

Nobel Prize in Medicines 1934



George Hoyt Whipple



George Richards Minot



William Parry Murphy

The Nobel Prize in Physiology or Medicine 1934 was awarded jointly to George Hoyt Whipple, George Richards Minot and William Parry Murphy "for their discoveries concerning liver therapy in cases of anaemia".

The Caroline Institute has awarded this year's prize for Physiology or Medicine to three American investigators, viz. Professor George Minot, of the Harvard Medical School (Boston), Dr. William Murphy, of the same College, and Professor George Whipple, of the School of Medicine (Rochester, New York), in recognition of their discoveries respecting liver therapy in anaemias. By anaemias is to be understood diseases in which the patient is anaemic. The medical man, in speaking of anaemia and anaemic, has not in mind the actual quantity of the blood, which is not easily determinable by simple methods, but rather certain shortcomings in the composition of the blood that allow of being readily established in his routine investigations, in the first place a diminution in the number of the red blood corpuscles per unit-volume of blood, and a diminution of the concentration in the blood of the haemoglobin, i.e. of the red pigment that gives the blood its colour, a diminution consequently in the colour-strength of the blood. In a word, the blood has become diluted

Of the three prize-winners, it was Whipple who first occupied himself with the investigations for which the prize has now been awarded. He began in 1920 to study the influence of food on blood regeneration, the re-building-up of the blood, in cases of anaemia consequent upon loss of blood. For the fact is that anaemia in the sense just mentioned also arises as a consequence of a loss of blood. The diminution in the quantity of the blood is made up for, comparatively quickly, by an influx of water from the tissues, that is to say by a process of dilution, of which the consequence is a reduction in the number of the red blood corpuscles and the haemoglobin per unit of volume - thus a case of anaemia. That being so, Whipple started to study the effect that various food substances might have on the process of the regeneration of the blood. It was known beforehand, it is true, that a plentiful supply of food is an important factor in restoring the blood to a normal consistency, but it was not known that independent of the quantity of the food and of its caloric value, different articles of food played differing parts. The method Whipple adopted in his experiments was to bleed dogs that are to say to withdraw from them a certain quantity of their blood, supplying them afterwards with food of various kinds. By that method he discovered that certain kinds of food were considerably superior to others, inasmuch as they gave stimulus to a more vigorous reformation of blood, that is to say stimulated the bone marrow - in which the blood corpuscles are produced - to a more vigorous manufacture of red blood corpuscles. It was first and foremost liver, then kidney, then meat, and next after that certain vegetable articles of food too, e.g. apricots, that proved in an especial degree to have a strongly stimulating effect. Whipple's experiments were planned exceedingly well and carried out very accurately, and consequently their results can lay claim to absolute reliability. These investigations and results of Whipple's gave Minot and Murphy the idea, that an experiment could be made to see whether favourable results might not also be obtained in the case of pernicious anaemia, an anaemia of quite a different type, by making use of foods of the kind that Whipple had found to yield favourable results in his experiments regarding anaemia from loss of blood.

Before entering upon a discussion of Minot's and Murphy's investigations in detail, I propose to say a little about pernicious anaemia. As the name tells us, it is a fateful disease, which, previous to the labours of our prize-winners, almost invariably, with only very few exceptions, ended fatally in the course of a few years, or in a still shorter time, a few months. Its cause is not known. It customarily makes its appearance in middle-aged persons, who lose colour, feel tired, and ultimately consult a doctor, who establishes the fact that their red blood corpuscles have become reduced in number from the normal figure of about five million per mm^3 to considerably lower values, e.g. one million per mm^3 , or to still less, eight, seven or six hundred thousand per mm^3 , and that the colour-strength of the blood has also diminished, though as a rule not in the same high degree as the number of the red blood corpuscles. Moreover, on examining the blood microscopically, the investigator finds that the red blood corpuscles in it are very different to normal red blood corpuscles. The latter are all alike in size and in form, whereas in pernicious anaemia there are to be noticed blood corpuscles of a great variety of sizes, some considerably larger than normal and some small ones; and their shapes vary too. They are diseased or immature forms of red blood corpuscles. Hence what the bone marrow has supplied to the blood is not of a completely satisfactory make or consistency. The course of the disease is customarily a cyclical one, periods of specially severe anaemia alternating with periods when the composition of the blood is more normal. The circumstance that the disease itself is subject to variations, showing now improvement, now relapses, renders it of course very much more difficult to determine the actual effect produced by any treatment administered to the patient. Previous to the results of Minot's and Murphy's experiments the principal mode of treatment adopted, and one that was practised all over the world, was the giving of large doses of arsenic, while in serious cases it was also customary sometimes to resort to splenectomy, that is to say to removal of the spleen by an operation, or to blood transfusion, i.e. the transfer to the patient of blood from another person, a method that is still to be recommended at a critical stage in severe cases. Hence it was quite a strange conception, and one lying remote from the customary beat, that came into the minds of

Minot and Murphy, when they bethought themselves, that it might possibly be feasible to treat a patient suffering from this disease by administering food to him. It was an idea, in fact, that had never been conceived of, up to that time. A consultation of the textbooks with regard to the matter, for instance, will show us that very little attention was paid to the diet. Some items of good advice are to be found given, indeed, respecting the patient's diet in pernicious anaemia, not as an integral part of the treatment though, but rather as an element in the nursing required in general. There was, however, one exception to that universal rule, for in one spot in the world the idea had really arisen and been put into practice. To that I shall return later on.

The first work published by Minot and Murphy in regard to this question dates from 1926. It was a short paper of nineteen pages, entitled: «Treatment of Pernicious Anaemia with a Special Diet». No mention here of a liver diet, but of a special diet, the special diet they had in view being one derived from Whipple's investigations, based on Whipple's diet, consisting of liver, kidney, meat and vegetables, the last two also in large quantities. As reports of observations began to come flooding in, showing that results had really been achieved by the application of the diet, there occurred by degrees a variation in the composition of the dietary in favour of liver, that food substance which, according to the showing of Whipple's investigations, had the strongest stimulating effect upon the erythropoietic, red-corpuscle forming function of the bone marrow. In their later publications we see, moreover, that they employ the designation: «a diet rich in liver». Hence their diet became more and more preponderatingly a liver diet. There were, it is clear, great difficulties in the way to prevent their arriving at any real discovery in this regard, for the fact is, as we know, that in order to be able to achieve any palpable results from a liver diet, it is requisite for the patient to have liver administered in very considerable quantities every day, in quantities running to three, four, five, or six hundred grams, or even still more, per diem - consequently, in the twenty-four hours, upwards of half a kilogram of liver, either in a raw state or in some cooked form. We can understand what obstacles that presented for the successful issue of the inquiry, since such quantities

of liver seemed very outrageous at that juncture, when there were no particularly strong reasons for expecting that the diet would have any important influence on a sufferer from pernicious anaemia. The opinion held respecting pernicious anaemia was, that it was so essentially different in nature to the blood-loss anaemia, that there did not exist, from a therapeutic point of view, any real reason for combining them together at all. As consequently there was nothing that could with any degree of certainty be expected to result from the application of the diet in question, and as the method of treatment demanded such unreasonably large quantities, it is clear that the experimenters must of necessity have been possessed of an extraordinary measure of far-sightedness, an extraordinary degree of energy and an extraordinarily clear grasp of all the circumstances of the case, as they were enabled to succeed in inducing the patients to submit to such a regimen notwithstanding its disagreeableness. If Minot and Murphy had not been imbued with such an irresistible urge to bring matters to a head, so to say, their discovery would never have been achieved. It was found, however, that, on the diet being put contemporaneously to the test at a large number of hospitals in the United States, results were actually obtained from the treatment that were astonishing, showing a more rapid improvement and blood formation, i.e. a more complete restoration to normal conditions, than had been seen to result from any other methods of treatment. It was also by degrees observed that, when once they had recovered a normal state of the blood, the patients remained well in health, which had not been the case with the methods previously applied, for with them, even in instances where very considerable improvement occurred, there had been the periodic relapses, which, as I mentioned before, are a characteristic feature of the disease. No sooner had these results been achieved in America, and been made public, than liver diet began to be tested in all parts of the world as a cure for pernicious anaemia, and from all quarters there came reports of the same experiences as to results. From everywhere confirmation came of Minot's and Murphy's observations being correct.

The success of the treatment, i.e. that by administering liver one could actually secure the disappearance of the symptoms of pernicious anaemia, meant

not only a great therapeutic triumph, but also a reversal of the theory up to then held respecting the nature of the disease. The former idea had been, as a fact, that the essential point in the conditions predisposing to pernicious anaemia was the presence in the organism of a poisonous agent, a poison arising in one way or another or originating from one quarter or another - ideas respecting that point were divergent, but in general there was agreement that there must be some poison that interfered with the proper functioning of the bone marrow, entailing as a consequence the production on its part of diseased, imperfect, immature red blood corpuscles. The discovery that the disease could be cured by the sufferer from it being given a diet of liver, led scientists, very naturally, at once to query in their minds whether the theory regarding the disease that had up to then been prevalent could be correct. Reflection upon the matter must as a matter of course lead to the conclusion, that it was not probable that the presence of a supposed poisonous substance could be the cause of the disease, it being seemingly due rather to the absence of a substance that was requisite for a satisfactory production of red blood corpuscles, a substance that must be present in liver, seeing that the patient's condition became normal when liver was supplied as a food. In fact, a new function of the liver had thus been revealed. It is interesting to observe the reaction of medical science to this altered aspect of the matter. There exist certain representatives of quasi-medical or medico-religious bodies, who are in the habit of alleging that medical science is a species of religion or philosophical system, based upon irrefragible tenets that do not allow of alteration or modification. That may have been so some hundreds of years ago, but in our days it is so no longer. The framework of medical science, as of other natural sciences, is a body of facts and upon them medical theories are based and built up. When a new and important fact has been established, the effect is somewhat like that of a bomb falling to earth: those theories that do not admit of being reconciled with it are exploded, being replaced at once by others that can be brought into better harmony with the newly

acquired item of factual knowledge. And that has been the case in the present instance.

With a view to affording a background against which the discoveries of the prize-winners may stand out in stronger relief, I propose to say a few words as to the function of the liver in general. We are all aware that the function of the liver is to secrete bile, to be discharged into the bowel. As is well known, the bile is of great importance in aiding the process of digestion. This function of the liver is termed its external secretion, its products by degrees reaching the surface of the body. Besides that, however, the liver has other functions; it has for instance also a so-termed internal secretion. The first fact respecting an internal secretion that science was able to reveal to mankind bore reference actually to the liver, being the discovery, made in 1855 by the great French physiologist Claude Bernard, of the liver's glycogenic function, i.e. of the important part played by the liver in the metabolism of sugar in the body. On demand the liver supplies the sugar that the body requires for its normal functioning. Claude Bernard gave that process the name of «une sécrétion interne», thereby creating the term: «internal secretion», of which we hear so much at the present day. Since his time the theory that he first enunciated has been built up and amplified very materially. Thus, it is known now, respecting a number of glandular organs, that, in addition to any external secretion that they may be capable of, they also possess an internal secretion, that they consequently manufacture products that are delivered directly into the blood, and which are subsequently conveyed via the blood vessels, to remote parts of the body, where in other organs they give rise to impulses, accomplish effects, that are of the very greatest, indeed often of a vital, importance for the body. To those products, which the internal secretion supplies, the English physiologist Starling has given the name of hormones. We are now acquainted with a very considerable number of hormones. Time, however, does not admit of my entering into the subject further; I will only call attention in passing to the latterly so much discussed sexual hormones,

those hormones, that is to say, that regulate the sexual functions, as to which in recent years especially Professor Zondek has made such fundamental investigations. Further, I may mention insulin, familiar to us all, a pancreas hormone, which medical men make use of in the treatment of diabetes. When the pancreas itself is incapable of producing this hormone, which is an essential requisite of the body, diabetes establishes itself. If under those circumstances the hormone is supplied to the body by the injection of insulin, derived from the pancreas of some animal, the symptoms of the disease can be kept away. This method of treatment, which consists of making the patient, in whose body some organ is not functioning satisfactorily, consume portions of the said organ, or absorb by injection, preparations of the said organ, is termed organotherapy. Another name is substitutional or replacement therapy, since the method consists in making substitution for, or replacing, the production that is wanting by supplies from outside. That type of treatment is not so absolutely new as many people may think. Thus, we may recall that a French physiologist, Brown-Séquard, as long ago as 1889, carried out investigations, which aroused great astonishment at the time, as to the effect of an injection into the body of testicular juice, got from the male genital glands. He gave himself injections of testicular juice and observed considerable rejuvenating effects both physically and mentally. That constituted the first achievement in the direction in question that science accomplished. Hence, it is Brown-Séquard who laid the foundation of organotherapy, and the rejuvenation treatments that we hear so much about at the present time, had forerunners at an earlier date. In this particular case, as in general in the field of medicine, it is seen that, by delving into the ancient records of the cultural achievements of the past, we may discover the nucleus of many of the methods that attract so much attention in our own times as novel and epoch-making. If we study Ebers, the papyrus of the ancient Egyptians, a venerable documentary record of the world of many thousand years ago, we shall find numerous evidences to show that the ancient Egyptians

made use of organotherapy. Owing, however, to their defective knowledge of details they were unable to secure such brilliant results or to carry on their labours so purposefully, as, thanks to our incomparably greater knowledge, we are now in a position to do.

On now examining, in the light of the above facts, the discoveries made by our Nobel Prize winners, we thus find that they have come upon a new, hitherto unknown internal secretory function of the liver, have discovered that the liver yields a substance that is of the utmost importance for the normal work of the bone marrow in forming new blood.

The liver treatment for pernicious anaemia, which from its very start showed itself to be of immense value, was as already said not an easy or agreeable one for the patients to submit to, owing to the large quantities of liver that they had to consume. Even after the composition of the blood had been restored by the liver treatment to a normal state, it was obligatory to make the patients continue to eat large quantities of liver, in order to keep up their recovered health. During the years that have elapsed since then, the technique of the treatment has undergone development: the active agent or stimulating substance in the liver has been successfully extracted, an extract being thereby obtained that contains the active substance in a more concentrated form. Latterly the concentration has been brought down to such small volume, that an injection of less than a gram of the substance in solution proves a sufficient quantity for maintaining the blood in a normal condition for a period of a fortnight. Hence one injection a fortnight should suffice for keeping such patients in a state of health. The fact of so small quantities being found to be all-sufficient leads one to think of the hormones to which I referred above, they being capable of accomplishing very great results with very small quantities, and one puts the query to oneself: Is it a hormone, this substance in the liver that is made use of for curing pernicious anaemia? As to that, it is not as yet quite decided what it would be most correct to call it - a hormone, or a vitamin, or something else,

and I do not propose to enter upon a discussion of that here; it may be that there are not essential differences either between the various concepts named.

In the foregoing I mentioned the fact that the idea of treating pernicious anaemia by food had arisen in one quarter previous to Minot's and Murphy's day. That quarter was Stockholm, for the late Dr. Warfvinge, superintendent physician at the Sabbatsberg Hospital, who died early in the present century, had actually conceived the said idea. He was a very distinguished clinician, specially interested in diseases of the blood, and he used to urge with great emphasis that in cases of pernicious anaemia the most essential thing was for the patients to eat meat, meat in large quantities and at every meal, that being more important than the administration of medicine or than any other form of treatment. He was very insistent in urging it upon his assistants at the hospital, that they should bring all the influence of their authority to bear on the effort to induce the patients to eat meat, to feed themselves up on it, to force themselves to get down as large quantities of it as they possibly could. What was that but a harbinger of the very treatment, to the discoverers of which there has now been awarded the Nobel Prize? Whipple's investigations have taught us that, next to liver and kidney, meat is the article of our regimen that exercises the greatest influence as a stimulus to the blood regeneration carried on by the bone marrow. With his keen clinical eye, Warfvinge had discerned that there was something of special importance in meat, and consequently he placed in the forefront of the treatment the item that the consumption of meat constituted. It appeared to me that it would possess a certain interest for those who are present here this evening to be reminded of that circumstance.

What is then the significance of this new method of treatment? In the first place there is the fact that, thanks to it, a sufferer from pernicious anaemia can with tolerable certainty be rescued from a premature death. Hence, for the individual, the method is of an exceedingly great importance. Its importance in a wider sense must of course be dependent on the seriousness of the disease in its effect on the

community at large, i.e. on the relative frequency of cases of pernicious anaemia. It is in fact quite a common disease, for in the United States, for instance, it is estimated that, previous to 1926, the year in which Minot's and Murphy's methods of treatment were first applied, about six thousand persons died of pernicious anaemia every year. I have calculated - very approximately that, since the date when their methods began to be generally applied, some fifteen or twenty thousand persons must have been saved from death in the United States alone. As regards conditions in Stockholm, there have been 450 cases of pernicious anaemia that have been treated at the Serafimer Hospital since I became attached to it, while, according to a recent estimate, in Sweden as a whole there must be something like three thousand persons who are suffering at the present time from pernicious anaemia. Hence the number of the lives to be rescued year by year by the application of the new method of treatment is quite considerable.

When medical progress in regard to the healing of diseases is on the tapis, there is one objection that is not infrequently brought up. People are apt to urge that, although it may be fine and merciful to effect those cures, yet, from the point of view of the community at large, it is not a thing to set much store by or that is beneficial, since disease, being a scavenging implement that Nature makes use of, clears off the elements in the population that are of inferior value, and leaves a residue that is of more vigorous stamina. That line of argument would lead us to the conclusion that, from the point of view of race improvement and race development, it is not to be considered any advantage to rescue those who are afflicted with diseases from which they cannot cure themselves. That reasoning is specially prevalent with respect to epidemic diseases. It is supposed by many people that, when such scourges beset a population, the victims that are swept off are the weaker and more delicate individuals, and that consequently, apart from the humanitarian point of view, it is after all advantageous to the community that the disease should run its course. That chain of reasoning, however, is based upon

ignorance of how matters stand in reality. For it is not the case that, when an infectious complaint sweeps over a populated area, it is the inferior elements that are snatched away. Those victims that fall a prey are not inferior in any other sense than in regard to their powers of resistance to that particular virus or injurious agent - in other respects they may very well be as physically fit as possible. A person's power of resistance to an infectious disease cannot be estimated from a weighing-up of his general physical powers; neither physical nor mental powers are deciding factors in the case. Any individual may be possessed of a feeble power of resistance to one infectious disease and of a strong power of resistance to another. Let me take as an example the influenza epidemic of 1918-1919, which most of those present will probably recollect. Now, what was the actual state of things then? Why, it was just among the young, vigorous members of the community that far larger numbers were cut off than was the case among other groups. It would happen for instance that a vigorous, full-blooded, muscular, intelligent, promising young man died of the disease, whereas a feeble specimen, of poor intellect and of no importance to the community, survived. That is how matters stand actually. Moreover, it should not be forgotten either, that those who pass through an infectious disease successfully have nevertheless had their vitality injured by it to a greater or less degree, have consequently forfeited some of their value as members of the community. Hence, everything that medical science can do to ward off and cure disease is of benefit to the community, just from the point of view of its being contributory to the health and vigour of the race. Circumstances are the same respecting pernicious anaemia. The sufferers from the disease are not of inferior value as human beings, except in the particular respect in question. If their inferiority therein can be removed by feeding them with liver, there is no reason why they should be inferior in value in any other respect. Hence liver therapy not only rescues persons suffering from pernicious anaemia from death, it also restores

them and renders them capable of living useful and active lives to the benefit of the community.

If, now in conclusion, I sum up the discoveries for which the prize has on this occasion been awarded, they are as follows: We have acquired new knowledge as to the very divergent effects exercised by different food substances in promoting and stimulating the bone-marrow's activity in the regeneration of the blood; we have been made acquainted with a new internal secretory function possessed by the liver, that is of the utmost importance; we have been furnished with a method of treatment for pernicious anaemia, and also for other diseased conditions, that will save the lives of many thousands of persons every year. Hence it must be said that our prize-winners fulfil in an ideal fashion Nobel's criteria for a prize-winner, since he lays it down that the prize shall be bestowed on the person or persons who have conferred the greatest benefit on mankind.

Now I turn to you, Professor Minot, Dr. Murphy, and Professor Whipple. I have tried to give an idea of what you have done, of the importance, of the greatness of what you have done. You have spread a new light over the process of regeneration of the blood, you have discovered a function of the liver, before you unknown to science, you have invented and elaborated a new method for the treatment of anaemia, especially pernicious anaemia, that dreadful disease, which hitherto has killed practically everyone who was afflicted by it. This new method, the liver treatment, has saved already thousands of lives, and will in the future save innumerable human beings from death.

The donator says in his will, that the prize should be given to those, who have conferred the greatest benefit on humanity. The Caroline Institute, in awarding you the Nobel Prize for Physiology or Medicine, has acted then exactly along the line of the intention of the donator. You belong to the very small number of men, of whom can in truth be said, that they have done immense services to mankind.



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