result of further developments. Fleming also showed that penicillin was extremely effective against cultures of many different kinds of bacteria, above all against those belonging to the coccus group, among them those that usually give rise to suppuration, pneumonia and cerebral meningitis, but also against certain other types, such as diphtheria, anthrax, and gas gangrene bacteria. But as numerous other species, among them the influenza, coli, typhoid and tuberculosis bacilli, grew even if they were exposed to moderate quantities of penicillin, Fleming was able to work out a method for isolating out from a mixture of bacteria those which were insensitive to penicillin. He found, further, that the white blood corpuscles, which are usually so sensitive, were not affected by penicillin. When injected into mice, too, it was fairly harmless. In this respect penicillin differs decisively from other substances which had been produced earlier from micro-organisms, and which were certainly found to be noxious to bacteria, but at the same time at least equally noxious to the cells of the higher animals. The possibility that penicillin might be used as a remedy was therefore within reach, and Fleming tested its effect on infected wounds, in some cases with moderate success.

Three years after Fleming's discovery, the English biochemists Clutterbuck, Lovell, and Raistrick, endeavoured to obtain penicillin in the pure form, but without success. They

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established, inter alia, that it was a sensitive substance which easily lost its antibacterial effect during the purifying process, and this was soon confirmed in other quarters.

Penicillin would undoubtedly still have remained a fairly unknown substance, interesting to the bacteriologist but of no great practical importance, if it had not been taken up at the Pathological Institute at the venerable University of Oxford. This time a start was again made from what is usually called basic research. Professor Howard Florey, who devoted his attention to the body's own natural protective powers against infectious diseases, together with his co-workers, had studied the lysozyme referred to above, the nature of which they succeeded in elucidating. Dr. Ernst Boris Chain, a chemist, took part in the final stage of these investigations, and during 1938 the two researchers jointly decided to investigate other antibacterial substances which are formed by micro-organisms, and in that connection they fortunately thought first of penicillin. It was certainly obvious that the preparation of the substance in a pure form must involve great difficulties, but on the other hand its powerful effect against many bacteria gave some promise of success. The work was planned by Chain and Florey, who, however, owing to the vastness of the task, associated with themselves a number of enthusiastic co-workers, among whom mention should be made especially of Abraham, Fletcher, Gardner, Heatley, Jennings, Orr-Ewing, Sanders and Lady Florey. Heatley worked out a convenient method of determining the relative strength of a fluid with a penicillin content, by means of a comparison under standard conditions of its antibacterial effect with that of a penicillin solution prepared at the laboratory. The amount of penicillin found in one cc. of the latter was called an Oxford unit.

In the purifying experiments then made, the mould was cultivated in a special nutritive fluid in vessels, to which air could only gain access after it had been filtered through cotton wool. After about a week the penicillin content reached its highest value, and extraction followed. In this connection advantage was taken of the observation that the free penicillin is an acid which is more easily dissolved in certain organic solvents than in water, while its salts with alkali are more readily dissolved in water. The culture fluid was therefore shaken with acidified ether or amyl acetate. As, however, the penicillin was easily broken up in water solution, the operation was performed at a low temperature. Thus the penicillin could be returned to the water solution after the degree of acidity had been reduced to almost neutral reaction. In this way numerous impurities could be removed, and after the solution had been evaporated at a low temperature it was possible to obtain a stable dry preparation. The strength of this was up to 40-50 units per mg and it prevented the growth of staphylococci in a dilution of at least 1 per 1 million - thus the active substance had been successfully concentrated very considerably. It was therefore quite reasonable that it was thought that almost pure penicillin had been obtained - in a similar manner, in their work with strongly biologically active substances, many earlier researchers had thought that they were near to producing the pure substance. The further experiments, which were made subsequently with the help of the magnificent resources of modern biochemistry proved, however, that such was not the case. In reality the preparation just mentioned contained only a small percentage of penicillin. Now when it has become possible to produce pure penicillin in a crystalline form, it has been found that one mg contains about 1,650 Oxford units. It is also known that penicillin is met with in some different forms, which possibly have somewhat different effects. The chemical composition of penicillin has also been elucidated in recent years, and in this work Chain and Abraham have successfully taken part.

The Oxford school was able to confirm Fleming's observation that penicillin was only slightly toxic, and they found that its effect was not weakened to any extent worth mentioning in the presence of blood or pus. It is readily destroyed in the digestive apparatus, but after injection under the skin or into the muscles, it is quickly absorbed into the body, to be rapidly excreted again by way of the kidneys. If it is to have an effect on sick persons or animals, it should therefore be supplied uninterruptedly or by means of closely repeated injections - some more recent experiments indicate that gradually perhaps it will be possible to overcome the difficulties in connection with taking the preparation by mouth. Experiments on mice infected with large doses of pyogenic or gas gangrene bacteria, which are sensitive to penicillin, proved convincingly that it had a favourable effect. While over 90% of the animals treated with penicillin recovered, all the untreated control animals died.

Experiments on animals play an immense role for modern medicine; indeed it would certainly be catastrophic if we ventured to test remedies on healthy or sick persons, without having first convinced ourselves by experiments on animals that the toxic effect is not too great, and that at the same time there is reason to anticipate a beneficial result. Tests on human beings may, however, involve many disappointments, even if the results of experiments on animals appear to be clear. At first this seemed to be the case with penicillin, in that the preparation gave rise to fever. Fortunately this was only due to an impurity, and with better preparations it has subsequently been possible to avoid this unpleasant effect.

The first experiments in which penicillin was given to sick persons were published in August 1941 and appeared promising, but owing to the insufficient supplies of the drug, the treatment in some cases had to be discontinued prematurely. However, Florey succeeded in arousing the interest of the authorities in the United States in the new substance, and with the cooperation of numerous research workers it was soon possible, by means of intensive work, to obtain materially improved results there and to carry on the preparation in pure form to the crystallization stage just mentioned. Large quantities of penicillin could be made available, and numerous tests were made above all in the field, but to a certain extent also in the treatment of civilians. Many cases were reported of patients who had been considered doomed or had suffered from illness for a long period without improvement, although all the resources of modern medicine had been tried, but in which the penicillin treatment had led to recoveries which not infrequently seemed miraculous. Naturally such testimony from experienced doctors must not be underestimated, but on the other hand we must bear in mind the great difficulties in judging the course of a disease. «Experience is deceptive, judgment difficult», is one of Hippocrates' famous aphorisms. Therefore it is important that a remedy should be tested on a large material and in such a way that comparison can be made with cases which have not been given the remedy but had otherwise received exactly the same treatment. There are now many reports of such investigations. The extraordinarily good effects of penicillin have been established in a number of important infectious illnesses, such as general blood poisoning, cerebral meningitis, gas gangrene, pneumonia, syphilis, gonorrhea and many others. It is of special importance that even sick persons who are not favourably affected by the modern sulfa drugs are not infrequently cured with penicillin. The effect naturally depends on the remedy being given in a suitable manner and in sufficient doses. On the other hand, experience has confirmed what might have been surmised, namely that penicillin is not effective in cases of, e.g. tuberculosis, typhoid fever, poliomyelitis, and a number of other infectious diseases. Consequently penicillin is not a universal remedy, but it is of the highest value for certain diseases. And it appears not improbable that, with the guidance of experience with penicillin, it will be possible to produce new remedies which can compete with or perhaps surpass it in certain respects.

Four years is a short time in which to arrive at definite conclusions as to the value of a remedy. But during these last few years experiences of penicillin have been assembled which, under ordinary conditions, would have required decades. And therefore there is no doubt at the present time that the discovery of penicillin and its curative properties in the case of various infection diseases for which this year's Nobel Prize is awarded, is of the greatest importance for medical science.

Sir Alexander Fleming, Doctor Chain, and Sir Howard Florey. The story of penicillin is well-known throughout the world. It affords a splendid example of different scientific methods cooperating for a great common purpose. Once again it has shown us the fundamental importance of basic research. The starting-point was a purely academic investigation, which led to a so-called accidental observation. This gave the nucleus, around which one of the most efficient remedies ever known could be crystallized. This difficult process was made possible with the aid of modern biochemistry, bacteriology, and clinical research. To overcome the numerous obstacles, all this work demanded not only assistance from many different quarters, but also an unusual amount of scientific enthusiasm, and a firm belief in an idea. In a time when annihilation and destruction through the inventions of man have been greater than ever before in history, the introduction of penicillin is a brilliant demonstration that human genius is just as well able to save life and combat disease.

In the name of the Caroline Institute I extend to you hearty congratulations on one of the most valuable contributions to modern medicine. And now I have the honour of calling on you to accept the Nobel Prize for Physiology or Medicine for the year 1945 from the hands of His Majesty the King.

For more details please visit:

http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/press.html