An Address

ON

THE EXISTENCE OF ORGANIC DISEASE IN THE ABSENCE OF OBVIOUS SYMPTOMS.

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GENTLEMEN,—The diseases which I wish to bring before your notice this evening form one of the many groups included under the general term of “latent diseases,” but this expression is liable to some ambiguity owing to the fact that it is used for widely different conditions. The expression “latent disease” is often applied to the period that may intervene between the infection of the patient and the production of obvious signs and symptoms. In some maladies, as, for instance, syphilis or hydrophobia, this period may be unduly prolonged in exceptional circumstances, but I do not propose to deal with the many problems connected with this subject this evening. In other instances gross organic diseases may be present without attracting the attention of the patient either by symptoms or physical signs, and it is well known, to quote an extreme case, that large external tumours may sometimes be present which must have obviously existed for a considerable period and yet the patient's attention has only been attracted to the condition perhaps for a few days. Again, it is not uncommon for the onset of acute diseases to be ushered in with extremely equivocal symptoms. Thus, to take a well-known illustration, the onset of pneumonia may be characterised by an almost complete absence of chest symptoms, together with the presence of others of a meningeal or abdominal type. In these circumstances, unless great care is exercised, very serious errors of diagnosis and treatment may be made.

Although perhaps all these conditions might fall within the title of this address I do not propose to discuss such diseases to-night but to restrict my observations to the consideration of the occurrence or presence of serious and generally chronic diseases where no marked symptoms are present but yet where a careful examination will not fail to reveal the presence of the malady. The importance of the subject is increased by the fact that in a very large proportion of such cases the insidious malady present is a fatal one and not uncommonly an immediately fatal one. For our purposes as practitioners it is essential to be as accurate as possible in our diagnosis of disease and for the purposes of diagnosis classification of disease is essential.

Diseases may be classified in a great variety of ways, from an etiological or pathological standpoint, and the latter in many instances, though not in all, is probably the more sound and scientific. For the purposes of the clinician it is certainly more useful and probably equally accurate to employ a classification based on the natural history of diseases—in other words, a classification based on the character of the symptoms presented. One may on this basis divide most maladies into three great groups: the acute, the chronic, and the latent, based on the presence or absence and the severity, if present, of the symptoms. The importance of the thorough study of symptoms must never be overlooked, especially when we remember that in many diseases symptoms only are present and probably in all diseases symptoms are the initial manifestations of the disorders. Our diagnosis of some diseases is entirely dependent on our accurate knowledge and capability of eliciting the presence of symptoms, and it is probable that the earliest recognition of all diseases is to be effected rather by an intelligent appreciation of the possible significance of symptoms than by the detection of physical signs. Not only is this the case, but it may be said that prognosis depending, as it often does, on the extent of a morbid lesion, is not always to be accurately gauged by physical signs. The extent of the lesions of organic disease is usually greater than what would have been expected from the physical signs, notwithstanding

the great value of these in the recognition of disease. For this reason, as well as for the preceding ones, the intelligent study of symptoms is a matter of fundamental importance.

Although most diseases can be divided into the acute, the chronic, and the latent, according to the violence, if present, or the absence of symptoms, as the case may be, it must not be overlooked that acute symptoms may be produced, not only by the onset of acute diseases, but also by chronic and sometimes also by diseases hitherto latent and therefore producing no symptoms. The development of acute symptoms in these conditions may be due to a variety of causes.

1. In some instances the occurrence of acute symptoms in the course of chronic and especially of latent disease may be due to an acute exacerbation in the morbid process. Familiar instances of this may be seen in perforative peritonitis. The perforation of a gastric or of a typhoid ulcer will lead to the production of symptoms more or less characteristic of the condition, provided the perforation occurs in a patient who has presented the symptoms of the underlying chronic or acute disorder, as the case may be. In a considerable proportion of cases, however, such perforation occurs in patients who have shown no symptoms of gastric ulcer or of typhoid fever; in other words, in cases where these diseases have run a latent course. The violent and acute symptoms characteristic of perforation occurring in such cases will produce a clinical picture which may be indistinguishable from that seen in such an acute disease as the most violent form of appendicitis. These diseases afford a very good illustration of the onset of acute symptoms being sometimes due to an exacerbation or sudden increase in the extent of the underlying lesion and not dependent on the onset of an acute disease in a previously healthy person.

2. The onset of acute symptoms in latent disease is not, however, always dependent on a sudden increase of the lesion, as in the instances mentioned; more often it is dependent merely on a progressive development of the underlying malady. The sudden occurrence of acute uræmia in chronic renal disease affords a good illustration of this mode of causation. It is often supposed that the sudden development of acute symptoms in latent and chronic diseases is to be regarded as a result of the development of an acute and additional lesion. Thus the occurrence of uræmia in chronic Bright's disease is sometimes looked upon as dependent on the development of acute nephritis. This, however, is by no means invariably the case, and both in experimental physiology and pathology many instances are to be found of the occurrence of sudden and violent symptoms as the mere result of a slowly progressive lesion. In the case of glands—such as the thyroid, the suprarenal, and the pancreas—it is well known that very large quantities of these glands may be removed experimentally without producing any marked result, and that the subsequent removal of a further small amount, and in some instances a very small amount, may be followed by the immediate production of all the effects characteristic of the total loss of the gland. Thus seven-eighths of the pancreas may be removed without any appreciable ill-effects; trenching on the remaining eighth is immediately followed by the development of marked results. Removal of all the thyroidal and parathyroidal tissue, with the exception of one para-thyroid, is not necessarily followed by permanent ill-effects; but the removal of that one para-thyroid or of all the para-thyroid, leaving the thyroid, is immediately followed by the development of the characteristic phenomena of athyroidæa. It can be seen from these illustrations that the sudden development of acute symptoms in the course of a chronic or latent disease is not necessarily to be regarded as indicative of the onset of an acute lesion.

3. The onset of acute symptoms in the course of diseases hitherto latent may be dependent, not so much on any further development of the initial lesion, but rather on the presence of a complication; many illustrative instances of this are available in clinical medicine. Diabetes mellitus may not uncommonly, especially in the middle-aged, run practically a latent course and the gross underlying disease may not be detected until diabetic coma ensues as the result of some intercurrent illness or perhaps as a sequel to traumatism or to fatigue. Many a case of diabetes has not been recognised owing to the patient not having sought advice owing to the absence of symptoms until a complication, such as coma or gangrene, has ensued as the result perhaps of a trivial injury. Another familiar instance of the same class of facts is afforded by the occurrence of retention of urine

revealing the presence of some chronic disease of the spinal cord, such as tabes dorsalis, which perhaps up to that time had not produced symptoms attracting notice.

From the above illustrations we see that the development of acute symptoms in the course of latent diseases is by no means uncommon, but the subject matter that I wish to bring before you more especially is the occurrence of latent diseases without obvious symptoms. From this point of view these latent diseases may be divided into two great groups—the first consisting of those instances where latent diseases occur as complications of other and obvious maladies, and the complication produces either no obvious symptoms, or else the symptoms produced by it are erroneously interpreted as dependent on the initial malady. The second group, which is equally, if not more, important, consists of the instances where the latent disease is not detected until complications have developed, the original latent malady being overlooked, either owing to the complete absence of symptoms or in some instances owing to their equivocal character.

Both of these groups are of great practical importance from the clinical point of view and although the immediate object of this address deals rather with the second group it will be convenient to consider shortly some characteristic illustrations of latent diseases occurring as complications of other maladies and producing no obvious symptoms. As an example of this the renal sequelæ occurring in diseases of the bladder and of other pelvic organs may be quoted. Both the mechanical and the septic complications affecting the kidneys in bladder and pelvic disease may be readily overlooked. A very considerable degree of hydronephrosis, even bilateral in its distribution, may be present as a result of obstruction without producing any more marked effects than a diminution in the specific gravity of the urine and an increase in the amount of urine passed. Pyelonephritis may also exist with little other change in the urine than the presence of a trace of albumin, together with the excretion of an increased quantity of urine of low specific gravity and slight evening pyrexia. The existence of either of these renal complications is a factor which has a profound influence on the prognosis of the underlying disease and also on the likelihood of the success or otherwise of even very simple operative procedures. These renal complications will serve as an illustration of a truly latent disease, often reaching a high degree of development without the production of any symptoms sufficiently important to attract the patient's notice.

Another malady of a widely different character, but which may be truly latent, is the well-known occurrence of latent cerebral abscess as a complication of ear disease. In such cases headache, vomiting, and other characteristic features of the malady may be completely absent and such patients may die with great suddenness from rupture of the abscess into the cerebral ventricles. This fatal event is not uncommon where there has been little reason for thinking that the patient was suffering from any grave disease. In many, but probably not in all, such cases the error of overlooking the existence of cerebral abscess may be avoided by a careful examination of the optic discs, as it is well known that a considerable degree of neuritis may be present without producing such an impairment of vision as to attract the notice of the patient.

Pericarditis is especially apt to run a latent course when it occurs as a complication of renal disease, especially of Bright's disease. In such instances there is often a further reason for the pericarditis being overlooked owing to the fact that pericarditis is frequently not the only complication present; uræmia in one or other of its many forms may coexist with it. It is exceptional for the latent pericarditis of renal disease to be unaccompanied by physical signs, although the characteristic pain and many of the other usual symptoms of pericarditis may be absent. A careful physical examination will usually reveal the existence of the complication, especially if we bear in mind the great frequency with which it occurs both as a complication of renal disease and as an accompaniment of uræmia, and hence examine our patients thoroughly.

Many other instances might be quoted of the occurrence of serious and sometimes fatal complications of gross organic disease with more or less complete absence of symptoms, but the above will suffice for our purpose.

In other cases serious complications occur which are overlooked owing to the symptoms produced being attributed not to the complication but to the underlying malady.

One of the most important and striking examples of this is afforded by the occurrence of so-called latent pleural effusion in cases of valvular disease of the heart and more especially, perhaps, in cases of aortic regurgitation. The latent pleural effusion of this type may develop to a considerable extent without producing any pain or other symptom attracting notice to the pleural cavity. In fact, in most cases no other effect than a gradually increasing dyspnoea is to be observed, and this dyspnoea, in the absence of a complete examination of the chest, may very readily be attributed to the cardiac malady and to cardiac causes when it is of mechanical and respiratory origin. Strychnia has often been prescribed in large doses for the relief of the dyspnoea of valvular disease where the proper remedy was paracentesis thoracis. Another reason why such latent pleural effusion is extraordinarily liable to be overlooked depends on the fact that it not infrequently occurs without the occurrence of marked general dropsy. Too much stress cannot really be laid on the important point in all cases of cardiac dyspnoea of a careful examination being made to determine the presence or absence of latent pleural effusion.

Although latent diseases are often overlooked when they occur as complications of declared maladies, yet the second group of cases described above where the disease is latent *ab initio* is by far the more important from a clinical point of view, as many of our most serious mistakes in diagnosis and prognosis are made by overlooking such maladies. In some instances, no doubt, it is impossible not only to diagnose but even to suspect the existence of a grave organic lesion and such cases are only revealed in the post-mortem room. Not infrequently, however, a diagnosis can be made, or, at any rate, a suspicion entertained, that the disease which is apparently acute is really an acute complication, development, or sudden manifestation of a previously existent latent malady. Instances of this kind can be quoted from almost all varieties of disease, but I propose in the remaining time only to deal with some of the more striking illustrations.

Amongst acute specific maladies typhoid fever is the one that affords the most striking as well as the most frequent illustration of this tendency to run a latent course. All clinicians are aware of cases of apparently sudden perforative peritonitis which are really cases of perforation of a typhoid ulcer where the typhoid fever has run a latent course or, at any rate, has produced quite trivial symptoms. Many such a case is erroneously diagnosed as a case of perforative peritonitis due to other causes. It is of great importance in all cases of apparent perforative peritonitis to cross-examine the patient carefully in order to determine whether symptoms of previous illness are really absent or, as is more often the case, whether they have been present, but of an equivocal and slight character. Whether rheumatic fever ever runs a truly latent course is perhaps open to question, but many cases are seen where extensive cardiac lesions are present and where no definite history can be obtained of any previous marked affection of the joints. Somewhat similar phenomena are seen also in the cases of the complications of diphtheria and of scarlet fever. Typical diphtheritic paralysis, often of a high degree of severity, is familiar to everyone as occurring occasionally where no definite history of a throat illness can be obtained. In the case of nephritis and Bright's disease the possibility of a more or less latent attack of scarlet fever is often a consideration that is forced on us. It is, however, in the case of chronic rather than in that of acute diseases that the most striking examples of the existence of latent diseases are afforded to us. The morbid processes which lie at the root of angina pectoris very commonly advance to a very high degree without the production of any symptoms and it is well known that the first attack of angina pectoris may be fatal. Fatty degeneration of the heart, especially in its more severe forms, is also a malady which may run a strictly latent course and the same is undoubtedly true of aneurysms limited to the first part of the arch and sometimes in others involving the thoracic aorta. I have seen an instance of a large aneurysm of the thoracic aorta which produced no symptoms of any kind until it had eroded the bodies of four dorsal vertebræ and then caused paraplegia. The fact that fatty degeneration of the heart is peculiarly apt to run a latent course is a matter of considerable practical importance owing to the great difficulty hitherto experienced not only in diagnosing the disease but also in excluding it. Latent fatty heart may

and does occur as an accompaniment or complication of many diseases as well as being the sole morbid process present and it may lead to sudden death in patients who are apparently not very seriously ill, as in some forms of alcoholic neuritis and also in some cases of hepatic cirrhosis. I have known a patient with hepatic cirrhosis to die suddenly from fatty heart where there was no evidence of the patient being seriously ill and where cardiac symptoms were conspicuously absent. The same fatality may occur in cases of alcoholic neuritis, so that in both these maladies the possibility of the presence of latent fatty heart must be considered. Some of the most serious and fatal of cardiac diseases are liable to run a latent course and this is a fact of capital importance in the diagnosis of these maladies.

Amongst pulmonary affections latent maladies are not so frequent; the one that is most liable to occur and to be overlooked is, I think, pleural effusion. Latent pleural effusion is, nevertheless, a malady that is very generally recognised and one that by some authorities is supposed to be more intimately associated with pulmonary tuberculosis than other varieties of pleurisy. It is also well known that the effects eventually produced by a latent pleural effusion are sometimes those that may first attract notice to underlying malignant disease of the lung or pleura. Phthisis is not very apt to run a truly latent course, although we are all familiar with instances where the most extensive phthisical changes may have occurred without the presence of very marked and obvious symptoms. It is usual, however, in such cases for symptoms to have been present, but either to have been overlooked or erroneously attributed to some other non-tuberculous affection.

It is remarkable that peritonitis may not only exist as a latent disease but that the most severe and violent forms of peritonitis may sometimes be present without producing any marked symptoms. I have known of a patient with perforated duodenal ulcer who was suffering from general advanced peritonitis who repudiated any idea of being ill and was walking about within a few hours of his death. The sole reason that led him to seek advice was some difficulty in passing urine, yet there was general peritonitis and the abdomen contained a large quantity of offensive pus. In the cases where peritonitis runs a latent course the form that is most likely to be present is the purulent one, and in the instance just quoted the peritonitis was not only general but the abdomen contained a very large quantity of free pus. It has been suggested by some writers that in cases of suppurative peritonitis the inflammatory process is so violent that the nerve endings are rapidly destroyed or their efficiency impaired and hence the painlessness of the disease.

One of the commonest diseases to run a latent course is gastric ulcer and even if, strictly speaking, symptoms are not completely absent, yet in a large proportion of cases they are very equivocal and may not lead to the suspicion being entertained of the presence of a gastric ulcer. The tendency of gastric ulcer to run a latent course or, at any rate, one where the classical symptoms attributed to ulcer are absent is of great practical importance for many reasons. In the first place, many of these ulcers perforate and although in a certain proportion of cases the perforation is, so to say, a local one, yet it is well known that perforation of a gastric or duodenal ulcer is one of the commonest causes of general diffuse peritonitis. It is a matter of considerable clinical importance that the absence of any marked gastric symptoms is really of little value in excluding gastric ulcer as a cause of general peritonitis. Another reason for bearing in mind the possibility of the presence of gastric ulcer is the fact that it is so often associated with chlorosis, so that it is difficult to exclude with certainty in any given case of chlorosis the possibility of the presence of gastric ulcer. Another reason for always bearing in mind in gastric affections the possibility of an ulcer being present without causing its characteristic symptoms depends on the fact that otherwise an erroneous diagnosis of gastric dilatation may be made. I have known of an instance where laparotomy was performed with the idea of treating gastric dilatation, where not only was an ulcer present which had not been suspected, but where this ulcer was of such a size as to involve nearly the whole of the posterior wall of the stomach.

Malignant disease of the stomach, the colon, and the rectum may not only exist without producing any marked symptoms but may reach a very high degree of development without causing even any impairment of the general health.

It is true that this is exceptional, but its occurrence is sufficiently frequent for the fact to be borne in mind. Some years ago I saw a case of a man, aged 30 years, who came under observation for a slight enlargement of the umbilicus which was clearly of a malignant nature. He presented no symptoms or physical signs of abdominal disease, but a few days afterwards succumbed to an attack of profuse hæmatemesis and a large primary carcinoma was present in the stomach. In this case the absence of symptoms was so complete that the patient refused to believe that there was anything seriously amiss with him and persisted in thinking that the induration of the umbilicus was dependent upon the irritation produced by a button. Profuse hæmorrhage may also be the first symptom produced by malignant disease of the rectum which may have reached a high degree of development without producing any local discomfort or any symptoms to attract notice. This is perhaps more especially the case where the disease occurs in elderly vigorous patients.

Many hepatic diseases are liable to run a latent course and in tropical countries this is not uncommonly the case with hepatic abscess. In this country, however, this is not a matter of any very great practical importance. Gall-stones probably produce no symptoms in the great majority of cases of their occurrence, and this is a point which must be always borne in mind in the diagnosis of the possible causes of jaundice. Although the mere presence of gall-stones does not in the majority of cases lead to symptoms, these are usually produced when there is any attempt at the passage of the stones. It is well known, however, that large stones may ulcerate through the gall-bladder into the intestine without the production of any symptoms indicative of obstruction of the bile-ducts. Hence in cases of intestinal obstruction from impaction of gall-stones a history of jaundice is not to be expected. Perhaps the most striking, and certainly the most common, instance of latent disease of the liver is afforded by cirrhosis in its many forms and especially perhaps by alcoholic or atrophic cirrhosis. It is well known that symptoms are not produced in this malady until the disease has advanced to a very great extent and, in fact, they ought to be called terminal symptoms owing to the period of the disease at which they are present. This is especially true of ascites and to a less extent of hæmatemesis, but it must be remembered that a high degree of hepatic cirrhosis may exist for many years and death may occur as an indirect result of some intercurrent illness. It is from this point of view that the recognition of the latent course that hepatic cirrhosis is apt to run is especially important. A patient may suffer from hepatic cirrhosis with no apparent ill effects for an unknown but prolonged period and then as the sequel of an attack of some intercurrent disease, such as influenza or typhoid fever (to quote instances which have fallen under my own observation), a characteristic toxic group of symptoms dependent on the destruction of the liver may develop and rapidly prove fatal. In some instances this does not occur during the height of the intercurrent affection but subsequently to it and during convalescence.

Another remarkable group of cases of rather uncertain nature is afforded by patients who come under observation suffering from acute general peritonitis apparently dependent on perforation, but where no perforation is found post mortem but a high degree of atrophic cirrhosis. Two such instances have fallen under my observation and both in children where there was apparently no symptom of ill-health prior to the sudden onset of the general peritonitis, and the violence of this in both cases suggested the presence of appendicitis or some other form of perforative peritonitis. No perforations were found at the post-mortem examinations, but on the other hand there was extensive hepatic cirrhosis together with acute general suppurative peritonitis.

Amongst cerebral affections, tumor cerebri, meningitis, and aneurysm of the large cerebral vessels all afford illustration of the existence of very grave organic disease without the production of symptoms. Aneurysm of the cerebral vessels is extraordinarily liable to produce no symptoms for a more or less prolonged period, in some instances not until the fatal rupture, and in other cases the symptoms produced are so equivocal as to render recognition of the underlying disease impossible. I have known of a case of aneurysm of the basilar artery where the initial symptom was stiff neck and after the persistence of this for a few days the patient developed irregularity of pulse and retention of urine to be followed very shortly by the coma

dependent on the rupture of the aneurysm. The existence of tumor cerebri without the production of obvious symptoms is so well known that everyone appreciates the difficulty of excluding with certainty the presence of tumour.

In the case of meningitis we meet with a remarkable instance of the existence of a grave and fatal disease without the production in some instances of the characteristic features of the malady. This absence of symptoms may occur not only in the acute disease but also in the chronic form, or, to be more accurate, in the condition which may remain as a result of a former attack of acute meningitis. Instances are known of diffuse suppurative meningitis where the onset of symptoms ultimately has been so sudden as to suggest the occurrence of a vascular lesion or even such a condition as meningeal hæmorrhage and where, as a result either of operative interference or post-mortem observation, it is certain that the condition must have existed for a considerable time before the occurrence of the symptoms. Every physician is familiar with cases of meningitis where the absence of the characteristic features of the disease has led to an erroneous diagnosis of hysteria or even malingering. There is a rare form of meningitis, of which three instances have been seen by me, where the patient may recover from an acute illness characterised by headache, fever, retraction of the head, with vomiting and other symptoms suggesting the presence of meningitis. Notwithstanding their recovery and the more or less complete absence of symptoms such patients die suddenly after a variable interval of apparent recovery of health. In one instance such a patient presented occasional vomiting but otherwise seemed perfectly well and was up and about. The post-mortem examinations in all these three cases showed thickening and opacity of the membranes at the base and distension of the fourth ventricle. None of them were really diagnosed, although in one the condition was suspected on account of the history of the acute illness and owing to the presence of some optic neuritis. These cases illustrate the manner in which the effects produced by the acute meningitis may lead to a condition that is rapidly fatal although not productive of marked symptoms.

Many diseases of the spinal cord, meninges, and even of the spinal column may not only exist but may reach a very high degree of development without the production of any characteristic symptoms. Thus a perforating ulcer or Charcot's joint may be the first evidence of the existence of such a chronic disease as tabes or syringomyelus, and fracture of the spine as the result of a sudden movement may be the first unequivocal evidence of the existence of sarcoma or other malignant disease of the bones. Again, the apparently sudden formation of a large psoas abscess may be the first indication of spinal caries, and in this malady it is not uncommon for paraplegia, or rather weakness of the legs, to be an early symptom of primary mischief in the bones.

Diseases of the kidneys afford perhaps the most striking instances of the existence of grave organic lesions without the presence necessarily of marked and obvious symptoms. We have already seen that diseases of these organs may occur in an insidious manner as consequences or sequels of pelvic diseases without affording sufficient symptoms to attract attention. Kidney diseases afford perhaps also the most frequent examples of the diseases grouped under the second heading of this address—viz., those where the original malady is overlooked until the occurrence of complications. Almost all the common affections of the kidney may exist in a latent form and advance to a high degree without producing marked symptoms. This is not only seen in such affections as hydronephrosis and pyelonephritis, but also in cystic disease, and most important of all in granular kidney and in certain forms of Bright's disease. The recognition of what may for shortness be called latent Bright's disease and latent granular kidney is of great practical importance owing to the beneficial effects that may be obtained as a result of the proper treatment of these diseases.

The occurrence of bilateral cystic disease without the development of marked symptoms is more a matter of theoretical interest than of great practical importance inasmuch as so little can be done for the disease when recognised. It is not uncommon for patients to come under observation on account of vague abdominal symptoms or for such a symptom as gradually increasing constipation and then on examination of the abdomen for the presence of cystic disease of the kidneys to be revealed, and in such instances the large size of the

renal tumours indicates that the malady must have existed for a very considerable time. In other instances, as is well known, extensive and bilateral cystic disease produces no symptoms of any kind and is discovered, so to say, accidentally where not suspected in the post-mortem room. Uræmia in one of its many forms, and even in its most acute form, may be the first intimation of the existence of cystic disease of the kidneys. The affection usually described as granular kidney is also one that is constantly coming under our observation in a more or less latent form and this is the case both where the renal affection is part and parcel of a widespread arterial degeneration and also in other instances where the main incidence of the pathological process is on the kidney itself. No doubt in the large majority of both classes of these patients careful cross-examination may elicit some symptoms of ill-health prior to the development of the complication that compels the patient to seek advice, but in a great many cases such symptoms are elicited with difficulty and only after the development of the complication. It is not unusual for these symptoms to be of a vague character, such as a failure in the general health and strength or possibly some impairment of the general nutrition, symptoms which may be due to a great variety of causes and which do not at first sight suggest a possible renal origin. A common complication that leads to the recognition of the underlying malady is cerebral hæmorrhage, but in these cases the cerebral hæmorrhage is usually profuse and often fatal, and therefore the recognition of the underlying cause is of no avail.

In another and perhaps more striking group of cases no symptoms of sufficient importance to attract attention on the part of the patient may occur until the onset of epileptiform seizures or some other manifestations of uræmia. Numerous instances have occurred where patients have died from acute uræmia after an illness lasting in some cases a few hours and in others only a few days. It is always worth while to examine carefully for the presence of a granular kidney in cases of sudden epileptiform seizures occurring for the first time in a patient of the age liable to granular kidney. I would especially draw your attention to the fact that one of the most fatal forms of chronic Bright's disease not uncommonly runs what is to all intents and purposes a latent course, no symptoms being produced until the terminal or fatal illness which may last but a few days. This form of Bright's disease is most commonly seen in young adults and is characterised post mortem by the presence of small white or mottled kidneys with a rough granular surface. These patients in my experience do not present, as a rule, any history of a definite attack of acute Bright's disease characterised by dropsy and they are often quite unable to give any information by means of which the onset of the disease can be ascertained, although doubtless in some instances it is a sequel of a former attack of acute Bright's disease, but I do not think that it is so in all for the reason just mentioned. A very considerable proportion of these cases do not come under observation until a fatal complication is present and this complication is especially likely to be uræmia. In some instances one of the so-called uræmic skin eruptions has been the first symptom that has attracted notice. In others the first symptom has been failure of vision owing to the development of retinal hæmorrhages and marked optic neuritis, and in others some inflammatory complication has supervened, more especially pericarditis. But uræmia in all its forms is unquestionably the most important and, I think, the most common complication. Thus a patient may be seen suffering from what is apparently an epileptiform seizure and perhaps presenting no very marked signs of ill-health, the onset of the fits having been quite sudden. Yet on examination the presence of marked arterial changes and albuminuric retinitis and the secretion of a copious dilute urine containing a large quantity of albumin all point to the conclusion that the disease is not only latent but has really existed for some considerable time, often for years. In the great majority of these patients it would not be correct to state that all symptoms are absent; there is often some progressive failure of health and strength, but even this in some cases is not marked and I have known the disease to be fatal from uræmic complications occurring at a time when the general aspect of the patient would by no means suggest the possibility of the presence of a grave renal disease. Thus, a young man, 25 years of age, presenting no history of a former acute illness, came under observation on account of neurasthenic

symptoms associated with, and apparently due to, business worries. A few days afterwards a papular eruption appeared all over the skin of the trunk and examination of the urine showed that it was of low specific gravity, abundant in quantity, and contained a large amount of albumin, notwithstanding the fact that his general nutrition was good and there were no obvious signs of anæmia. In less than a week acute uræmia developed with marked dyspnoea which was fatal in 48 hours. This form of Bright's disease may very readily be overlooked unless the urine be examined in a routine fashion. The state of the optic discs will also often afford evidence of the existence of the malady, as it is probable that where it has existed for any length of time changes both in the retina and in the retinal vessels can be detected. One of the reasons leading to the malady being overlooked is perhaps the fact that dropsy is not a marked feature and may even be entirely absent and, according to my experience, this is generally the case. The state of the heart and of the vessels will often raise a suspicion of the presence of this form of chronic Bright's disease, but pronounced arterial changes to be detected by the finger are not always present and cardiac hypertrophy may unquestionably sometimes be absent. The other form of chronic Bright's disease, the so-called large white kidney, is not so apt to run a latent course and owing to the anæmia produced and the frequency of dropsy the recognition of the malady is easy.

In conclusion, the great lesson that is to be learnt from the occurrence of all these numerous varieties of latent disease is the one that most of them can be detected or at any rate suspected as the result of a complete physical examination. In other words, it is the symptoms that are absent, not the physical signs. The only precaution that it is necessary to take is to examine as far as possible all the organs of the body and not to be contented with a physical examination restricted to those parts to which the patients draw attention. Thus many a patient complaining of heart symptoms perhaps dependent on organic disease of the heart is really suffering from renal disease with secondary heart difficulties; the real cause of the disease would be completely overlooked if the examination were confined to the organ to which the patient's symptoms are referred.

The Goulstonian Lectures

ON

THEORIES OF IMMUNITY AND THEIR CLINICAL APPLICATION.

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LECTURE III.¹

Delivered on March 24th.

ACTIONS, OTHER THAN ANTITOXIC AND BACTERICIDAL, OF CURATIVE SERA.

MR. PRESIDENT AND GENTLEMEN,—We have seen that the introduction of the serum of one animal into the tissues of another, especially of a different species, leads to the formation of antidotes to that particular kind of serum. In some instances, indeed, the serum of one animal may be toxic for another. The introduction, therefore, of a quantity of horse's serum into the human body may not be—indeed, is not—always a matter of indifference. We know that in the case of diphtheria antitoxin a certain percentage of cases have eruptions, pains of the joints, &c., which are probably to be assigned to the alien serum. Perhaps the

juvenile serum is of a more primitive nature than the adult, since children are said to stand prophylactic injections of diphtheria antitoxin better than those already grown up. But in the case of antitoxic sera these side-issues do not interfere with their efficiency. Nor will any harm arise from a dose beyond what is necessary for mere neutralisation of the toxin; on the contrary, the excess may dissociate a union of toxin and cell already completed. There is not at present any evidence to show that the toxin formed by the bacillus diphtheriæ in the human body is not efficiently neutralised by the antitoxin formed in the horse's tissues.

With bactericidal sera the case is rather different, because for their efficient action both amboceptor and complement are required. It is obvious that efficiency will be attained only if both components are present in sufficient quantity, but it is the number of amboceptors resulting from the process of immunisation which will determine to a large extent the potency of the bactericidal serum, since they are present in normal blood only in small quantity. The complement, as we know, is much more unstable and may, on keeping of the bactericidal serum, either disappear or be converted into complementoid. On the other hand, complement is present in quantity and variety in normal serum, so that the introduction of amboceptors alone in the bactericidal serum will often suffice for its efficient action. But the quantitative relations of amboceptor and complement are of extreme importance. It has been known for some time that a medium dose of a bactericidal serum may save an animal from a lethal infection whilst a larger or smaller quantity fails to do so. The explanation seems to be as follows: If the two components are present in corresponding quantities the amboceptor will unite with the bacterium by its haptophore group, the complement will then fit into the complementophile group of the amboceptor and the bacterium will be destroyed. But with an excess of amboceptors an alteration of equilibrium takes place and the affinity of the complementophile group of the engaged amboceptor for the complement may be altered. If increased there is no harm done, because the complements will unite with the already engaged—viz., effective—amboceptors. If the affinity remains equal the complements will be equally distributed and only half will take part in the bactericidal action and the efficiency of the serum will be correspondingly reduced. If the affinity is diminished the result will be even more unfavourable, for then the complements will become first attached to all the unengaged amboceptors and only the remainder will be available for effective bactericidal action. Consequently in certain circumstances too much bactericidal serum may do more harm than good. Even if sufficient complement be introduced with the bactericidal serum it may lead to the formation of anti-complement and so, although a suitable complement as such will usually be present in the immune serum used for curative purposes, it may become engaged with the anti-complement and so be rendered useless. On the other hand, in active immunisation, although so far as we know there is no increased production of complement, that already existing in the organism will fit and activate the amboceptors formed during the immunising process.

To give a concrete example. Pigeons infected with vibrio Metchnikovi cannot be saved by the injection of the inactivated (heated) serum of rabbits immunised against the vibrio, unless some fresh rabbit's serum (containing complement) be added. The pigeon's blood possesses no suitable complement for the rabbit's amboceptors. On the other hand, by active immunisation of pigeons with dead culture of vibrio Metchnikovi they are soon rendered able to stand a multiple of the lethal dose, so that their blood must contain a suitable complement for their own amboceptors. For these reasons the treatment of enterica by weak immunisation with dead culture (Petruschky) may sometimes be more effectual, even after infection, than a bactericidal serum, or, perhaps, in spite of apparent theoretical objections, a combination of the two modes of treatment may be useful.

In his Croonian lecture (1900) Ehrlich says: "From this it appears that in the therapeutic application of anti bacterial sera to man therapeutical success is only to be attained if we use either a bacteriolysin with a complement which is stable in man, or at least a bacteriolysin the amboceptor of which finds in human serum an appropriate complement. The latter condition will be the more readily fulfilled the nearer the species employed in the immunisation process is to man. Perhaps the non-success which as yet has attended the employment of typhoid and cholera serum will be converted

¹ Lectures I. and II. were published in THE LANCET of March 21st (p. 775) and March 28th (p. 853), 1903, respectively.