therefore has become absolutely necessary to obtain some evidence as to what kind of impulses come down the spinal cord during an epileptic fit, in order to pass out to the muscles. Unfortunately we have no means of getting hold of nerve energy, we have no physical instrument by means of which we can measure or record nerve energy in the same way that we can electrical energy, but most fortunately we have at our disposal, thanks to the genius of du Bois-Reymond, a method by means of which we know precisely when a nerve impulse is passing along a nerve fibre. As you know well, he discovered that when a nerve impulse passes along a nerve fibre an electrical change is produced in the electrical state of that nerve fibre. When nerve fibres are cut across or injured at one point the seat of injury becomes electro-negative to the rest of the nerve fibre, and thus an electrical difference is established between the parts of the nerve thus treated. Du Bois-Reymond found that if a single nerve impulse passed along that nerve, that that electrical difference would be diminished, and the little current which was set up by the passage of the impulse, and which by being of an opposite direction diminished the original difference was called by him the *negative variation*, but is usually known to other observers as the *action current*. If therefore we have in our hands an index of this kind it is reasonable to assume that if we could only tap as it were the fibres coming down the spinal cord from the brain, and connect them to a delicate galvanometer or electrometer that such a recording instrument would reveal the little action currents if such were produced by the epileptic nerve impulses streaming down the cord. Professor Gotch and myself have for several years employed this electrical method, as it may be termed, to investigate the passage of such and other nerve impulses in the spinal cord; we have succeeded in showing that the impulses which the cortex delivers and sends down the cord are of the characteristic form of tonus followed by clonus, and consequently we have now the proof that the "motor" part of the epileptic disturbance is seated in the cortex of the hemispheres.

Granted that this is so, we would naturally next inquire whether both hemispheres are involved in the epileptic disturbance. Observation of many clinical cases would seem to show that one hemisphere may start discharging a few seconds before the other; but in the majority of cases both are involved simultaneously, to judge by the incidence of muscular spasm in the limbs of both sides of the body.

This introduces us to the very large question of bilateral representation. The amount of attention that has been paid to this matter is very great, and a large number of observers (*vide infra*) have stated that if excitation be applied to one hemisphere and bilateral epileptic convulsions are the consequence, we are to deduce therefrom the view that one half of the brain is capable of throwing the muscles of both sides of the body into the characteristic condition of tonus followed by clonus. I have repeatedly shown that, whether we divide the commissures or whether we perform the converse experiment—namely, remove the excitable region of one hemisphere and then administer absinthe—the only effect is to produce the characteristic spasms in those muscles which are on the opposite side of the body in relation with uninjured cortex. Gotch and I have also approached the matter by the electrical method, and have shown² that in the cat, as well as in the monkey, unilaterality of representation prevails. Therefore we must conclude that, under ordinary circumstances, when the limbs of both sides of the body are in active convulsion both hemispheres are involved in the fit.

To sum up: Whatever be the point which the epileptogenous agency first attacks, we must conclude that the principal seat of the disturbance of a general or idiopathic fit must be the cerebral hemispheres, and especially their cortical mantle. Further that the condition of the cortex during the attack is one of congestion, and not anæmia; and finally that in all probability this portion of the encephalon is actually the place of origin of the disturbance.

² We have also, in the *Philosophical Transactions*, 1891 (Croonian Lecture), given the literature of this subject so far as it is known to us.

DR PAUL AUBRY has been deputed by the French Government to attend the International Congress of Criminal Anthropology, which, as already announced, is to be held at Brussels in August, 1892.

GOULSTONIAN LECTURES ON THE CHEMICAL PATHOLOGY OF DIPHThERIA, COMPARED WITH THAT OF ANTHRAX, INFECTIVE ENDOCARDITIS, AND TETANUS.

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LECTURE II.

Examination of the Nervous System.—All parts of the nervous system were examined. The motor nerves were cut out with a piece of muscle attached, so as to admit of the examination of the intra-muscular branches. The only method which is of value in the study of peripheral nerve degeneration is staining the fresh nerve with osmic acid, so that the white substance of Schwann is stained black, and counterstaining with carmine to bring out the nuclei and axis cylinder. In all the animals the same changes were found in the nerves, and the following description of the pathological condition refers to specimens taken from the animals as illustrating the points to be referred to.

Motor Nerves.—After the motor nerve with the piece of muscle attached has been stained in osmic acid, it is separated from the muscle with its intramuscular branches as far as possible. This is a photograph of one of the intramus-

Fig. 1.—Nerve to triceps.

cular branches to the triceps muscle. In this small intramuscular nerve mounted whole as a specimen, it is seen that the nerve is stained black with osmic acid, except at two points just before it divides into two branches. At these points the nerve is attenuated and degenerated. This serves as a type of the degeneration in the nerves. All the parts near the origin of the nerve were quite normal. When the nerve is teased with needles from the normal part to the end of the small branches, it is found that at the upper part the fibres are normal; a little lower down they show a breaking up of the white substance of Schwann, which is becoming thin and is but little stained by the osmic acid, while lower down still the white substance disappears altogether. This is at the portion of the nerve unstained by osmic acid. Beyond this the white substance again appears, but it is very pale and granular, and broken up; lower down still it regains its dark colour. The primitive sheath of the nerve is intact throughout; the axis cylinder

may be intact down to the spot at which the white substance completely disappears, and even through this part, so that here the majority of nerve fibres consist only of axis cylinder and the primitive sheath. Below the point at which the white substance has disappeared the axis cylinder is in many instances broken.

Fig. 2.—Nerve to soleus.

When the axis cylinder is ruptured, the upper end is often seen bulbous, and both peripheral and central parts become wavy. After such rupture of the axis cylinder, the nerve fibre undergoes below the rupture the Wallerian degeneration, the features of which are well known, and consist of a breaking up of the white substance along the whole course of the fibre, the axis cylinder also degenerating, portions becoming isolated. Many of the fibres, however, below the segment of degeneration do not undergo degeneration, showing that the axis cylinder is intact. Another branch of the nerve may show a less degree of change, and a third branch may show the earliest stage of the degeneration, of which I shall speak later. It will be seen that the degeneration affects primarily a portion of the nerve. It is a degeneration of the nerve fibre itself. There is no interstitial change, no increase of nuclei, which, in fact, themselves undergo an atrophy in the most advanced part. The part of the nerve fibre primarily affected is the white substance of Schwann, which breaks up and finally disappears. The axis cylinder itself may be unruptured when the white substance has completely disappeared, but it often becomes ruptured lower down the nerve fibre, which then undergoes below the rupture the Wallerian degeneration. The different branches of the motor nerve itself are affected to a varying degree, so that in an individual motor nerve there are many fibres which can still innervate the muscle, owing to the integrity of the axis cylinder. This is one reason why the condition observed during life is a paresis and not a paralysis.

In the nerve we have just been considering, the degeneration is seen right across the nerve, but in many nerves the change affects only a few fibres lying side by side or a single bunch of fibres. This is well seen in many specimens of the phrenic nerve from these animals, and also in the anterior root of the spinal nerves.

Fig. 3. Phrenic Nerve; a, cylinder.

This photograph shows the degeneration in the phrenic from another animal, but is interesting as demonstrating how very partial this segmental degeneration may be. At one edge the white substance is seen to be breaking up; as one proceeds to the other edge, the fibres show an increased breaking up of the white substance, with its gradual attenuation and loss; one fibre shows the axis cylinder passing intact through the attenuated part.

The earliest stage of this change in the motor nerve is the breaking up of the white substance in a portion of the nerve, while the axis cylinder may still be unaffected.

Fig. 4.—Nerve to biceps.

In this photograph of the nerve to the biceps muscle, this breaking up of the white substance with the integrity of the axis cylinder is well seen, so that in this early degeneration it is not uncommon to find that the nerve above and below the affected portion is quite normal. In some instances, however, this early segmentation of the white substance is associated with rupture of the axis cylinder of nerve fibres from the phrenic under a higher power. In these the attenuation of the white substance which follows its breaking up may occur in the middle of an internode, or it may also occur near the node. The more minute changes in the nerve fibres may be studied in some specimens; the white substance is seen granular and becoming attenuated from without inwards, while the axis cylinder can be traced as a straight line in the centre of the nerve fibre. In the nerve fibres lying by the side of such a one, the white substance shows similar appearances, but the axis cylinder is wavy and has become attenuated.

Multiple Interrupted Degeneration.—There may be more than one segment of the nerve affected by the degeneration, and when this is so the whole nerve is liable to degenerate towards the periphery, and presents to the naked eye a nodular appearance, the nodules being between the parts of the nerve which were first degenerated.

In such a nerve in which there have been from three to five degenerated segments, the later stages of the degeneration may be seen. In this photograph of nerve fibres lying

Fig. 5.—Nerve to gastrocnemius.

side by side, in most of the fibres only a primitive sheath and nuclei are to be seen with a few badly stained droplets of white substance, and here and there a trace of the degenerated axis cylinder. Such is the change in the motor nerves. The muscles to which the nerves go are also degenerated,

this degeneration being proportional to the degree of nerve change. If the nerve is completely degenerated the muscle fibres show an advanced fatty degeneration in minute granules, staining black with osmic acid. When the degeneration is less, fatty fibres are found mixed with normal ones, or only parts of fibres may be fatty, and when the nerve change is only slight there may be only longitudinal striation of a few fibres, or indeed the muscle may appear normal. The very partial fatty degeneration of the muscle is evidently dependent on the fact that the axis cylinders are in many instances intact.

The heart muscle is, however, in all these cases in an advanced degree of fatty degeneration. On what this cardiac degeneration depends it is difficult to say. I have not found any degeneration in the vagus nerve. It possibly depends on the altered condition of the blood which has been already described, or indeed, the diphtheria albumoses may have a special action on the heart.

Sensory Nerves.—The sensory nerves are affected in a manner similar to the motor. Sensory nerves of the leg or trunk may show one or more degenerated portions. In one case the long saphenous nerve showed five degenerated portions which gave the nerve a nodular appearance.

Sympathetic Nerves.—The trunk of the sympathetic may be similarly affected. The segment of degeneration in one instance went right across the nerve, and was of the same character as in the motor nerve, except that here of course the axis cylinders are more profoundly affected than in the medullated nerve fibres. On each side of the degenerated portion there is an increase in the number of nuclei. Above it the nerve was normal, below many fibres were degenerated.

From the facts just recorded it is evident that the paresis observed is due to degeneration of the nerves themselves, and that any of the nerve fibres in the body, whether medullated or non-medullated, may be affected. The spinal ganglia, spinal cord, medulla, and brain were in all cases found normal. The distribution of the nerve change may be seen by a description of what was found in one of the animals (No. 4 on the list already given). In one leg it was found that all the motor nerves investigated showed a greater or less degree of degeneration. The change was most marked in the nerves to the sartorius, the vastus, semitendinosus, less marked in those to the semimembranosus, biceps, gastrocnemius, and soleus. In the long saphenous nerve—a sensory one—there was well-marked degeneration. Transverse sections of the sciatic in the upper part were normal. At the lower part the whole nerve was teased and was found normal. The fact is clear, therefore, that the degeneration affects the terminals of the motor branches and not the main trunk. There may be one or two degenerating fibres in the sciatic nerve if the spinal nerve roots supplying it are affected, but in this particular instance the sciatic nerve was normal.

Passing to the trunk, still in the same animal, one of the large branches to the psoas muscle showed well-marked degeneration. A cutaneous nerve of the abdomen was found normal, and of three pairs of spinal roots examined—one in the cervical, one in the dorsal, and one in the lumbar region—degeneration was found in only one anterior root in the dorsal region, the remainder of the anterior roots and all the posterior roots being normal; the spinal ganglia were also normal.

In the arm nerves the branches of the musculo-spiral to the triceps and to the flexor muscles of the forearm showed well-marked degeneration, while the branches of the brachial plexus to the pectoralis and to the biceps showed an early stage of the degeneration. The musculo-spiral, examined just above the origin of the branches to the triceps, was normal. The phrenic showed degeneration; the recurrent laryngeal also; but the trunk of the vagus in the neck was normal. The cervical sympathetic showed well-marked degeneration at the lower part, while above it was normal, and in the head branches of the third nerve to the eye muscles showed well-marked degeneration.

From this it is seen how widespread is the change in the peripheral nerves, whether cerebral, spinal, or visceral, as the result of the injection into the circulation of so small a dose as 0.1565 g. (in two doses) in a rabbit weighing 1,565 g., which is a dose of about 2½ grains in a rabbit weighing 3½ lbs.

Microscopical Examination of the Nerves after Single Doses of

the Albumoses.—It has already been stated that in rabbits which have a single large dose, although they show fever for a few days, there is no paralysis. One animal, which received 0.084 g. per kilo. subcutaneously, was killed in 115 days, and another, which had a dose of 0.117 g. per kilo. intravenously, was killed in 94 days. When killed both were fat and well nourished. On microscopical examination it was found that in both animals the phrenic nerves and the small branches of the motor nerves showed well-marked degeneration with rupture of a few axis cylinders, but no well-marked Wallerian degeneration below the degenerated portion. The heart was fattily degenerated. A single dose of the poison, therefore, although its effect had apparently passed off during life, was found after death to have left a definite nerve lesion, which had not been repaired. These two experiments, with the others previously mentioned, show most clearly that the diphtheria albumoses, although fever producers, are nerve poisons, selecting the peripheral nerves for their action, just as strychnine selects the motor cells of the cord for its action. I take it that with these single doses the injury to the nerves had been effected, and the degeneration was not progressing when the animals were killed, whereas the successive introduction of small doses into the circulation keeps up the action on the nerves, so that a visible affection of motility results. In a case of diphtheria that died, I found in the small branches of the phrenic portions of the nerve degenerated, thus demonstrating what has been known before, that a nerve degeneration may be present during the acute disease.

Relation of the Nerve Degeneration to the Changes in the Nervous System in Diphtheria Palsy in Man.—Since Déjerine's¹ work on the subject, it has been recognised that the paralysis following diphtheria is due to a parenchymatous degeneration in the peripheral nerves; but both before this period (1878) and after it many observers have described changes in the cells of the anterior cornua of the spinal cord, and some have gone so far as to ascribe all the symptoms to a mild poliomyelitis. The symptoms, however, are not those of an affection of the anterior cornua of the spinal cord, as there is an absence of any special wasting of the affected muscles and of the reaction of degeneration. The changes that have been described as occurring in the cells of the anterior horns (such as fatty degeneration, vacuolation, pigmentation, atrophy) are probably only phenomena added to the change in the peripheral nerves, and the poison which produces a change in these nerves and fatty degeneration of the heart may, after a time, affect the nutrition of the nerve centres, causing first fatty degeneration, then atrophy of the cells. The great argument in favour of the change being essentially peripheral is the fact that sensation is affected, and no changes have been described in the posterior cornua of the cords or in the sensory ganglia. In my experiments the cord and spinal ganglia were quite normal. The nature of the nerve change observed in the experiments with the diphtheria albumoses was first described by Gombault² as the result of chronic poisoning by lead in guinea-pigs. He called the change "*névrite segmentaire péri-axile*," or a neuritis affecting the nerve fibre around the axis cylinder. His animals showed no paralysis, and he left them alive six months or longer, so that, as his figures show, he had the appearances both of degeneration and of restoration in the nerve fibres.

It is clear from the changes observed in the nerves following the injection of diphtheria albumoses that the condition is one of simple degeneration, affecting first of all the white substance of Schwann, which breaks up and finally disappears, then the axis cylinder, which is attenuated and finally ruptured in some fibres, so that below this ruptured axis cylinder the fibre undergoes the Wallerian degeneration, and the muscle fibre becomes fatty. Many of the fibres which show a degenerated white substance of Schwann do not show a ruptured axis; and this, combined with the fact that the small branches of the motor nerve are affected to a varying degree, and that the motor nerves of the body are not all in the same degree of degeneration at the same period demonstrates why diphtheritic palsy is not a complete, but only a partial, paralysis.

In the degenerated nerves in human diphtheritic palsy an

¹ Sur la Paralysie Diphthérique, *Archives de Physiologie*, 1878.

² Gombault, *Archives de Neurologie*, 1880-81, p. 11.

increase of nuclei of the nerve fibres has been described, and also nodular swellings on the nerves formed by cellular elements.³ These changes probably only indicate an attempt at repair of the nerve; they are not met with in the cases of simple nerve degeneration seen in the artificially-produced diphtheritic palsy.

Meyer, who very thoroughly examined a case of diphtheritic palsy in man, gives figures which show quite clearly that the change in the peripheral nerves is of the same nature as that which I have described as occurring in the experimental rabbits. He discusses the nature of this change, and refers to Gombault's work, but lays a great deal too much stress on the nodules which occur on the nerves, and which are, as I have shown, the intervals between the degenerated portions.

Action of the Organic Acid.—When the organic acid found in diphtheria is injected in watery solution into the circulation of rabbits, it produces a moderate degree of fever which may last one or three days, or may be extremely slight, but nothing further happens to the animal. It may waste a little, but it does not get paralysed, even after a single dose of 0.155 g. per kilo. of body weight. Similarly, two successive doses, equal to 0.095 g. per kilo, produce only slight fever on the days of inoculation, but otherwise no effect. No paralysis in twenty-four days. This is a dose of the albumoses sufficient to produce a definite palsy. The animal was killed on the twenty-fourth day. The heart's blood coagulated in a normal manner, and all the internal organs of the body were normal in appearance. On a microscopical examination, however, it was found that the heart showed well-marked fatty degeneration, although not to such a great extent as in the experiments with the diphtheria albumoses. There were a few fatty fibres in the diaphragm, but the parts of the vastus, semimembranosus and gastrocnemius examined were quite normal. The phrenic nerve was examined in its upper half, and found normal, while the nerves to the semimembranosus, the vastus, and the gastrocnemius all showed the different stages of the characteristic degeneration already described.

The organic acid, therefore, found in the bodies of diphtheria patients is like the albumoses, a nerve poison, capable of producing the same anatomical change in the nerves. One animal which received a single dose of the organic acid, equal to 0.043 g. per kilo. of body weight showed well-marked fever, but no paralysis. Killed in 119 days; it was fat and well nourished, but showed early fatty degeneration of the heart and diaphragm and well-marked segmental degeneration in the phrenic nerve. One animal received intravenously a very large dose of the acid on successive days, the total dose being equal to 0.32 g. per kilo. of body weight. No fever, paralysis, or loss of weight ensued, and as the dose given was more than twice the lethal dose of the albumoses, the experiment shows what slightly poisonous properties the organic acid possesses.

Although, therefore, this organic acid is not nearly so toxic as the albumoses, it has the same action in producing a nerve degeneration. It is not surprising that both the toxic bodies found in a specific disorder should have a similar action; it would, indeed, be more surprising if their physiological effects were different.

Having considered the chemistry and physiological action of the toxic bodies present in the bodies of patients dead of diphtheria, we will now discover the chemical composition of diphtheritic membrane.

Diphtheritic Membrane.—The chemical examination of the diphtheritic membrane presented some trouble owing to the small quantity obtainable. Membrane removed during life with clean forceps or a cast of the trachea coughed up after tracheotomy was placed directly into absolute alcohol, partly to preserve it and partly to kill any micro-organisms present. It was after a varying time removed from the alcohol and extracted with sterile 10 per cent. NaCl solution. The membrane formed a gelatinous mucoid-looking mass in the salt solution, and as this would not filter, it was largely diluted and passed through a Chamberland's filter. The filtrate was dialysed till all the salt was removed, concentrated at a low temperature and precipitated by alcohol. The precipitate which consisted only of proteid matter was used for experiment. Without going into the chemical details, the membrane consists of the following proteids: One almost insoluble

in saline solutions at the ordinary temperature, which is the fibrin of the membrane; others extracted with saline solution, and consisting of a large quantity of hetero-albumose, which is precipitated by dialysis; and two other albumoses in traces—namely, proto- and deuto-albumose. The presence of these bodies shows that the membrane is in a process of digestion, hetero-albumose being the first product from the fibrin, proto- and deuto-albumose the final products. Practically nothing is extracted from the membrane by alcohol; the acid body found in the tissues is present, but only in minute quantities.

Physiological Action.—The extract of the membrane which was used for inoculation was whitish yellow, not quite soluble in distilled water, and slightly alkaline. It consisted solely of proteid, a mere trace of hetero-albumose, with traces of proto- and deuto-albumose. Thirty mgm. were injected into a rabbit weighing 560 g., which is equal to a dose of 53 mgm. per kilo. of body weight. The first result of the injection was fever, high on the first day, less on the second day, but present also on the fifth day, after which the temperature was normal. Weakness of the hind legs appeared on the first day; on the second the right hind leg was more paretic than the left; on the third day it was the same, and had lost 30 g. in weight; on the fourth day the left hind leg was more paretic than the right; and on the fifth day this condition was increased, the legs being held in slight abduction. From this time onward the animal did not jump except on rare occasions, but walked one leg after the other like a cat. The condition remained practically the same till the thirteenth day, when it became ill in a manner similar to that described in the previous animals. The hind legs, although kept extended when placed in that position, were not completely paralysed; flexion was still possible if a little help were given. The forelegs were paretic; the breathing was extremely rapid; and the temperature varied between 96.2° and 96.8°. The animal died during the night. The *post-mortem* examination showed the blood coagulated in some parts, but when the uncoagulated blood was removed it was found slow in coagulating. As regards the rest of the *post-mortem* examination, the results were precisely similar to the condition described in the other animals. Micro-organisms were absent from the body, and there was the same degeneration of the peripheral nerves, of the skeletal muscles and of the heart, and the same integrity of the central nervous system as has been already fully described.

This result is important, as it shows that in the diphtheritic membrane there exists a poison associated with the proteid and precipitated by alcohol, which produces exactly the same result as the albumoses found in the blood and spleen of diphtheritic patients. But it is a poison much more virulent, since a single dose produces a result which only multiple doses of the albumoses can effect. A single small dose of the albumoses, as has been demonstrated, will not produce the progressive paresis observed in this case. For example, a dose of 0.123 g. of diphtheria albumoses in a rabbit weighing 1,050 g., which is twice the dose per kilo. in the animal under consideration, produced only moderate fever and nothing else. Also at the same time that this experiment with the extract of diphtheritic membrane was performed an animal was injected with three times the dose of albumoses on three successive occasions, namely, 0.157 g. per kilo. in all, and yet the nerve lesions were as well marked in the animal which had the diphtheritic membrane extract as in that which had the albumoses, and death occurred in about the same time, namely, fourteen days. Similarly one of the animals that had nearly twice the dose, namely, 0.083 g. of albumoses in two successive doses, although it became paralysed, recovered to a great extent, and lived over ten weeks. The toxic effect of the extract of the diphtheritic membrane cannot, therefore, be ascribed to the mere presence of the small amount of albumoses. There is something else, which is in all probability of a ferment nature. This dialysed saline extract of diphtheritic membrane also possesses a different local action to that of the albumoses. It may produce simply oedema which will pass off, but in one instance 12 mgm. injected under the skin of a guinea-pig weighing 710 g. produced a fever during the first two days of experiment; the fever subsided on the third day, and death occurred on the sixth day. Nothing was found in the body except, at the site of inoculation, a greyish yellow sloughy-looking area containing no

³ Meyer, *Virchow's Archiv*, vol. 85, 1881, p. 181, etc.

pus, and about half an inch long. The poison had produced a local necrosis of the tissue.

These results bring my own work into touch with what has already been done on the chemical products of the bacillus diphtheriæ or the so-called Klebs-Loeffler bacillus.

Bacillus Diphtheriæ.—I do not intend to go fully into the history of the diphtheria bacillus. Suffice it to say it was first recognised by Klebs, first isolated in pure growth by Löffler, and that Roux and Yersin were the first to show that when introduced into the circulation of a rabbit this bacillus produced a paralysis which is progressive and which is, from the description given, of the same nature as that I have already brought before you. Roux and Yersin's results were confirmed by Brieger and Fraenkel. All observers are agreed that the bacillus diphtheriæ is limited to the superficial layers of the membrane and does not distribute itself over the body. It is not found in the blood or in any of the organs. Similarly, even when subcutaneously inoculated, although it kills the animal, yet its growth is limited to the site of the inoculation. This fact, taken with that established by the brilliant researches of Roux and Yersin, namely, that the bacillus produces paralysis, is a very powerful argument that the bacillus diphtheriæ is the *vera causa*, the living contagium, or, as I prefer to call it, the primary infective agent in diphtheria.

Chemical Poison Isolated by Roux and Yersin.—The chemical poison isolated by Roux and Yersin was of a very virulent nature. They grew the bacillus in veal peptone broth, that is, using peptone as a food for the organism. Such a culture medium is unsuitable for obtaining the products of a pathogenic organism because it is unlike any liquid medium that exists in the body, and the proteid bodies which are produced by pathogenic organisms are of the same chemical nature as the peptic albumoses which are used in preparing the culture medium. These facts, however, by no means vitiate Roux and Yersin's results. They found that the broth culture when freed from bacilli will kill rabbits after producing paralysis, chiefly affecting the hind legs and the respiration. This poison was precipitated by alcohol, and by phosphate of lime, and may be dried, and they calculated that as little as 0.0004 g. was capable of killing 8 guinea-pigs of 400 g. each, or 2 rabbits of 3 kilos. each. Roux and Yersin's conclusions were that this poison was a ferment (diastase), not only from its acting in such small doses, which had a prolonged effect on the body lasting over days, but also from the fact that heating attenuated the poison and boiling destroyed it. At the end of one of their papers they conclude that: "L'infection n'est pas produite par un microbe envahissant les tissus, mais par la diffusion dans l'organisme d'une substance toxique, préparée à la surface d'une muqueuse, pour ainsi dire en dehors du corps."

Brieger and Fraenkel repeated Roux and Yersin's experiments and confirmed them. They attempted to determine accurately the chemistry of the diphtheria product, which they called "tox-albumen," but their chemical analyses and reactions are quite vitiated by the fact that they had peptone in their culture medium. They found, like Roux and Yersin, that the proteid or mixture of proteid precipitated from the culture medium by alcohol acted in very small doses, such as 5 to 20 mgs., when injected into the circulation of an animal, but they drew the hasty conclusion that a poison like this diphtheritic product existed in all infectious diseases.

I have obtained the products of the bacillus diphtheriæ⁴ by using as a culture medium a 1 to 2 per cent. solution of alkali-albumen in broth prepared from beef without the addition of peptone. After twenty-two to thirty-two days it is found that the bacillus has transformed the alkali-albumen into albumoses, which give the reactions of proto- and deuto-albumose. Small quantities of the organic acid were also obtained. A single large dose of these albumoses, equal to 0.115 g. per kilo. of body weight, produced a weakness of the hind limbs, and, to a less extent, of the whole body on the first day. This passed off, but the rabbit lost weight for ten days or more. It afterwards regained its weight, and when killed, on the hundredth day, it was fat and well nourished. The microscopical examination revealed the same changes as have been described as following the injection of a single dose of the albumoses found in patients dead of diphtheria.

⁴ Cultures of which were given to me by Dr. Klein.

The heart showed advanced fatty degeneration, and there was well-marked degeneration of the phrenic nerve and the nerve to the vastus muscle—the only two nerves examined.

Multiple Doses of the Albumoses formed by the Bacillus Diphtheriæ.—One rabbit received intravenously three doses of the albumoses, equal to 0.111 g. per kilo. of body weight. There was well-marked fever, which subsided after the last dose, but beyond this there were no symptoms—no paralysis, no diarrhoea, and no loss of weight. No change occurred in the tendon-reflexes. The animal was killed on the thirtieth day. The *post-mortem* examination showed well-marked fatty degeneration of the heart, and a similar, although slight, change in the diaphragm and triceps brachii, while the portions of the vastus internus, semimembranosus, semitendinosus, and gastrocnemius examined were normal. The phrenic nerve and the nerves to the muscles mentioned (with the exception of the nerve to the semitendinosus) showed a degeneration precisely similar to that which has been described as following the intravenous injection of the albumoses found in the tissues in diphtheria patients. One or more branches of each of the motor nerves mentioned was found degenerated, but there were only a few ruptured axis cylinders, and no well-marked Wallerian degeneration, explaining why no paralysis was observed in the animal during life. A larger dose than the one under consideration produces the same symptoms that follow the injection of the albumoses from diphtheria patients. Thus an adult rabbit received three doses of the albumose of the bacillus diphtheriæ (on successive days), equal in all to a dose of 0.169 g. per kilo. of body weight. After the first two doses there was high fever, but after the third a depression of temperature (1° to 2° F.) occurred, which lasted two days. Severe watery diarrhoea set in, and lasted until the ninth day. The wasting was very rapid until the twelfth day, when the animal had lost a quarter of its original weight. It then gained slightly in weight. A general weakness of the muscles was present on the fourth day, but no definite paralysis until the eleventh or twelfth day, when the hind legs were distinctly affected, and the animal walked one leg after the other, like a cat. The paresis continued. The tendon reflexes were normal up to the ninth day, when they began to diminish, and on the seventeenth day they could scarcely be obtained. The animal has not at present succumbed.

Conclusions.—From the facts under consideration, it is clear that:—

1. The bacillus diphtheriæ forms from proteids products of the same chemical nature as those found in the bodies of patients dead of diphtheria, namely, albumoses and an organic acid.

2. The albumoses formed by the bacillus diphtheriæ in artificial cultivation have in single and multiple doses the same physiological action as those found in cases of diphtheria in man; this action is the production of fever, of diarrhoea, and of loss of body weight, and of a progressive paresis of the muscles dependant on a degeneration of the peripheral nerves.

3. The bacillus diphtheriæ is, therefore, the primary infective agent in diphtheria.

The relation of Roux and Yersin's poison to those I have described as present in the bodies of patients suffering from diphtheria is made clear from the fact that a much more virulent poison exists in the diphtheritic membrane than in the body of patients suffering from diphtheria, so that in a table we can bring the chemical pathology of diphtheria into the same line as that of anthrax, and head all the changes by the term diphtheria digestion.

Diphtheria Digestion.

Primary Infective Agent.	Secondary Infective Agent.	Digestive Products	
Bacillus diphtheriæ	Diphtheria ferment (Roux and Yersin's poison) In membrane	Hetero-albumose Proto-albumose Deuto-albumose Organic acid	} In membrane. } In body.

It is evident that the primary infective agent in diphtheria is the bacillus diphtheriæ; that this liberates in the mem-

brane a ferment which, when absorbed, digests the proteids of the body, forming albumoses and an organic acid. These digested products are the agents in producing death, in causing fever, the depression and the paralysis which follows diphtheria. It is clear from the cases of diphtheria which have been described that the diphtheria products found in the body do not all come direct from the membrane. In Case 1, for example, only small flecks of membrane were found in the larynx, and yet in the body a large quantity of the diphtheria products was discovered. The large amount of albumoses and organic acid found in the spleen also shows that something more than absorption from the membrane is going on. There is no reason to suppose that these products merely accumulate in the spleen, and their specific physiological action shows that they are foreign to the organism. It is more probable that the ferment absorbed from the membrane digests the more or less stagnating proteids in that organ, and we know, indeed, that the spleen contains a proportionately larger quantity than the blood of bodies formed from proteids, such as uric acid, xanthin, etc.

ON LABYRINTHINE DEAFNESS TREATED BY PILOCARPIN.

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Of the various papers I have published on the treatment of deafness by pilocarpin the last appeared in the *BRITISH MEDICAL JOURNAL* for May 17th, 1890. In this, in order to arrive, if possible, at an explanation of the effects produced by the drug, I entered at some length into a consideration of the pathology of labyrinthine deafness, and in elucidation of the behaviour under treatment of the fresh series of cases now to be reported, I will here briefly recapitulate my former remarks upon this subject.

The anatomical evidences of labyrinthine disease in its early stages are congestion and small-cell infiltration, and sometimes suppuration or complete destruction of the membrane of the labyrinth. The inflammation may extend along the sheath of the auditory nerve, but is commonly limited to the labyrinth itself, its walls becoming thickened, and its cavity occupied by caseous deposit with, perhaps, bands of fibrous tissue. There may be destruction of the membrane of the labyrinth, causing degeneration and atrophy of its nerve endings, or, as is more commonly the case, these latter are constricted, and their action is paralysed by the organisation of fibrous tissue in the thickened membrane. The pathological features appear to be much the same in the great majority of cases, whatever the initial cause. How so unpromising a condition as labyrinthine deafness can be benefited, or, as in some cases, practically cured by the subcutaneous injection of pilocarpin, cannot as yet be proved by reference to known facts; but a possible explanation is to be found in the stimulation by the drug of the secretory nerve fibres. Its effect in promoting the formation of wax in the outer ear (usually absent in cases of labyrinthine disease) may be the accompaniment of increased healthy secretion in the middle ear, and consequent softening, or even removal, by the absorbents of old accumulations therein, pressure upon the nerve endings being thus relieved, and their functions more or less restored. The action here supposed to take place in the ear after the lapse of sometimes very considerable periods is certainly paralleled by what has been observed in peripheral neuritis affecting other parts of the body.

It has been urged in opposition to this view that in many cases of labyrinthine disease pilocarpin is quite useless. It is, however, obvious that it must remain so in all those cases in which there is either bony thickening or, whether from locomotor ataxy or from direct inflammatory action, there is destruction of the membrane and atrophy of its nerve endings. It would, in short, be impossible, from purely negative evidence, to come to a legitimate conclusion as to the scope of the employment of pilocarpin in labyrinthine disease.

Large numbers—indeed, most of the supposed cases of this affection sent to me as unamenable to its action—have proved to be quite unsuitable for its exhibition, being examples of every other sort and condition of ear disease, including long-standing perforation of the drumhead.

Inasmuch as my last paper on "The Treatment of Labyrinthine Disease," with its record of cases, was productive of various adverse criticisms, some of which appeared to call in question the maturity of my conclusions, I determined, before writing again on the subject, to thoroughly reinvestigate it during an additional prolonged period, both in hospital and private practice. The interim has afforded me the opportunity of testing the permanency of the good results reported to have accrued from the use of pilocarpin.

As the outcome of my further study of the disease, its symptoms, and its modes of treatment, I would offer to such practitioners as have not yet had experience of its relief by means of pilocarpin the following observations:—

(a) The case must first be carefully diagnosed as actually one suitable for treatment with the drug. Labyrinthine deafness, it must be remembered, is not a disease of common occurrence.

(b) The larger number of the patients that hear better in a noise (when in a train or omnibus, for example) do not derive much, if any, benefit from pilocarpin, if used independent of other remedies.

(c) The best test of hearing is to employ a large tuning-fork with a wooden handle, acting as a sounding-piece, to put on the head. Some of the small tuning-forks commonly used are worthless to the aural surgeon.

(d) Cases in which the tuning-fork on the forehead is heard indifferently or scarcely at all may be suitable for treatment with pilocarpin.

(e) Patients with a syphilitic history are usually much relieved, and the possibility of hereditary syphilis in a given case must be borne in mind.

(f) The very large number of patients that say they hear worse after a cold are mostly unsuitable cases.

(g) Patients who say they can hear when they are spoken to very distinctly or whose deafness began with a difficulty of discriminating sounds, or who cannot make out general conversation, and hear worse when tired, nervous, or feeling out of health are more promising cases than the last mentioned.

(h) In arriving at a diagnosis, the state of hearing as tested by the watch and the condition of the drum-head should be noted.

(i) Some cases of marked aural vertigo derive benefit from pilocarpin.

(j) If middle-ear disease is associated with mischief in the internal ear, the Eustachian catheter should be passed from time to time for the injection of vapours.

My usual method of administering pilocarpin is to inject into the back of the arms a solution of the nitrate of a strength equal to $\frac{1}{2}$ gr. to 10 minims. The dose at first, $\frac{1}{2}$ gr., is gradually increased to $\frac{1}{4}$, $\frac{1}{2}$, or, if well borne, $\frac{3}{4}$ gr. The effect is speedily manifested by diaphoresis and copious salivation. After each injection I give half a drachm of salvolatile in a small tumblerful of water. The patient is then made to lie on a sofa, and is well-covered with rugs, the head being enveloped in a shawl. When the effects are wearing off the wraps are removed, but only by degrees, in order to avoid the risk of catching cold. In the event of faintness or other discomfort from the exhibition of the drug I give brandy at once, which I keep ready at hand, and find the best restorative. Untoward symptoms need not be apprehended if the precaution of beginning with the small dose above mentioned be strictly adhered to.

Due attention to the foregoing particulars will enable me to reduce to comparatively few the number of cases amenable to treatment with pilocarpin. The histories of the following patients, some of whom, with others similarly affected, were sent to consult me by well-known practitioners, have been given mostly in the patients' own words, and speak for themselves. They serve, it will be found, both to illustrate the remarks just made and to corroborate the deductions arrived at in my previous papers.

CASE I.—Miss A. E., aged 39, treated by me three years ago, in answer to a letter I sent in February, 1892, writes as follows: "I am delighted to tell you that the improvement in my hearing is fully maintained.