A Lecture

ON

CHANGING STANDPOINTS IN METABOLIC DISEASES:

DIABETES, NEPHRITIS, JAUNDICE.*

BY

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THE recent work on diabetes, nephritis, and jaundice reveals one trend common to the study of them all—a shifting of the main interest from the urine to the blood. Of three factors—the blood, the kidney, and the urine—if the state of two be known that of the third can be deduced. But it is only of late that resort has been made to routine examination of the blood for any other purposes than to count its corpuscles, to estimate its haemoglobin, and to search for microbes. Yet already biochemical examination of the blood has thrown much valuable light on obscure problems.

In the main the function of the kidney is to keep the composition of the blood constant, but in the past it was not realized that in part this was effected by changes in the renal threshold. This word has lost some of its significance for us by the fact that builders no longer make a threshold higher than the floor. Indeed, now we know that the so-called threshold may vary in its height, the metaphor of a sluice-gate is a more exact one. But the metaphor employed is not important if this point is clearly perceived—that for any substance in the blood which can be of use to the tissues the kidney interposes a barrier in the way of its excretion; and if the amount of this substance in the circulation does not exceed a certain level the kidney does not excrete it. This rule applies, at any rate, to sugar, salt, haemoglobin, biliary constituents, and water. On the other hand, there is no such barrier to purely waste products such as urea or uric acid. Their percentage in the urine is chiefly determined by the concentrating power of the kidney. The threshold of the kidney may be affected by disease of that organ, or may be altered to compensate for disease elsewhere, while disease of the kidney may also affect its power of concentration. The composition of the urine does not vary, therefore, with the composition of the blood, and the problem presents infinite complications unless the blood is directly examined.

I propose to illustrate this thesis by reference to the change in our views on diabetes, nephritis, and jaundice, that has followed biochemical examination of the blood.

DIABETES.

The presence of sugar in the blood is essential to life, and a threshold to retain some is therefore necessary. As soon as it falls too low there is profuse sweating, faintness, and mental confusion; and if the fall is extreme there will be convulsions, coma, and death. It is really a condition of internal asphyxiation, since some sugar is necessary for the oxidative processes of the cell. An excess of sugar in the blood is not so dramatic in its consequences. It tends to impair the translucency of the crystalline lens, to excite neuritis, and to increase the liability to septic infections, but its most constant effect is to exhaust the cell-islets of the pancreas. This sets up a vicious circle, since the failure of the cell-islets results in still further hyperglycaemia, which in its turn exhausts the cell-islets still more. In the attempt to prevent the loss of a valuable foodstuff the kidney raises its threshold for sugar, so that one can never assume from the fact that a diabetic becomes free from glycosuria as the result of treatment that his blood sugar is becoming more normal. On the contrary, it usually continues to rise, even despite the dietetic restrictions.

Where the renal threshold for sugar is low, as in so-called renal glycosuria, there are no serious consequences. Some two years before the discovery of insulin I posed the ques-

tion in a discussion at the Medical Society, "Is not hyperglycaemia the enemy?" But no answer was forthcoming.

Since then I think a general agreement has been reached that hyperglycaemia is the enemy—particularly because of its disastrous effects on the cell-islets. The resting blood sugar should normally be 0.1 per cent., rising in about twenty minutes after a meal to 0.15 per cent. and returning to normal in about one and a half hours. Within certain limits the body can function with a blood sugar that departs in either direction from these figures—but too great a fall is immediately dangerous, and too great a rise is ultimately serious. Anyone with a resting hyperglycaemia is a potential diabetic.

Now the level of normal blood sugar depends on two main factors: the endocrine balance and the threshold of the kidney. The endocrine balance is the resultant of the action of the sympathetic group of ductless glands—that is, the thyroid, pituitary, and adrenals—which mobilize sugar into the blood, and the reaction of the pancreas which stores it in the liver and muscles. Overaction of the former or underaction of the latter alike result in hyperglycaemia. It is clearly of no use to treat a case of glycosuria by insulin if there is no hyperglycaemia, and it may be positively dangerous. Fortunately we may lay it down as a general rule that when both sugar and diacetic acid are present in the urine of an undieted patient hyperglycaemia is practically certain to be found. But when as a result of treatment glycosuria vanishes while acetonuria persists, there are two possible explanations—one that the patient is being dieted too strictly, the other that the kidney has raised its threshold for the excretion of sugar; the acetone bodies continuing to pass out by simple diffusion. In the first instance a slight relaxation in the diet by allowing more carbohydrate will diminish or even abolish the acetonuria, in the latter it will not, since the extra carbohydrate cannot be utilized.

It is in this matter of hyperglycaemia that insulin helps so much; it promotes the utilization of sugar by the liver and other tissues, and thus renders the rise of the kidney threshold unnecessary, for the blood sugar automatically falls for six hours after its injection. But, further, insulin promotes the completer combustion of fat so that acetonuria is controlled. It might be thought that this was the direct consequence of better utilization of the sugar which burns up the fat; no doubt this is generally the case, but there are instances on record (Widal and others) where the acetonuria was abolished by insulin without the glycosuria being controlled at all.

In general it may be said that the more severe the diabetes the higher the blood sugar is likely to be. But this is not invariably the case. I have at present a typically severe instance in a young woman whose blood sugar has never been found above 0.153 per cent., and in whom 20 units of insulin a day are required to bring it down to 0.125 per cent., at which level she can still only tolerate very little carbohydrate. She does better, however, when her fats are reduced.

I should like here again to enter my protest against the statement that once insulin treatment is started it can never be discontinued. Many patients take this to mean that if they cease having it their last state will be worse than their first. There is no justification for this, but it has led, in my experience, to a number of patients declining the aid that insulin could undoubtedly bring. I would, on the contrary, positively assert that the sooner insulin is used after the onset of symptoms the more likely is permanent benefit to be derived. The most disappointing cases have been those of long standing who have become more or less adapted to a raised blood sugar, though even these have received some benefit. The most successful cases have been in young people who had early treatment. I have at the present time under my observation three girls, aged 5, 8, and 24 respectively, who have now had no insulin for several months, yet who have been persistently free from glycosuria with a normal blood sugar. They all had very high blood sugars at the beginning of treatment; in two of them it exceeded 0.4 per cent. I no longer regard diabetes as a necessarily progressive disease; but before the days of insulin the conditions were such that it almost inevitably progressively damaged the cell-islets by hyperglycaemia.

* Introductory to a post-graduate course at the Prince of Wales's Hospital, Tottenham.

In young and growing persons it is possible that if this is prevented by insulin the new cell-islets, as they form, can escape damage. By combining alimentary rest, which quiets down the general metabolism, with insulin to combat hyperglycaemia, the outlook in diabetes has been enormously improved. And I would add that slowing metabolism by rest in bed for a month at least at the beginning of treatment, and careful eradication of septic foci, which in themselves tend to produce hyperglycaemia, should be regarded as essential parts of the treatment. Moreover, I believe that the question of the blood sugar in diseases other than diabetes will amply repay the study it is beginning to receive.

NEPHRITIS.

From the point of view of function rather than structure nephritis may be hydraemic or azotaemic, though mixed types occur. In the hydraemic type the renal threshold is raised for salt and water, both these substances being unduly retained in the blood and tissues. Nitrogen retention, however, does not occur, so that the blood urea is normal. The great drain of proteins into the urine leads to their diminution in the blood, while lipoids tend to increase there. These are the facts we have learned from a study of the blood. Ordinary parenchymatous nephritis is usually of this type. In the azotaemic type the concentrating power of the kidney is damaged. Therefore there is a failure to eliminate solids, both those for which the kidney interposes a threshold and those for which it does not. Nitrogen retention therefore occurs, and instead of the normal 20 to 40 mg. of urea in the blood we may find 80, 90, or even more. As it is the power of concentration which is impaired, the output of water is not involved, and indeed, since the blood pressure rises, it is actually increased. Possibly this increased output of water is compensatory so as to enable the solids to escape in more dilute solution. Chronic interstitial nephritis illustrates this type.

Now it is clear that the treatment will materially differ according to whether there is hydraemia or azotaemia. Since the blood proteins are low in the former we should not severely restrict the intake of protein in the food. Meat extracts should of course be prohibited, since they have hardly any nutritive value and have to be excreted by the kidney. The intake of salt should also be greatly reduced. Since it has been shown that the lipoids increase the tendency to oedema, the fat in the diet should be cut down as much as possible. On the other hand, as the kidney can eliminate urea quite well, we can take advantage of its diuretic effect by giving it in doses of 45 to 60 grains three times a day. Its influence in getting rid of oedema is sometimes remarkable.

When nitrogen is being retained, however, the restriction of protein is a wise procedure. Let me say at once that even then it is not the urea which is toxic, but other non-protein amine bodies. If the hypobromite method is used these are estimated as well as the urea, but if the urease method is employed only the urea is estimated. By employing both and comparing the results I have been able to find that in uraemic conditions the amount of these unknown amine bodies is increased both relatively and absolutely in the blood and cerebro-spinal fluid. The vomiting and diarrhoea are attempts to eliminate these toxic nitrogenous substances by other channels. Von Noorden has shown that as much as 8 grams of nitrogen can be eliminated by the bowel, while not more than 3 grams can be got rid of by the skin. In the vomit of a uraemic patient under my care Dr. Canti found a higher percentage of urea than in the blood. This points strongly to vicarious excretion and suggests the inadvisability of hastily checking such methods of elimination. But in such cases drastic nitrogen restriction is clearly called for, and I am accustomed to follow von Noorden's plan of giving nothing but fruit juice and sugar for a few days. The same method is also applicable to acute nephritis where nitrogen retention is apt to be severe. Here the benefit of fruit juice and sugar is often very striking, and in my opinion it is a far better treatment than milk diet. Recently I saw a doctor's son who developed acute nephritis with haematuria after tonsillitis. After forty-eight hours

of stewed fruits, sugar, and lemon squash the blood disappeared altogether and the albumin fell to a trace; in a few days the urine was normal.

The occurrence of mixed types, particularly in parenchymatous nephritis, undergoing secondary contraction of the kidney, raises difficulties. Where facilities for repeated blood examinations exist we can adapt our treatment accordingly, but where they do not we may take the blood pressure and the excretion of water as a guide. When the oedema has subsided there is no point in continuing the administration of urea, and when the blood pressure shows a tendency to rise we may infer a failure in the concentrating power of the kidney and prescribe a more restricted intake of proteins.

JAUNDICE.

The new work on jaundice centres round van den Bergh's test for bile pigment in the blood serum. This depends on Ehrlich's diazo-reaction. A freshly prepared mixture of diazotized sulphanilic acid and sodium nitrite is added to the serum, and if a pink colour appears at once it is called a direct reaction; if only after the addition of alcohol, an indirect reaction. If there is a pink colour at once which deepens further on the addition of alcohol, it is called a biphasic reaction.

In considering the formation of bile pigment it is convenient to modify slightly McNee's description of the structure of the liver. A liver lobule may be compared to a number of test tubes packed in damp sawdust. Each test tube represents an hepatic alveolus lined by secreting cells, blind at its central end, while its lumen represents the bile capillary. The sawdust represents Kupffer cells which are bathed in the blood from the capillaries of the portal vein. They form part of the reticulo-endothelial system, which is also largely represented in the spleen pulp. They take up red corpuscles and any free haemoglobin from the blood stream and turn the blood pigment into bile pigment. But the final stage of this process, which apparently involves the breaking off of a protein fraction, is carried out in the cells lining the test tube. Bile pigment in this final form gives a direct reaction, but if it is still combined with protein it only gives an indirect reaction.

1. Obstructive Jaundice.

Now it will readily be understood that if there is an obstruction to the bile ducts some of the completely formed bile pigment will be reabsorbed into the blood stream. This will give the direct reaction, and is the condition found in the jaundice of gall stones and new growth of the head of the pancreas, for instance. In gall stones without jaundice the bile content of the serum is normal.

2. Toxic and Infective Jaundice.

Here, the polygonal cells being diseased, some of the bilirubin from the Kupffer cells is unable to enter them, and therefore passes direct into the blood stream, still in the combined form. The blood serum will therefore yield at first an *indirect reaction*, but as disintegration of the cells proceeds the bile capillaries become obstructed also and the reaction becomes biphasic, the direct portion of the reaction becoming intenser as obstruction becomes more marked. Such jaundice occurs in many general conditions of infection and toxæmia. Here the jaundice does not appear to be merely due to catarrh of the smaller bile ducts as was formerly thought, for a series of changes in the liver cells can be demonstrated, ranging from simple cloudy swelling (as in pneumonia), through fatty degeneration (as in chloroform poisoning), partial necrosis and dislocation of the liver cells (as in spirochaetal jaundice), to almost complete necrosis (acute yellow atrophy). In salvarsan poisoning any one of these stages may be met with.

3. Haemolytic Jaundice.

When blood destruction is excessive more bile pigment is found than the polygonal cells can deal with; some will be excreted normally, while the rest goes into the blood in the combined form. The serum will therefore only yield the *indirect reaction*, and bile pigment will usually be absent from the urine, while constantly present in the faeces.

That blood pigment can be turned into bile pigment without the aid of the liver was shown by Virchow. The

haematoidin of old blood clots is chemically identical with bilirubin in its combined form, yielding the indirect reaction, as we now know. The experiments on geese which were formerly held to prove the contrary were done in ignorance of the fact that what corresponds to the spleen in higher animals is largely enclosed within the liver of birds. McNee suggests that haemolytic jaundice depends on blood destruction in excess of normal, whereby the cells of the reticulo-endothelial system, especially in the spleen, are thrown into increased activity which may result in or be actually dependent on an increase in the size of the spleen. The blood serum comes to contain a greatly increased amount of bilirubin of the same type as that arising from the normal physiological destruction of effete red corpuscles in health.

This conception would explain much which has been hitherto obscure. It has been recognized that "splenic anaemia" is a consequence of several different conditions producing splenic enlargement, and that it is often relieved by splenectomy. On removal the spleen may be found to be the seat of tuberculosis, or endothelioma, among other conditions. Apparently we may now conclude that any disease of the spleen stimulating the formation or activity of the reticulo-endothelial cells sufficiently may produce splenic anaemia. It would also explain why splenic anaemia may go on to Banti's disease, in which cirrhosis of the liver and jaundice supervene, since the Kupffer cells of the liver are structurally and functionally an extension of the reticulo-endothelial system of the spleen. It explains why the spleen may enlarge in the crises of pernicious anaemia, and throws light on the occasional jaundice (without necessarily biliuria) in that disease.

Van den Bergh has also shown that in some apparently healthy fallow individuals the bilirubin in the serum may reach nearly three units. Since the threshold for its excretion in the urine is four units, such individuals show no bile in the urine: the unit=1 part of bilirubin in 200,000 parts of serum. The condition has been called "simple familial cholaemia"; usually the spleen is not enlarged nor the fragility of the red corpuscles increased. There would appear, however, to be all stages between this and the condition known as acholuric family jaundice. In this form the patient may be born jaundiced or become so soon after birth. The jaundice persists with little or no variation for many years, but bile pigment is present in the stools as in health, while it is absent from the urine, in which any darkening present is due to excess of urobilin. Nevertheless bile pigment, giving the indirect reaction, is present in the serum. The spleen is always enlarged. There is considerable anaemia with a low colour index, poikilocytosis, nucleated red cells, and reduction in the number of leucocytes. Yet the patient has good or fair health, and shows a normal resistance to intercurrent diseases. This condition tends to appear in more than one member of the family and in successive generations. Some of the patients are liable to attacks during which the colour deepens, when pain may be experienced over the spleen or liver, or both, and there may be slight pyrexia. Neither alcohol nor syphilis appears to play any part in the etiology. Enlarged abdominal veins, ascites, oedema of the legs, and haematemesis have never been recorded, and the liver does not appear to be cirrhotic, although it is sometimes fatty.

Attacks of haemoglobinuria have been noted in this condition, which could be produced by exposure to cold, and in this connexion it is interesting to note that in one family a cold bath would intensify the jaundice. All this points to haemolysis as a cause of the jaundice. The serum from a patient agglutinates normal red corpuscles, but not his own red corpuscles or those from another individual suffering from the same disease. The most striking pathological feature of the condition is the undue fragility of the red corpuscles, for they are haemolysed by a dilute salt solution which has no effect on ordinary corpuscles. We may conclude that in acholuric family jaundice there is a chronic haemolysis of unduly fragile corpuscles as a primary event, but that the threshold for the excretion of bile is not reached, while the enlargement of the spleen and liver is secondary, to deal with the increased haemolysis. What the cause of this undue fragility may be is still unknown.

Latent jaundice is a term applied to conditions where the bilirubin content of the serum does not reach four units, so that the usual symptoms are missing. The haemolytic type of this is seen in pernicious anaemia, anaemias due to worms, and in all the newly born. Its occurrence is of prognostic value when salvarsan is being given, as it is evidence of the approach of poisoning by the drug. An obstructive type of latent jaundice occurs in cirrhosis. In this connexion it is interesting to note that in the ordinary jaundice so common in the newborn (icterus neonatorum) the blood serum gives an indirect van den Bergh's reaction, so that it is haemolytic in origin. Before birth the foetus has a polycythaemia of about 6½ million per cubic millimetre. On the second day after birth this excess has disappeared and probably there will not be more than 4½ million. In a sense this polycythaemia may be regarded as a protection against the risk of loss of blood at birth. Once this has passed, haemolysis occurs and haemolytic jaundice follows. The fact that latent jaundice is always present for a time after birth supports this view. Severe jaundice in the newborn is generally due to suppurative pylephlebitis from septic infection through the umbilical cord or to congenital syphilis. Rarely it results from congenital atresia of the bile ducts.

Dissociated jaundice has been described by French observers—the bile pigments going one way, the bile salts another. But as they did not take the condition of the blood into account, judgement must be reserved on this. There may, indeed, be renal dissociation in obstructive jaundice, both pigments and salts being found in the blood while only bile salts are filtered out by the kidney. I saw a case of catarrhal jaundice in which bile salts appeared in the urine before the pigment, and it is stated that this is common in the later stages of this condition. In my experience of jaundice as a whole the converse condition is commoner—that is, for bile pigments to be present in and the bile salts to be absent from the urine.

GENERAL CONCLUSIONS.

The biochemical examination of the blood has therefore cleared up many doubtful points as to different forms of glycosuria, has explained the progressive damage produced by hyperglycaemia, and has provided the best guide for regulating treatment by insulin. In nephritis it has brought out clearly the distinction between hydraemic and azotaemic forms of the disease which materially affects their rational treatment. It has re-established after many years the existence of haematogenous jaundice, and has enabled us to classify our cases on a rational basis. In the time that remains I should like to say something about the fresh light this method has thrown on the subject of so-called acid intoxications. For a time there was a tendency to apply wholesale to clinical conditions the results obtained by the experimental injection of acids into animals. Carnivorous animals can protect themselves against a certain amount of acid by the formation of ammonia from the tissues, while herbivorous animals use their excess of alkaline salts for the same purpose. Where these measures are inadequate there is dyspnoea, acetonuria, and ultimately coma. It is not surprising that it was thought that herein lay the explanation of diabetic coma, associated as it is with the formation of diacetic acid, which is largely excreted in combination with ammonium salts. Then it was found that in diabetic coma the reaction of the blood, or, to speak more exactly, its hydrogen-ion concentration, was not necessarily altered in the direction of acidity. It should be remembered that an acid may be toxic in its effects simply because it is an acid, like hydrochloric acid, or because it contains a molecule which is poisonous to protoplasm, like prussic acid. In the first instance the lethal dose is large, in the second it may be so small that the reaction of the blood is not appreciably affected. Now diacetic acid contains a toxic enolic group which is equally deleterious in the form of a neutral diacetate. This stimulates the respiratory centre, causing dyspnoea, washing out CO₂ by overventilation of the lungs, and exhausting the alkaline reserve of the blood. The only benefit of intravenous infusion of sodium bicarbonate is to restore some of the alkaline reserve for a time. But it fails

to check the production of this poisonous enolic group, which ultimately overwhelms the body. Insulin, on the other hand, strikes at the root of the mischief.

But it remains true that any increase in the hydrogen-ion concentration of the blood produces dyspnoea. It is the lactic acid which is formed from the breaking down of glycogen which causes us to be "out of breath" after strenuous exertion. Ventilation of the lungs is thereby increased and more oxygen is taken in which rebuilds the lactic acid into glycogen, oxidizing one quarter of it in the process. Thus the blood is restored to normal and we are no longer breathless. Similarly the dyspnoea of uraemic asthma is due to the failure to excrete acid sodium phosphate, and the resulting acidaemia may be temporarily relieved by alkalis. But a man may also be breathless at a high altitude without any exertion, and his blood will be found to be more alkaline than usual. Here the mere lack of oxygen due to its low tension in the atmosphere directly stimulates the respiratory centre, nervous tissues being the most sensitive to this lack. The resulting dyspnoea washes out CO_2 from the lungs so that the blood actually becomes more alkaline, a condition which the kidney tries to rectify by excreting more alkali. This type is seen clinically in the dyspnoea of heart disease, which is due to oxygen lack, largely the result of capillary stasis, which allows of more complete reduction of haemoglobin. It is therefore usually associated with cyanosis, but there need be no increased production of acid. Indeed, the increased pulmonary ventilation may actually produce alkalaemia. Clearly it is no use to give alkalis, therefore, in cardiac dyspnoea. If digitalis is not contraindicated on other grounds it should be tried, because a cardiac tonic will help to relieve capillary stasis and the consequent anoxaemia. With the same purpose in view oxygen should be given, and it should be given through a rubber catheter introduced through the nose into the naso-pharynx. The catheter is attached to a Wolff bottle containing warm water through which oxygen is bubbled. Given in this way it can definitely increase the oxygen saturation of the blood, as has been proved by direct examination of the blood removed by puncture of an artery; given in the ordinary way it has no such effect.

The conclusion of the whole matter may be briefly stated thus: when acidaemia is associated with dyspnoea, the acidaemia is the *cause* of the breathlessness; when alkalaemia and dyspnoea are associated the alkalaemia is the *result* of the dyspnoea. Recognition of these facts is of great importance in selecting the appropriate measures of treatment.

A PLEA FOR A CLINICAL PHYSIOLOGY.

BY

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It is universally recognized that physiology has been of the greatest assistance to medicine, although the investigations of the physiologist have been carried on without immediate reference to their practical application to medicine. His chief purpose has been to discover the nature of the various manifestations of life. From such investigations material has been provided which can be used in the practice of medicine. This has brought physiology into close relation with the practice of medicine, and physiology occupies an important position in the medical curriculum.

While recognizing the value to medicine of physiology, including the method of animal experimentation, and that the progress of medicine could not have been made without its assistance, the question nevertheless arises whether physiology, as understood to-day, adequately supplies the kind of knowledge which is required for the continuation of medical progress. While it has revealed many matters essential to medicine, can it be relied upon to give that intimate knowledge of living processes which is necessary for the solution of medical problems?

This question does not refer to academic physiology as a whole but only to that portion related to medicine. In discussing the matter it is necessary to deal with certain defects in knowledge, not to disparage experimental physiology, but to indicate how it can be rendered of greater value to medicine. The doubt as to the adequacy of physiology for medical progress arose from the following circumstance.

Physiology and the Reflex Arc.

At the St. Andrews Institute for Clinical Research we recognized that the knowledge of living processes at present available was not sufficient to enable us to understand the nature of the most common symptoms or the action of a single remedy. A great mass of symptoms had been accumulated, and, in place of merely adding to their number, we resolved to try and find the laws that governed their production. We recognized that all phenomena in nature are subject to certain laws, and that the symptoms of disease, being phenomena in nature, are therefore subject to such laws.

In the course of this inquiry we recognized that symptoms were, in the main, due to an increased or decreased activity of certain organs, which came about through an interference with those processes and structures which are concerned in regulating their activity. These processes are spoken of in physiology as "reflex," and we put forward the theory that symptoms were due to the disturbance of normal reflexes.

Shortly after this view was published I was informed by one or two physiologists that any physiologist could have told us that symptoms were produced in that way. But when the matter was looked into, it was found that no physiologist could possibly have given us this information, for the simple reason that physiology to-day cannot supply the knowledge of the processes and structures which regulate any single organ of the body, whether a simple structure like a capillary, or a voluntary muscle, or a hollow muscle, or a secreting organ.

Physiology and the End-result.

The academic physiologist is mainly concerned with end-results. An end-result is the outcome of a chain of events. The chain of events is represented by the activities of certain structures which are concerned in producing the reaction of the organ to a stimulus. When, for instance in an experiment, the sympathetic nerve, or the vagus, is stimulated, the physiological instrument records only a movement of the heart or the output of blood from the heart. Such records may be interpreted as an augmentation of the heart beat, or a decrease. But no information is afforded which will explain the manner in which these reactions are brought about. We know now that there is interposed between these nerves and the heart muscle a series of structures which are involved in the production of the end-result. It is the modification of the activities of these structures which results in the manifestations of health and the symptoms of disease. A knowledge of them and the part they play in the movements of the heart in health and disease is essential for the practice of medicine. The physiologist has provided the knowledge up to a certain point, and it is necessary for progress that a form of physiological investigation should be employed that will give us a deeper insight into vital activities.

The Principle of the Reflex Arc.

In our attempts to get a better knowledge of the nature of ill health and of disease, we sought for some principle which would guide us in our work. We adopted as a guide what we call the "principle of the reflex arc." This is based on the fact that the functional activity of organs is dependent upon impulses which are brought to them by nerves, or structures having the same function as nerves. *The origin of every manifestation of activity is therefore to be found in some structure other than that which exhibits the manifestation.* The application of the reflex arc involves the search for the structures concerned in the production of the manifestation.