as the central zone was diseased and unable to assist, some of the iron had to remain in the still functional cells of the outer zone.

If we take this view of the matter, then pernicious anæmia merely becomes a very severe form of anæmia generally, but no distinct disease. It becomes easy to understand how other forms may gradually become pernicious, and how pernicious anæmia itself may recover by gradually passing into milder forms.

You will say, Surely the condition of the blood, the marked difference in the relation of the red corpuscles to the hæmoglobin, and the changes in the corpuscles themselves are diagnostic marks indicating a fundamental divergence. But even this is not so irreconcilable a state as one is apt to imagine. I have at this present time a young girl under my care (Case 1) in whom the red corpuscles are but 33 per cent., whilst the hæmoglobin is as much as 28 per cent; yet there is no doubt that she is simply a chlorotic, with, it is true, symptoms of gastric ulcer. She shows no evidence of dangerous illness nor extreme feebleness; moreover, she is rapidly improving under Bland's pills. The corpuscles may be most variable in size and shape in pernicious anæmia, but they are by no means normal in these particulars in other anæmias; chlorosis is recognised to have a partiality for microcytes. It is only to be expected that the cells should most depart from their normal type in the severest form of the disease. Indeed, clinically, we are continually finding transition forms which more and more bridge the gap that still separates the pernicious from simple anæmia. Often it is hard to tell the one from the other, and cases which begin with all the signs and symptoms of simple anæmia end fatally. Moreover, if we take a case of the most fatal and another of the mildest type of anæmia, these two certainly do not differ as much as a chronic tuberculous gland disease of the neck does from an acute military tuberculosis.

[The lecturer concluded by discussing the relative influence of the blood, the capillary endothelium, and the heart in producing the cedema so common in anæmia.]

GOULSTONIAN LECTURES

ON THE

CHEMICAL PATHOLOGY OF DIPHTHERIA,

COMPARED WITH THAT OF ANTHRAX,

INFECTIVE ENDOCARDITIS, AND

TETANUS.

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LECTURE III.

THE specific action of the diphtheria products is brought into greater prominence when it is contrasted in parallel experiments with the chemical bodies found in anthrax and in infective endocarditis.

Infective Endocarditis.—The case of infective endocarditis examined was under the care of Dr. Cayley, at the Middlesex Hospital, and I performed the *post-mortem* examination when I was pathologist to that hospital. The history of the case may be briefly stated. The patient was a young unmarried woman, aged 21. The illness began eight weeks before death with pain in the left breast, and was characterised by wasting and intermittent fever during the six weeks' stay in the hospital. The temperature rose to 103° F. or 104° F. every day, and only once did shivering occur. The cardiac signs were those of double mitral disease. Four weeks before death the right brachial artery became plugged by an embolus, and three weeks before death the left femoral. Albuminuria occurred four weeks before death.

At the *post-mortem* examination, twelve hours after death, there was chronic disease of the mitral valve, with fungating vegetations spreading over the endocardium of the left auricle, and ulcerated on the surface. The blood was imperfectly coagulated, and was lakey in colour. There was a recent embolus in the left middle cerebral artery and older emboli (sur-

rounded by organising thrombus) in the right brachial and left femoral arteries, while at the origin of the superior mesenteric artery there was a softening embolus. The right kidney showed two scars of old infarcts, and there were two caseated infarcts in the spleen. The spleen was greatly enlarged, dark and congested. The liver was fatty, the kidneys fibro-fatty, and the lungs oedematous.

This was, then, a case of ulcerative endocarditis not associated with abscesses or pyæmia.

The mitral valve was examined microscopically, and the blood and spleen chemically, while cultivations were made from the blood and from the vegetations on the mitral valve.

Microscopically the mitral valve showed the fibrous thickening of chronic disease with recent vegetations capped by fibrin.

This is a photograph under a low power (70 diameters) of a

section of the free edge of the vegetations. The fibrils of the fibrin are seen capping the thickened connective tissue containing collections of round cells. Along the free edge of the fibrin is a fringe of micrococci, very thick, and invading the fibrin. Outlying clusters of the cocci are also seen, and in some parts the micro-organisms are seen in groups in the tissue of the valve itself. In this case, then, the micro-organism has, as its culture medium, the fibrin capping the vegetations.

Bacteriological Examination.—No micro-organisms were found by making cultivations of the blood of the right ventricle. From the vegetations, with proper precautions, a pure cultivation was at once obtained of cocci with the same microscopical appearances as those seen in the valves—namely, they were cluster or staphylococci, and not streptococci. Only one culture out of the five made showed any contamination; four were pure, and showed only the growth of the staphylococci. Without going further into the bacteriological procedure, this organism may be described as growing on agar in bluish-white opaque circular colonies, and on gelatine in a similar manner, but rapidly liquefying the medium. Microscopically it is a staphylococcus, forming clusters and not chains.

Pathological Action.—This coccus does not produce pus when introduced under the skin of a guinea-pig or into the circulation of a rabbit. In a guinea-pig it produces a febrile disorder lasting over eleven weeks, accompanied by extreme wasting and ending in death. When injected into the circulation only a slight illness results, from which the animal recovers. When killed no micro-organisms were discovered in the blood. The pathological effects of this micro-organism

have yet to be completely worked out. I contented myself, as a commencement, with determining what sort of illness it produced in animals, and whether it formed abscesses. The kind of illness produced, and the absence of abscesses when subcutaneously introduced, showed that it had the characteristics of the coccus found in the valves of the heart. Each case of infective endocarditis must be studied by itself, for the disease is by no means an entity. Some cases of ulcerated cardiac vegetations occur as part of a pyæmia proceeding from pelvic or other abscesses where the primary infective agent appears to be the staphylococcus or streptococcus pyogenes. In others, again, no primary pus focus is found, but there are multiple abscesses due to infective emboli from the ulcerated valves. Other organisms, such as Friedländer's pneumococcus, may also possibly play a part in the disease. In the case under consideration, however, there was only one micro-organism, and that one not a pus-former.

Chemical Examination.—A chemical examination was made of the blood and spleen by the same methods I have already described. The result showed that the same two classes of products are present in the blood and spleen as in anthrax and diphtheria—namely, digested proteids or albumoses, and a non-proteid product which, when first separated and purified, is strongly acid. The albumoses are proto- and deuto-albumose, chiefly the latter, indistinguishable by chemical reactions from the similar bodies we have already discussed. The final product is separated by dissolving in alcohol and purified by precipitation with ether. It is insoluble in chloroform, and is an amorphous yellowish-brown substance, with a strongly acid reaction. The amount of the products is seen in the following table:

In Infective Endocarditis.

	Albumoses.	Alcoholic Extract.
From blood	0.236	Trace
From spleen	6.705	1.29
	6.941 grammes	

The large amount of albumoses and alcoholic extract present in the spleen is remarkable. Here again, as in diphtheria and anthrax, the spleen is the repository and manufactory of the chemical poison.

Physiological Action of the Albumoses.—The physiological action of the albumoses was tested side by side with that of anthrax albumoses while the experiments on diphtheria were progressing, so that the animals could be compared. The albumoses of infective endocarditis are producers of fever, and retard the coagulation of the blood. The effect of the intravenous injection of a dose of 0.122 gramme per kilo. of body weight is with the anthrax albumoses a great rise of temperature lasting for three days; with the ulcerative endocarditis albumoses the fever produced is much less marked. With a larger dose (0.2 gramme per kilo. of body weight) the fever in the case of the anthrax albumoses is not so well marked, while in the case of the albumoses of ulcerative endocarditis it is more marked than with the smaller dose. With a still larger dose (0.3 gramme) the anthrax albumoses cause only a slight rise of temperature, succeeded by a fall and death in two hours, while the albumoses of ulcerative endocarditis cause a moderate rise of temperature, which is continued for two days. The anthrax albumoses, therefore, are much more toxic than those from ulcerative endocarditis. The fever produced by them is well marked with a small dose, but with larger doses it is less, and with a lethal dose it is very slight indeed.

In the experiments just described there is no paralysis produced, but wasting is observed in some of the animals.

These figures show that the anthrax albumoses produce a greater effect on nutrition than those of ulcerative endocarditis. When multiple doses of these products are given, fever is produced but no paralysis, contrasting greatly with diphtheria products. The effect on the temperature of three doses of anthrax albumoses on successive days, equal to 0.122 g. per kilo. of body weight, and of the albumoses of ulcerative endocarditis also in three doses, equal to 0.153 g.

per kilo., is that there is a rise of temperature each day following the injection, which is continued for one day after the last inoculation. The anthrax animal died in forty-two days, having lost two-fifths of its body weight, while the ulcerative endocarditis animal showed no loss of weight, and was killed on the fifty-third day. This last was an adult animal; a young animal injected with the same dose of endocarditis albumoses died on the third day after the last injection.

Alteration in Weight.

Dose per Kilo. of Body Weight.	Anthrax Albumoses.			Albumoses of Ulcerative Endocarditis.		
	Gain.	Loss.	Time after inoculation.	Gain.	Loss.	Time after inoculation.
0.122 g.	200 g.	—	28 days	—	90 g.	16 days
				30 g.	—	28 "
0.2 g.	—	530 g.	12 "	100 g.	—	11 "
		80 g.	102 "	652 g.	—	102 "
0.3 g.	—	—	—*	70 g.	—	10 "
0.153 g., in three doses	—	—	—	85 g.	—	100 "
				210 g.	—	4 "
0.122 g., in three doses	—	130 g.	4 "			
		1020 g.	42 "			

* Death in two hours.

Post-mortem Examination.—The post-mortem examination of the animals that died or were killed showed the absence of any pathogenous micro-organisms. A microscopical examination of the phrenic nerves and of the motor nerves was made, and revealed no morbid condition, no nerve degeneration such as was observed in the case of the diphtheria products. The contrast with diphtheria is therefore well marked. Fatty degeneration of the heart was found in some of the animals, especially those which had been inoculated with the anthrax albumoses, and the animal which had the largest single dose of the albumoses from infective endocarditis. This fact helps to explain the fatty degeneration of the heart following the injection of the diphtheria products. Occurring in the animals inoculated with anthrax and ulcerative endocarditis albumoses, it tends to show that the fatty degeneration is due to an effect on the nutrition of the heart by the albumoses circulating in the blood stream.

Tetanus.—The case of tetanus examined was under the care of Mr. Hulke at the Middlesex Hospital. It was a typical case of acute tetanus, following a penetrating wound of the sole of the foot caused by a nail. The symptoms began one week after the accident, and death—which occurred ten days after the accident—was preceded by rapidly succeeding tetanic spasms. The post-mortem examination revealing no definite morbid lesion, a chemical examination of the blood was made, and 0.5972 g. of albumoses (chiefly deuto-albumose) was obtained, with a small quantity of a substance extracted by alcohol, the nature of which is still undetermined. I wish at present only to draw attention to the fact that in tetanus, as in the other diseases examined, the same two classes of poisons are present.

Action of the Tetanus Albumoses.—A single dose, equal to 0.143 g. per kilo. of body weight, was injected into the circulation of a rabbit. A depression of temperature occurred on the day of experiment. After this the animal appeared for a few days quite well; it showed no paralysis, but on the twelfth day it was found to have lost one-sixth of its body weight. It died on the twenty-first day, greatly emaciated, having lost nearly one-half of its original weight. This progressive wasting shows that the tetanus albumoses resemble those found in diphtheria.

The continuation of the subject of tetanus I must leave for a future communication.

GENERAL CONSIDERATIONS.

Having now brought forward the facts in the chemical pathology of the infective disorders, diphtheria, anthrax, and

ulcerative endocarditis, chosen for investigation, it is necessary to consider generally the bearing of the results.

In summing up the effect on the body of the introduction into it or upon it of a primary infective agent, the symptoms may be referred to two causes: (1) mechanical, (2) chemical. The mechanical effects are illustrated by the fact that the infective agent may, as in diphtheria, produce a membrane which spreads down the air passages and endangers life. The effect of this mechanical obstruction, which is to some extent relieved by intubation or tracheotomy, is well recognised as a danger in diphtheria. Another example of mechanical effect is seen in infective endocarditis, in which not only do the fungating vegetations interfere with the proper action of the heart, but the emboli broken off from them, by plugging large vessels, cut off or diminish the blood supply to a part, and so lead to grave results. Although such mechanical effects may be looked upon as merely pathological accidents, their consequences have to be considered in dealing with the pathology of these diseases. They sink, however, into comparative insignificance when the rôle of the chemical products of the primary infective agent is elucidated. What has been made clear to me during the course of the research, and what I have attempted to bring before you, is that these chemical products are specific in their action; that inasmuch as the bacillus anthracis is separable from other pathogenous micro-organisms as producing a definite disease—anthrax—so the chemical products of the bacillus are separable to a certain extent chemically, to a greater extent physiologically from those formed by other pathogenous micro-organisms. Similarly with diphtheria, the bacillus diphtheriæ produces products differing in their physiological action from those found in anthrax and in infective endocarditis. The specific primary infective agent produces, therefore, specific chemical products by means of which it acts.

It is evident from this that we have another basis for the study of infective disorders, in addition to the purely bacteriological one, which is the study of the primary infective agent. The following now well-known bacteriological rules are recognised: to prove that a particular micro-organism is the cause of a disease, (1) it must be found always associated with the disease, (2) it must be separated from the diseased tissues in pure culture, (3) it must be injected into susceptible animals and reproduce the disease, (4) it must be again obtained from this experimentally-produced disease. To this I would add another—namely, that the chemical poison must be obtained from the tissues in the natural disease, and products with a similar physiological action proved to be formed by the primary infective agent when grown outside the body. This will no doubt aid progress in pathology, because in some instances, as in cholera and leprosy, animals susceptible to the disease are not forthcoming. If, for example, it be definitely proved that certain chemical poisons with a specific action are present in the bodies or evacuations of cholera patients, and if the vibrio cholerae asiaticæ produces the same products, then we must look on this micro-organism as the cause of the disease.

It is possible, that in some infective disorders, such as measles, scarlet fever, and small-pox, in which the primary infective agent is as yet unknown, a chemical examination of the tissues on the lines laid down may aid in the discovery of the living contagium.

In this way, too, it will be possible to decide whether such a disease as membranous croup of the larynx really exists. There is no evidence at present that there is any disease other than diphtheria which can produce a false membrane in the larynx. And now that it is known definitely that diphtheria is a disease caused by the bacillus diphtheriæ, and that the chemical substances found in it are readily recognisable by the fact of their producing a definite nerve lesion, it will be possible for any observer to separate the chemical substances from the "croupous" membrane or from the body after death, and decide their nature. This chemical procedure will be a more certain test than a bacteriological examination.

I should like to insist on the point that in studying the chemical pathology of an infective disorder it is not sufficient to investigate the artificial chemical products of the primary infective agent; a chemical examination of the tissues of persons dead of the disorder must also be per-

formed. How important this is is shown by one fact which has been brought out in these experiments—namely, the pathological rôle of the spleen.

Rôle of the Spleen.—The spleen is an organ with an obscure physiology and a still obscurer pathology. Anyone who has tried to understand what has happened to a spleen in a case of infectious disease must have been struck with the utter hopelessness of coming to any definite conclusion regarding that organ from a merely physical examination. From the physiological point of view it is known to undergo certain mechanical changes which can only be of slight import, and (besides being a birthplace for white blood cells) to contain in a comparatively large amount the crystalline products of the breaking up of proteids such as uric acid, etc. The chief point about the organ, however, from a pathological point of view, is that the blood flows through the walls of the vessels into spaces; thus we have a more or less stagnating fluid, the proteids of which can be digested either by micro-organisms or by ferments. In anthrax and infective endocarditis this organ is greatly enlarged; in diphtheria it is usually normal in size. In all three cases it is the proteids of the spleen from which the specific poisonous products are mainly formed; they serve as the food of the infective agents, primary or secondary.

Food for the Infective Agents.—Besides the spleen, there are other parts of the body in which the primary infective agent finds suitable media in which to grow. Thus pathological effusions, whether already present in the body or formed by the primary infective agent, are suitable culture media. These effusions, speaking generally, may be considered as slightly alkaline solutions of proteids which are outside the active metabolism of the body—that is, the proteids are not in a living fluid like the blood. The bacillus anthracis, for example, when injected under the skin of an animal, forms this effusion by its products, and thus provides its own culture medium. The interstitial fluids of the tissues of the body, containing as they do the amount of proteid, sodium chloride, and phosphates necessary for the growth of the primary infective agent, probably serve as culture media.

Lastly, in diphtheria and in infective endocarditis fibrin serves as the medium in which the micro-organism flourishes. In diphtheria the false membrane is composed of fibrin, which, as I have shown, is in a state of digestion, and the exudation of this fibrin is no doubt produced by the earliest products of the bacillus diphtheriæ. In the case of infective endocarditis which I have brought before you, the nidus of the micro-organism was formed by the fibrin capping the vegetations. Without a suitable medium the primary infective agent cannot develop, cannot produce its poisonous products.

Products formed by the Primary Infective Agent.—I have attempted to make clear the fact that in these infective disorders the primary infective agent or living contagium produces its effect in man by means of its specific chemical products, which it forms from the proteids of the body with or without the intervention of a ferment. It may be that in all cases the chemical substances are produced by means of an unorganised ferment excreted by the primary infective agent; but the point that concerns us is that in only one of the diseases examined—namely, diphtheria—is there any evidence to show that this ferment plays a direct pathological rôle. In this disease, in which the bacillus diphtheriæ is limited to the superficial parts of the membrane and does not diffuse itself throughout the body, it was seen that there was something excreted by the bacillus and absorbed into the body, in the tissues of which were digested products. This excretion of the bacillus was looked upon as a ferment, and was called the "secondary infective agent." In anthrax and infective endocarditis, on the other hand, the primary infective agent is in the body itself, and there is no evidence that a ferment plays any direct part in the causation of the symptoms of the disease. I very much suspect that in tetanus—a disease which resembles diphtheria in the fact that the primary infective agent is limited to the site of inoculation—a ferment or excretion of the bacillus acts as a secondary infective agent. But this is quite undecided. The secondary infective agent cannot be expressed in any chemical terms; only in terms of what it can accomplish,

either (1) of its physiological action, or (2) of its capacity for forming from proteids chemical bodies which resemble it in physiological action. The secondary infective agent is one possessing properties which, like those of unorganised ferment, are usually expressed by the term vital; it is, as it were, one of the vital properties of the living cell cast off in a form which is unorganised.

Products of the Infective Agents.—The products of the primary or secondary infective agents are chemical bodies belonging, as I have shown, to two groups—a proteid and a non-proteid. The proteid form the class of digested proteids or albumoses and peptone; the second group are final products from the digested proteids, and are analogous to the leucin and tyrosin of pancreatic digestion.

The organic constituents of the body consist of proteids, carbo-hydrates, fats, and certain so-called extractives, which, like urea, uric acid, etc., are nitrogenous and the result of proteid metabolism. There is no evidence at present that pathogenous micro-organisms can form from fats and carbo-hydrates poisonous bodies; they may break them up, but the chemical bodies produced have but little physiological action; while the proteids are substances which, from their enormous molecule and from the presence of nitrogen, are capable of being split up into poisonous bodies.

The chemical difficulty with proteids is that there is no knowledge of the size of their molecule, and, what is of greater importance, of their molecular construction. The percentage composition gives no idea of the size of the molecule, and the only idea we have of the molecular constitution of a proteid is from a study of the chemical constitution of the nitrogenous bodies resulting from its destruction.

It is not, therefore, surprising that with regard to the first class of poisonous products under consideration, namely, the albumoses, no very definite chemical knowledge is forthcoming, and that, as I have stated, all the albumoses I have been describing give the same chemical reactions. An ultimate analysis to determine the percentage composition is of but little value in the case, as it is the molecular constitution we wish to know. We have, therefore, to express the albumoses in terms of their physiological action and to be content with demonstrating that the diphtheria albumoses differ from peptic albumoses and those found in anthrax and in infective endocarditis in producing a paralysis consequent on a nerve degeneration, and that the anthrax albumoses are more poisonous than those of infective endocarditis.

The chemistry of the final products (the anthrax base, the organic acid in diphtheria, etc.) is, however, a subject which will probably yield very fruitful and definite results. Such an investigation is, perhaps, one of the most difficult in organic chemistry. For us, as physicians and pathologists, the physiological action of such substances is of more importance than their chemistry; but as they are factors in disease, and in some diseases the chief factors, the more complete our knowledge of them, the more likely will the means be found to combat them. In anthrax, for example, it is the final product, the alkaloid, which is the cause of death; the albumoses play a very subsidiary part in the production of the fatal result. In diphtheria, on the other hand, the albumoses play the more important rôle, while the organic acid has only an insignificant action. There may, indeed, be other diseases in some of which the albumoses play the chief pathological rôle, in others the final product, whether base or acid.

Comparison with other Poisons.—These poisons found in infective diseases do not stand alone, they are related to others found both in the vegetable and animal kingdoms. Albumoses (which I have called phyalbumoses) are widely spread in vegetable tissues; they exist in the seeds and probably other parts of plants. Alkaloids or bases are also obtained from plants, and it appears to me a very promising field of research, to determine whether the vegetable alkaloids are associated with digested proteids, whether in fact the vegetable cell produces, like the bacillus anthracis, two classes of products, the albumoses and a base. This is, however, a question for the vegetable physiologist.

In some seeds (*abrus precatorius* and *ricinus communis*) there are proteids which have a distinct and powerful poisonous action. In the jequirity seed, for example, there are, as I have shown, two poisonous proteids, a globulin and an albu-

mose, both of which produce in very small doses a general disease, two of the features of which are the production of ecchymoses and the occurrence of sanguineous diarrhoea. The jequirity proteids resemble in many respects those of snake venom, and are like the albumoses of diphtheria and of infective endocarditis in producing a watery diarrhoea. I think, indeed, that the jequirity poison more closely resembles the secondary infective agent in diphtheria than any other poison I know, as it partakes of the nature of a ferment in its ready destruction by heat. Whether it produces a peripheral nerve degeneration or not I do not know.

SUMMARY OF ACTION OF THE POISONS OF INFECTIVE DISORDERS.

Slow Coagulation of the Blood.—One of the effects common to many of these proteid poisons is their power of preventing or hindering coagulation of the blood. This we have seen to be the case with the diphtheria albumoses, the effect of which in this respect is well marked and lasts a long time after they have been injected into the circulation. The albumoses of infective endocarditis also have this power, which is also possessed by the albumoses of peptic digestion, by the jequirity poison, and by many kinds of snake venom.

This action shows that these poisons have a profound effect on the blood, and may account for the grave defects in nutrition which have already been described. The animal, for example, poisoned with the diphtheria or anthrax albumoses goes on wasting after the fever has subsided, the loss of weight being greatest in the case of the diphtheria products, and being proportional to the dose of the poison given. In connection with this there is the fatty degeneration of the cardiac muscle, which has been shown in these experiments to follow the injection of not only the diphtheria products, but also, although to a less extent, the albumoses of anthrax and of infective endocarditis. There is no definite evidence that cardiac degeneration is directly dependent on a nerve lesion either central or peripheral, and the fact that it is well marked after the injection of the anthrax albumoses, which produce no degeneration in the nervous system, points, in my opinion, to the conclusion that it is to the change in the blood which these poisons bring about that we must ascribe the fatty change. This fatty degeneration may, indeed, only be the final result of the poisons being special cardiac poisons; the skeletal muscles do not become fatty like the heart unless there be nerve degeneration as in diphtheria.

Effect on Nutrition.—Closely dependent, no doubt, on the effect on the blood, is the profound effect on nutrition following the injection of the albumoses of infective disorders, whereby wasting, often to an extreme degree, is produced. The albumoses of tetanus and diphtheria may be classed together as causing great wasting, while those of anthrax are less effective in this respect, and those of infective endocarditis are least so.

Effect on the Body Temperature.—From the experiments which have been described, it is clear that the albumoses have a profound effect on the body temperature, while the final products are but slightly active. Ott and Calmar first showed that ordinary peptic albumoses caused a rise of temperature, and several observers have worked at the effect of injecting into animals "septic material" freed from micro-organisms. These experiments were performed at a time when the chemical characteristics of the products of pathogenous micro-organisms were unknown. The time has passed by for using impure material for physiological experiment. The most typical effect on the body temperature is seen in the case of the anthrax albumoses. A medium dose produces a rapid and high rise of temperature, and a continuation of the fever for some days; a larger dose produces a less pronounced rise and a shorter duration of the fever period, while a fatal dose causes only a slight rise with a sudden fall, ending in death in a few hours. The albumoses of infective endocarditis are also active in causing fever. Those of diphtheria and of tetanus must be classed together, as they both tend to depress the temperature, especially the albumoses of tetanus. The albumoses of diphtheria do, however, in small doses, cause a moderate but prolonged rise of body temperature. The degree of fever is, in all cases, dependent on the dose of the albumoses given.

Effect on the Nervous System.—Many of these poisons select

the nervous system for their action. One of the features of the action of albumoses is the production of coma, and in anthrax this coma is the special action of the base or alkaloid. Coma is a feature of jequirity and of snake poisoning. The final action of the albumoses in diphtheria is the production of coma, but their special action is to produce a paralysis dependent on nerve degeneration. It is quite possible that other products from diseases will be found to produce a peripheral palsy.

The effect on the respiration which is observed in snake poisoning is ascribed to the action of the poison on the central nervous system, and when working at jequirity I came to the conclusion that its action on the respiration was also central. In diphtheria, however, where there is peripheral degeneration of the phrenic nerve, it is difficult to say how far the respiratory attacks are dependent on a peripheral nerve degeneration, and how much they are due to an effect on the centres of respiration. Apart from mechanical obstruction, dyspnoea is one of the features of diphtheria in its acute stage, and it is possible that it may be due to an effect on the central nervous system; but here, again, it is difficult to exclude a peripheral action on the phrenics, for, as I have shown, the diphtheria products are special nerve poisons, and they may cause degeneration of the nerves even during the short course of the acute disease.

Question of Immunity produced by the Chemical Products.—There is one question which I have left untouched, namely, that of the conferring of immunity against the disease by the means of the chemical products. This is, of course, an important effect. We have been considering the chemical products of an infective disorder or of the primary infective agent as specific in reproducing, when injected into animals, the symptoms of the disease. But it is evident, if the chemical products are capable of protecting an animal against the invasion of the primary infective agent, that this action must be essentially a specific one. For example, we could not suppose that the chemical products of anthrax would protect against diphtheria, or those of diphtheria against anthrax, but that only the products of anthrax could protect against the invasion of the bacillus anthracis. I wish to speak of the matter only in a general manner. I am, however, not at all sure that in all diseases there is this protection; I cannot conceive how the products in diphtheria could protect against the acute disease.

In discussing the chemical products formed by the primary infective agent outside the body or in the natural disease, I have not mentioned any substances except those that are effective in producing the symptoms of the disease. There are some who have considered that such chemical products may consist of a "vaccine" and a "toxine." There is not the slightest evidence of this. There is no evidence of the existence of any chemical "vaccine" separable from the chemical "toxine," and I need, perhaps, hardly point out that such a "vaccine" has never been isolated. It was a term invented to explain phenomena which were not properly understood. There is also no evidence that there is any particular chemical substance which stops the growth of a pathogenic micro-organism. When grown in a flask it will not develop indefinitely, and it stops, not because there is an antitoxineformed, but because it is choked by its own chemical products in the same manner as peptic or tryptic digestion may be inhibited by the accumulation of the digestive products.

In bringing these lectures to a conclusion, I wish to express my thanks to the medical officer of the Local Government Board for granting me permission to bring the subject before this College. The work was done for the Local Government Board and in the laboratories of the conjoint Colleges, where every facility is given for the prosecution of research.

THE MEDICAL PROFESSION IN CALCUTTA.—The recent census gives the following return of persons earning their living by the practice of medicine and subsidiary arts in Calcutta: Practitioners holding diplomas, 1,081; *kabirajs*, 163 male and 14 female; dentists, 4 male and 3 female; midwives, 2 male and 810 female; hospital assistants and apothecaries, 95 males; compounders, nurses, etc., 666 male and 29 female. Under the head of chemists and druggists are entered 158 males and 245 females.

ON SOME SOURCES OF ERROR IN TESTING FOR SUGAR IN THE URINE.

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It has happened to me not infrequently to be consulted by patients who were being treated for glycosuria, but in whose urine I found no trace of sugar. The explanation of this not uncommon error is the fact, not generally recognised, that normal urine contains two substances—namely, uric acid and creatinin—which resemble glucose in their reaction with the tests commonly employed for the detection of sugar.

The urines which are most likely to be erroneously diagnosed as saccharin are those of high specific gravity—1030 or more—and which contain the normal reducing agents in larger quantity than usual. Such urines, added to Fehling's solution previously boiled, rapidly decolorise the blue liquid, and would precipitate suboxide of copper, but for the fact that the ammonia resulting from the disintegration of the nitrogenous creatinin keeps the suboxide in solution. The phosphatic sediment which results from the action of the alkali in Fehling's solution has sometimes been mistaken for cuprous oxide. The reducing action of uric acid and creatinin upon cupric oxide has led to the erroneous assumption that a trace of sugar is to be found in all normal urines. That no sugar is present in normal urine is conclusively proved by the observation of my son, Mr. G. Stillingfleet Johnson,¹ to the effect that when all the uric acid and creatinin have been removed from such urine by precipitation with mercuric chloride, which has no action upon glucose, all reducing action disappears, and no trace of sugar is to be found.

Moore's liquor potassæ test has, to my knowledge, misled an inexperienced observer in this way. Liquor potassæ often contains lead from the bottles in which it has been kept, and when this lead-contaminated liquor potassæ is boiled with albuminous urine, the sulphur of the albumen combines with the lead to form a dark sulphide, which an unpractised experimenter may mistake for the brown colour produced in saccharine urine.

Some years since² I introduced the picric acid and potash test for glucose; and after ample experience of all other tests including Dr. Pavy's ammonio-cupric modification of Fehling's, I feel justified in declaring that for accuracy and ease of application, both as a qualitative and quantitative test, it surpasses all others.

One great advantage is that all the ingredients employed in this method are stable, whereas it is notorious that all alkaline copper solutions speedily undergo change in keeping. The picric acid test, though not affected by uric acid, is, like copper, reduced by creatinin.

When a drachm of normal urine is boiled with the same volume of a saturated solution of picric acid, and half a drachm of liquor potassæ, a claret-red colour is produced, a colour which, compared with the standard, indicates what, if glucose were present, would be 0.7 grain per fluid ounce.

A good practical rule is this: That if in any specimen treated as before stated a red colour appears through the liquid in a test tube about half an inch in diameter, no glucose is present.³ The smallest quantity of glucose in addition to the creatinin, when acted on by the picric acid and potash test, renders the urine so intensely dark-red that no light passes through the liquid.

The presence of albumen, whether in small or large amount, does not interfere with the quantitative analysis of saccharin urine by the picric acid process, and this constitutes another advantage over the copper method, which requires a previous separation of the albumen.

And here I once more insist upon the fact that in picric acid we have the most absolutely trustworthy qualitative test for albumen; whilst Esbach's process with picric acid is a very accurate quantitative method.

¹ *Proc. Roy. Soc.*, vol. xliii, pp. 493–534.

² *Lancet*, November 18th, 1882.

³ For full particulars as to the picric acid test for sugar, see the author's *Medical Lectures and Essays*, p. 795, J. and A. Churchill; also *Two Lectures on Albumen and Sugar Testing*, Smith, Elder, and Co.