THE CROONIAN LECTURES ON DEGENERATION OF THE NEURONE.

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LECTURE III.

THE CHEMISTRY OF DEGENERATION.

OSMIC acid has long been known to have the property of staining fat (including myelin) black, but, owing to difficulty in penetration, it could not be made use of for studying the degeneration of the central nervous system in the same way as the peripheral, although Exner¹ was enabled to show by his method the existence of fine medullated fibres—tangential system and inter-radial—in the grey matter of the cerebral cortex, and Tuzek applied this method and demonstrated the important fact that atrophy of the tangential fibres of the frontal and central convolutions was the earliest and most constant morbid change in dementia paralytica. I have had the opportunity of confirming this observation in at least 50 cases by the Marchi-Pal method. This degeneration does not appear to be peculiar to general paralysis, as similar atrophy may occur in other diseases of the cerebrum, associated with paresis and dementia—as, for example, in alcoholic and epileptic dementia; it does not, however, exist in purely efferent systemic degenerations—for example, amyotrophic lateral sclerosis—although in this disease, as I shall show, the whole motor efferent system of neurones, from cortex to peripheral muscle, is degenerated. About ten years ago Marchi introduced his method of staining degenerated nerve fibres, using it for the purpose of demonstrating the degenerations which followed experimental ablations of the cerebellum performed by Luciani, and the most striking results were obtained. By this method Marchi showed a descending cerebellar system in the antero-lateral column of the same side as the half of the cerebellum that had been removed. Russell, Ferrier, and Turner have, however, shown that this tract does not proceed direct from the cerebellum, but through a relay in Deiter's nucleus.

It is now the method adopted by all investigators for determining the path not only of tracts of fibres, but of actual individual fibres, in the central nervous system. It has, in the hands of numerous investigators, served to demonstrate accurately the course and termination of nervous paths. There are a few fallacies in connection with it for the inexperienced, but if care be taken to avoid these, no method is so delicate or so reliable. By this method I was able experimentally to trace the course of the fibres of Gowers's tract, which I showed to consist of three sets of fibres—one, the more numerous, terminating in the middle lobe of the cerebellum after looping over the fifth nerve and running down on the surface of the superior cerebellar peduncle; another set terminating in the corpora quadrigemina; and the third, few in number, joining with the fillet fibres and ending in the optic thalamus. By this method single fibres can be followed in their course along the whole cerebro-spinal axis, from the cortex to the lumbar-sacral region, when they are efferent; and from the lumbar-sacral region to the optic thalamus when they are afferent. I was unable to find any evidence in monkeys for the existence of a cortical fillet (described by Flechsig), as after cutting off the posterior column nuclei and tracing the resulting degenerated fibres of the fillet upwards, they all terminated in the optic thalamus. Subsequent observations by independent observers have confirmed these conclusions.

THE CHEMISTRY OF THE MARCHI METHOD IN RELATION TO DEGENERATION.

In working with the Marchi method I was struck by the fact that in the neighbourhood of an experimental lesion vessels could often be seen with phagocytes containing black-stained particles in their sheaths. These were undoubtedly carrying away the products of degeneration. I also found that muscles which had undergone fatty degeneration reacted to the Marchi

stain; that is to say, pieces of muscle which had been hardened in Müller's fluid, like pieces of the degenerated central nervous system, when placed in the Marchi fluid (1 part of 1 per cent. osmic acid and 2 parts Müller's fluid) revealed fatty degeneration by the fat particles being stained black. I had long before noticed that the fat particles in degenerated muscle were stained by the hæmatoxylin when the Weigert or Weigert-Pal

Fig. 1.—Photomicrograph showing degenerated nerve fibre in a longitudinal section of the spinal cord ten days after experimental lesion. In places the thin axial core can be seen stained black. The greater part of it, however, is covered up by the degenerated myelin sheath, also stained black.

method of coloration was used; therefore, I came to the conclusion that a non-phosphoretted fat, the result of degeneration of proteid, would be stained by either of these methods. Putting this fact by the side of another—namely, that degenerating nerves of the central nervous system, stained by the Weigert or Weigert-Pal method, appear uniformly blue throughout; whereas in a transection of the normal nerve fibres only a ring of myelin stains blue, the central axon being unstained—the conclusion is that the proteid of the axon has degenerated and become converted into a fatty substance; but it is otherwise, as I shall now show, with the Marchi method, which really depends for the success of the reaction on the differential staining of the phosphoretted fat contained in the myelin (protagon) from ordinary non-phosphoretted fat, such as olein, palmitin, stearin, etc. In sections of a normal nervous tissues stained by the Marchi method the nerve fibres in transection present the following appearances. The central axial core is unstained; the ring of myelin is stained a greenish ash-grey colour; degenerated fibres are stained black throughout, so that no differentiation can be seen between the myelin sheath and the axial core. It might be said that this was due to the axial core having broken up, and its place been occupied by the degenerated myelin; but I have observed longitudinal sections of nervous tissue showing degeneration in the earliest stages, in which the axis-cylinder may be seen stained black as well as the myelin. (Photomicrograph. Fig. 1.) Moreover, there are chemical reasons for supporting this view. Examination of numbers of tissues, vegetable and animal, containing or consisting of simple non-phosphoretted fats, by the Marchi method showed that these fatty bodies gave the black reaction. I was led to the conclusion that probably the myelin in the process of degeneration underwent a chemical decomposition by which the complex phosphoretted fat was split up into simpler bodies, namely, glycerophosphoric acid, stearic acid, and

choline; by the taking up of water, lecithin would undergo the decomposition shown below.²

To prove this I took the spinal cord from a case of right hemiplegia of fourteen days' duration, the result of thrombosis of the middle cerebral artery, and divided it longitudinally into as nearly as possible equal halves, reserving a small portion for microscopical examination by the Marchi method (Fig. 2). The

Fig. 2.—Section of first cervical segment of the spinal cord from a case of thrombosis of the middle cerebral causing left hemiplegia. It will be observed that there is scattered degeneration in the homolateral pyramidal tract and also in the direct tract, and in the anterolateral region, probably due to some softening of the optic thalamus. There is a very marked degeneration in the left crossed pyramidal tract. The patient died at the end of twenty-one days. The result of the chemical examination of the two halves of the cord showed a diminution of lecithin on the left side, with an increase of ether extract, showing that a portion of the lecithin had been converted into stearin, which stains black with the osmic acid.

two halves of the cord were dried in a sulphuric acid exsiccator, and it was found that the right half lost the most in weight by this process. Both halves were then dried at 100° C. and extracted in a Soxhlet's ether apparatus, so that all the fatty matter was extracted. It was found that on the degenerated side the ether extract appeared like butter, whereas on the non-degenerated side it was more crystalline in appearance. The degenerated right side yielded a larger proportion *pro ratâ* of fatty matter than the left; but the phosphorus (the details of the estimation of which are given fully in the paper in the *Archives of Neurology*) obtained from the right half was less than the left. The conclusion, therefore, was that the phosphoretted fat (lecithin) had broken up in the way I have mentioned. This result I have stated in my article on the Pathology of Nutrition, Clifford Allbutt's *System of Medicine*, vol. i. I have since examined another cord with the same results, and two others in conjunction with Dr. J. Wakelin Barratt. Some of the increase of the fat cannot, however, be accounted for by the decomposition of the lecithin; it therefore probably comes from the degeneration of the proteid of the axis-cylinder process, which we have seen to give the black fat-staining reaction.

THE POSSIBILITY OF DEGENERATION CAUSING AUTO-INTOXICATION.

While examining a case of acute general paralysis, with numerous epileptiform seizures, I was struck by the fact that the perivascular lymphatic sheaths of many of the vessels were filled with cells staining black like the Marchi reaction, and I came to the conclusion that very probably in this disease a decomposition of the myelin of the proteid matter of the nervous system occurred incidental to the degenerative process, and that the cerebro-spinal fluid, and possibly also the blood, would yield some of the products of degeneration,

and perhaps the presence of such might account for some of the symptoms which occur in this disease (Fig. 3). On account of the laboratory of the London County Asylum not being licensed for experiments, I was fortunate enough to obtain

Fig. 3.—Photomicrograph of a small vein from an experimental lesion. The section was stained by Marchi's method, and in the external wall of the vein are seen phagocytes stained black by the fat contained in them taking up the osmic acid. Magnification 350 diameters.

the co-operation of my friend Professor Halliburton, who was good enough to associate himself with me and conduct a series of experimental inquiries relating to this subject, a full account of which has been published in the *Phil. Trans.* of the Royal Society. At first it was thought that choline only existed in the cerebro-spinal fluid and blood of patients who were suffering from general paralysis of the insane. This was no doubt due to the fact that in this disease choline was easily detected both chemically and physiologically, because in no other affection of the nervous

Fig. 4.—Crystals of the platinum double salt of choline crystallised from 15 percent alcohol.

system is there such a rapid and widespread degenerative process affecting the nervous system, but subsequent observations have shown that practically in any degenerative process affecting the nervous system, if extensive enough,³ choline can be detected in the blood, although normally it does not exist in sufficient quantities to be recognisable.

Thus, it was found in two cases of combined sclerosis, in two cases of beri-beri, where the disease had been of sufficient duration to give the Marchi reaction in the nerves; but in another case which had died in the early stage from heart failure there was no evidence of choline. This led to further researches, and it was found that as soon as the myelin began to undergo decomposition in the peripheral portion of the experimentally-cut sciatic nerves, the blood of the animals so operated upon gave the physiological and chemical reactions indicating the presence of choline.

Fig. 5.—Crystals of the platinum double salt of the base separated from cerebro-spinal fluid in cases of general paralysis of the insane. Crystallised from 15 per cent. alcohol.

Fig. 9.—Injection of 5 c.cm. of pathological cerebro-spinal fluid in an animal anesthetized with A.C.E. mixture, but which subsequently received an injection of atropine. It will be observed that now instead of producing a fall choline causes a rise of blood pressure. The same effect is produced by the injection of 5 c.cm. of a 0.2 per cent. solution of choline hydrochloride. (T, time in seconds; S, period of intravenous injection; A, abscissa, in Figs. 6, 7, 8, 9.)

These facts show that my original surmise was true, that the protagon splits up into simpler bodies with elimination of choline. Many observers have found that extract of brain matter gave a physiological reaction similar to that of choline, namely, upon injection of a solution of an alcoholic extract of

brain matter, a fall in the blood pressure was produced. This was noticed by Schäfer and Oliver, Swale Vincent, and Halliburton. The latter two have continued these researches, but arrived at somewhat different conclusions; it appears, however, to me that Halliburton is right in assuming that the effect produced is due to the existence of choline, for he finds that brain extract, like choline after injection of atropine, produces a rise instead of a fall of blood pressure (Fig. 9). Again, the alcoholic extract of fresh brain tissue yields the characteristic octahedral crystals which choline forms with platinum chloride (Figs. 4 and 5). In consideration of this fact, we must conclude the probability that choline is continually being formed as a normal product of lecithin metabolism, and is continually escaping into the cerebro-spinal fluid which drains into the subarachnoid cavity and carries away the waste products of this metabolism. This view was put forward by Professor Gumprecht at the recent Congress at Wiesbaden. Although it is probable that choline is continually escaping into the cerebro-spinal fluid; either it must disappear very rapidly by absorption of the fluid, or it must be in very small quantities, for normal cerebro-spinal fluid did not give the physiological or chemical reaction indicating the presence of choline. Gurlewitz, Schäfer, and others corroborate this statement. Hunt, in a recent paper, finds choline existing in the suprarenal gland. I have often thought it possible that one function of the suprarenal capsule, which Schäfer and Oliver, in their valuable experiments, proved to possess a powerful stimulating action upon the peripheral neuromuscular mechanism of the arteries, is to produce a substance which will neutralise the influence of these blood-pressure-lowering substances. Choline is not found in the urine, it is therefore probably oxidised into urea; it belongs to the same trimethylamine series of bodies as muscarine, neurine, and betaine; but it is not a powerful toxic substance, whereas neurine is. Many of the contradic-

Fig. 6.—Effect of injecting 5 c.cm. of a solution of choline hydrochloride (0.2 per cent.). The fall of blood pressure (B.P.) is accompanied by a dilatation of the intestinal vessels; this is shown by the rise of the lever of the Marey's tambour connected with the intestinal plethysmograph (I.O.). Dog.

tory results which have been obtained, as regards the toxic effects of choline, are due to impure materials containing neurine having been used. Neurine, which is very much more poisonous than choline, has certain specific poisonous properties, and acts especially upon the respiratory movements. In general paralysis and other diseases where a large amount of nervous tissue is undergoing degeneration, choline may exist

Fig. 8.—Effect in a dog of saline solution of the alcoholic extract of 70 c.cm. of blood removed during a seizure from a patient suffering from general paralysis of the insane. There is no effect on respiration (R.), but there is a well-marked fall of blood pressure (B.P.). In the same blood choline was identified chemically.

in sufficient quantities in the cerebro-spinal fluid, taken from the cadaver soon after death, or even from the living subject by lumbar puncture, to give well-marked physiological and chemical reactions indicating its presence (two specimens by lumbar puncture were kindly forwarded by Dr. Turner, of the Essex County Asylum). It was also found in the blood taken for the purpose of treatment from patients suffering from prolonged seizures in general paralysis, and from cases of beri-beri with right heart failure and asphyxia, and in the blood of other cases such as combined sclerosis, experimental section of the sciatic nerves, etc. *We may therefore assume the premiss that choline is a product of nerve degeneration, the result of breaking up of protagon or lecithin, that it escapes into the cerebro-spinal fluid, thence into the blood in larger quantities than it can be disposed of by oxidation, and that its accumulation in the blood might produce auto-intoxication.* The

Fig. 7.—Tracing of intestinal oncometer (I.O.) and arterial blood pressure (B.P.) in a cat. 10 c.cm. of cerebro-spinal fluid were injected; the same effect was obtained in the same animal by injecting 2 c.cm. of 0.2 per cent. solution of choline; the fall of blood pressure is at first mainly cardiac in origin, for the oncometer tracing first follows the fall of arterial blood pressure passively; it, however, soon rises, indicating dilatation of the peripheral vessels.

principal physiological actions of choline were found to

agree entirely with the effect produced by the injection of the cerebro-spinal fluid, or the alcoholic extract of the cerebro-spinal fluid and blood (see figs. 6, 7, 8, and 9) dissolved in normal saline solution obtained from these cases of disease associated with degeneration of the nervous system. They are as follows: A fall of arterial blood pressure, partly due to its action on the heart, but mainly due to the dilatation of the peripheral vessels, especially in the intestinal area (see figs. 6 and 7), for the fall occurs just the same after both vagi have been cut. This dilatation could actually be seen to take place through the glass lid of the *intestinal oncometer* when the solution was injected into the vein, or if the intestine were irrigated by directly allowing the fluid to flow into the oncometer. The action on the splanchnic vessels is due to the direct action of the substance on the neuro-muscular apparatus of those vessels, for after the influence of the central nervous system has been removed by the section of the cord or of the splanchnic nerves, choline still causes the typical fall of arterial pressure. (See figure.) Neurine, a very toxic substance, was not found in the blood or cerebro-spinal fluid, although it is possible that under certain conditions, such as the existence of micro-organisms, it might be produced. Neurine produces a fall of arterial blood pressure, followed by a marked rise and subsequent fall to the normal level. It produces a marked effect upon respiration. This is first greatly increased, but with each successive dose the effect is less, and ultimately the respiration becomes weaker and ceases altogether. The animal can still be kept alive by artificial respiration. It is probable that Cervello is right in asserting that neurine acts like curare on the nerve endings of striated muscles.

Another fact of interest and importance is the existence in the cerebro-spinal fluid of a relatively large amount of proteid matter—three times as much as normal. Seeing that the cerebro-spinal fluid in the cranial cavity is greatly increased in general paralysis, the quantity of proteid matter is very abundant. Examination of this proteid matter showed us that it contained a considerable amount of phosphorus; we were, therefore, led to believe that there was a nucleo-proteid present not found in normal cerebro-spinal fluid. As a rule, the fluid itself was not used for experimental purposes, but an alcoholic extract dissolved in saline solution, and the quantity we injected—5 to 10 c.cm.—would not contain enough nucleo-proteid to produce intravenous coagulation when diluted by the mass of blood; but in one specimen which contained a larger quantity than usual of proteid, 10 c.cm. of the cerebro-spinal fluid injected into a cat produced death by intravenous coagulation. It is therefore probable that a nucleo-proteid escaping into the cerebro-spinal fluid of the perivascular lymphatics may favour congestive stasis, and even coagulation in the veins of the brain in general paralysis—especially during the epileptiform seizures, when presumably the nervous tissue is undergoing disintegration. Congestive stasis in the vessels is the rule, and not infrequently intravenous coagulation and thrombosis of the large veins and even of the longitudinal sinus sometimes occurs. Thus, the disintegrating nervous tissue, by providing a substance which favours stasis and coagulation, may be the

means of setting up a vicious circle, whereby, owing to the circulatory disturbances, acute destructive processes of the nervous tissue are brought about. This hypothesis is supported by the fact that most of the nerve cells in the degenerating tissue of the cortex are devoid of the normal Nissl granules.

Now it has been shown by Held that these Nissl granules are the result of coagulated nucleo-albumen, for sections of alcohol-hardened nervous tissue treated by artificial gastric juice still show the granules, and these stain in a characteristic manner. Moreover, Macculum, by his modification of Lillienfeld and Monti's molybdate method, has micro-chemically demonstrated the existence of abundant phosphorus in these granules; we may therefore conclude that the disappearance of the same from the degenerating cells may be associated with the existence of a nucleo-proteid in the cerebro-spinal fluid. The researches of Halliburton have shown that the *tissue fibrinogen* of Woodriddle, which causes coagulation of the blood when injected intravenously, is a nucleo-albumen; and Halliburton has shown that the nucleo-albumen of brain tissue, like that of other tissues, has a powerful action in producing intravascular clotting. Seeing that in no disease do we find nervous tissue undergoing such rapid and extensive decay as in general paralysis, it is quite reasonable to presume that the existence of nucleo-proteid in the cerebro-spinal fluid contained in the perivascular lymphatics may be one factor in occasioning vascular disturbances and congestive stasis, especially in those regions in which mechanical conditions favour venous stasis, namely, the frontal and central convolutions. The accompanying diagrams show the regions where pia-arachnoid thickening and atrophy are most

Fig. 10.—External and upper surface of hemisphere, showing distribution of veins. The shading shows the usual area of pia arachnoid thickening. A large branch is seen running back into the lateral sinus, connecting it with the great central anastomotic vein. The lateral sinus is diagrammatically represented as continuous with the longitudinal sinus, and the torcular is not shown.

marked, and the area will be seen to correspond to the distribution of veins opening into the longitudinal sinus; and it will be observed that if there is a tendency to venous stasis

Fig. 11.—Mesial surface of hemisphere, showing the veins opening into the longitudinal sinus draining the upper portions where the thickening of the pia arachnoid occurs. Only a small portion of the longitudinal sinus is represented. These drawings are from Testut, modified to show the area of pia arachnoid thickening and its correspondence in great measure with the area drained by veins opening into the longitudinal sinus.

it would most likely take place in these veins, because the blood has to run contrary to gravitation. Again, we know that the veins run into the longitudinal sinus in a direction opposed to the current, so that any conditions which give rise to general venous congestion would make themselves felt, especially in the area drained by these particular veins. Of course it may be argued that the great anastomotic vein of Trolard has an important connection with the lateral sinus, and that this would prevent, in a measure, such mechanical disturbances. Still, look at it as we will, we must consider that the flow of blood in the veins I have indicated is at a mechanical disadvantage compared with that of the other veins which drain directly into the torcular or into the lateral sinus. That venous congestion does play an important part in the production of the congestive, epileptiform, and apoplectic seizures of general paralysis, is shown by the fact that a brisk purge or an enema will often prevent or cut short these seizures, presumably by relieving portal congestion and general venous turgescence. If, as we have seen, choline has the property of dilating the intestinal vessels in such a marked manner, it is possible to conceive that it may cause portal congestion, and thus act as a factor in the production of venous stasis. The effect produced experimentally was only transitory, because the quantity of choline introduced was rapidly diluted by the mass of blood, and probably oxidised also, yet, when the whole mass of blood contains this substance in appreciable quantity continuously, it means the possibility of constant toxic effect; therefore, although choline can hardly be regarded as a dangerous toxic substance, still, under circumstances, it may serve as an additional factor in the production of complications in this disease.

The Marchi reaction applied to the central and peripheral nervous systems shows rather different results; one striking difference is the comparatively rapid disappearance of the products of degeneration in peripheral nerves as compared with the central nervous system. For example, if the posterior spinal ganglia be removed, and the animal kept alive for months, no traces of the products of degeneration can be found in the roots and peripheral nerves, whereas in the posterior columns of the spinal cord I have found well-marked evidence of the products of degeneration.

Dr. H. Head, who has worked extensively on the changes in the cord and peripheral nerves, the result of lesions of the posterior spinal ganglia, has observed the same conditions. From a large experience of this method of studying degeneration, produced by all kinds of lesions of the cord and brain in animals, also from disease occurring in man, I have been struck by the long persistence of the products of degeneration in the central nervous system, as compared with the peripheral. Is this connected with the anatomical difference which we know to exist between the nerve fibres in the central nervous system and peripheral—namely, the existence in the latter of a chain of tubular cells of mesoblastic origin, forming the nucleated sheath of Schwann? And we may ask, Do these cells have a phagocytic action upon the products of degeneration, utilising the same for the formation of fresh protoplasm and myelin, and does the peripheral portion of the nerve fibre depend solely for its nutrition upon the central cell of origin? There is some evidence in favour of the view that nerve regeneration may take place from the periphery, but there is no evidence to show that regeneration of fibres of the central nervous system, where this sheath is absent, can take place.

There are two forms of degeneration but both may react to the Marchi stain, namely:

1. Secondary (Wallerian) degeneration due to interruption of the axon when it is cut off from its cell of origin, as, for example, in a focal transverse lesion of the spinal cord produced by disease or injury; tracts of fibres which have their cells of origin above the lesion, degenerate downwards, are recognised by the black-stained products of degeneration mapped out in definite areas corresponding to definite systems of efferent neurones, while tracts of fibres conducting afferent impulses, having their cells of origin below the lesion, have a normal appearance. The converse applies to tracts above the lesion, namely, all the afferent tracts which have their cells of origin below the lesion have their limits definitely mapped out by the black-stained products of

degeneration, while those with their cells of origin above have a normal appearance; therefore, secondary degenerations, whether occurring as the result of experiment or disease, may be considered of traumatic origin and arising from conditions outside the neurone, very frequently due to vascular occlusion and local softening.

2. Primary degenerations are clinically and pathologically quite different from secondary. They arise as a result of altered conditions of the blood and lymph, due generally to the introduction or generation within the body of poisonous substances, and are insidious in origin, progressive in character, and generally fatal in termination. They are influenced by hereditary or acquired tendency to nervous degeneration, and election of the particular system or systems of neurones not only constitutes definite groups of clinical phenomena, which admit of empirical classification into definite diseases, but also show that certain poisons have elective affinities for particular systems of neurones; but the election of certain structures may also be determined by occupation and habits, which induce stress on some particular system of neurones; or vascular conditions may lead to circulatory disturbances, which will determine the appearance of degenerative changes earlier and their more rapid progress in certain parts of the nervous system than in others. In connection with the latter contributory factor, we have already referred to the reason why certain portions of the brain should show more atrophy and degeneration in general paralysis than others.

Again, I have found the left hemisphere, which presumably is used more than the right in all right-handed people, more often atrophied in general paralysis. The two hemispheres in this disease seldom weigh equally, and the left hemisphere in two-thirds of these cases weighs less than the right. We know that the speech affection is one of the most characteristic and earliest clinical phenomena of this disease; possibly this difference in the weights may be the result of excessive activity of the left hemisphere while in a process of decay. At the same time, this tendency of the left hemisphere to waste more rapidly than the right might be explained on mechanical principles, for venous congestive stasis might take place more easily in the left hemisphere than in the right, owing to the fact that the blood in the internal jugular vein on the right side has a more direct course to the right auricle than the left.

NOTES.

¹ Exner's method is as follows: Small pieces of brain, 1 c.cm. in size, are placed in 1 per cent. osmic acid for 5 to 10 days: cut in alcohol with a wet knife; after sticking on cork with shellac, the sections, which must be very thin, are mounted in glycerine. If they are allowed to remain in alcohol they spoil; they are best transferred on a section-lifter in a drop of strongly-ammoniated water. The preparation should be examined at once; the essential in this process is the use of the ammonia, whereby the neuro-keratin supporting structure is swollen up into a homogeneous mass. The finest fibres of the cortical layers are demonstrated remarkably well by this method. ² Liebreich and Diakonow considered that protagon was a mixture of lecithin and cerebrin, but numerous researches by Gamgee, Blankenhorn, Baumstark, Kossel, Freytag, and Ruppel have shown that protagon is a single chemical substance, without, however, its precise constitution being determinable. Noll, in an interesting paper refers to these researches and describes a method for the quantitative estimation of protagon. By this method he was enabled to show that protagon rapidly diminished in quantity in degenerating nerves, and finally completely disappeared. He made comparative quantitative estimations of the two sciatic nerves after cutting the nerve on one side in dogs and horses. The protagon diminished in quantity, until on the twenty-eighth day it had completely disappeared. In one case he examined the central ends of the sciatic nerves, and found a considerable diminution on the side of section. He also did an experiment relating to phosphorus, and his results, he states, are in agreement with our results with regard to the splitting up of lecithin. Choline can be detected chemically in the blood and cerebro-spinal fluid in the following manner: The blood or fluid is mixed with two or three times its volume of absolute alcohol. The filtrate is evaporated over a water bath to dryness. The residue is taken up with absolute alcohol and again filtered; the filtrate is evaporated to dryness and treated with 15 per cent. alcohol in distilled water and a drop of platinum chloride solution added. Octahedral crystals of the double salt of choline and platinum chloride are formed.

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ANTISTREPTOCOCCUS SERUM IN ERYSIPELAS.

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As antistreptococcus serum has not yet established itself as an efficient remedy in erysipelas, and as notes of cases treated with it, whatever the result, are useful in indicating its efficacy or the reverse, I offer no apology for the following brief account of a case treated by it.

Mrs. H., aged 26, was taken ill on April 11th, 1900, and complained of headache, backache, sore throat, and pain in the limbs. The next day, when I first saw her, the temperature was 104.6°, the pulse 130, the same symptoms persisted, and the nose was red, swollen, and blocked up. I diagnosed facial erysipelas, gave a saline aperient, and ordered 20 minims of liquor ferri perchloride with 2 gr. of quinine, to be taken every four hours, and the face to be covered with a mask of cotton wool.

The next day (April 13th) there was no doubt of the diagnosis, the eruption having spread on to the cheeks. That night, however, the face being very painful, the patient threw off the mask, and had the face constantly bathed with butter milk. The next morning she was much worse, the temperature 105°, the face a deep red, and the eruption had spread to the eyelids and forehead. I prescribed an ointment consisting of equal parts of lanolin and ichthyol to be smeared over the face, and ordered 4 grs. of quinine to be taken every six hours, alternating with half a drachm of liquor ferri perchloride, which was also taken every six hours. The diet consisted of peptonised milk and Brand's beef essence (plain milk caused vomiting).

On April 15th the submaxillary region was involved, and the iron was dropped, as it caused vomiting and diarrhoea. The patient was delirious, and half an ounce of brandy was given every four hours. By April 16th the patient was so unconscious that all the excretions were passed under her, and half an ounce of brandy was being administered every hour. On April 22nd, the temperature being 104° and the pulse 120 and very thready, digitalis and strychnine were given with the quinine, the hair was cut short, and an icebag applied to the head, the delirium being of a low muttering character. A bedsore had formed over the sacrum and another on one buttock.

On April 24th she was practically moribund; the pulse could hardly be felt and could not be counted. At 10 A.M. I injected 20 c.cm. of Burroughs and Wellcome's antistreptococcus serum under the skin of the abdomen. At 2 P.M. she became conscious for a time, though she became delirious again. At 6 P.M. the temperature had come down to 103°, and the pulse was of better tone. I injected another 10 c.cm. of the serum. Next morning the temperature was 99.6°, the pulse 98, and decidedly stronger. I gave another 10 c.cm. of serum. She was quite sensible, and complained of the prick of the hypodermic needle. She had another 10 c.cm. of serum the same evening. The next day she was not delirious, had some tea and toast, and asked for the bedpan when she needed it. This day and the next two days she had a daily dose of 10 c.cm. of serum, and on April 27th she sat up and ate boiled fish for dinner. From this time onward convalescence was uninterrupted, and the temperature remained normal, except for a rise to 102.6° on May 6th, when she complained of pain in her joints. This was entirely subdued by 15 grs. of sodium salicylate every four hours, the temperature next morning being 99°.

One noteworthy feature of the case was the almost entire lack of sleep. At various times the following doses were given: Dover's powder, 15 grs.; sulphonal, half a drachm; potassium bromide, 2 drachms; sulphonal, 35 grs., with ½ gr. morphine; trional, 1 drachm; none of these drugs produced more than twenty minutes' sleep, until the temperature had reached the normal point.

I have no hesitation in saying that the antistreptococcus serum, of which she had 80 c.cm. in all, saved the patient's life; as, in my opinion, when it was administered, she could not have lived more than twenty-four hours without it.

IMPACTION OF A BEAN IN THE AIR PASSAGES
TRACHEOTOMY: EXPULSION THROUGH
THE WOUND: RECOVERY.

By BRUCE HAMILTON, L.R.C.P., M.R.C.S.,
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THE following case of a foreign body in the bronchus presents several features of interest:

A boy, aged 12, when playing with haricot beans, had his elbow accidentally jerked upwards, with the result that a bean which he had been holding in his hand was shot into his mouth; coughing and retching instantly commenced. Attacks of coughing and retching recurred at intervals of a few minutes, and a little blood-stained mucus was coughed up. There was no evident laryngeal stridor, but the boy was greatly alarmed, and repeatedly sought to relieve his distress by cramming his fingers down his throat, an act that at once induced noisy retching; a period of comparative calm invariably followed.