THE CROONIAN LECTURES

ON

DEGENERATION OF THE NEURONE.

Delivered at the Royal College of Physicians of London

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LECTURE IV.

SOME CHRONIC TOXIC CONDITIONS IN RELATION TO
DEGENERATION.

I SHALL to-day refer to the effects of chronic poisoning of the system, especially in reference to two factors, which are the most potent, the most prevalent, and the most persistent poisons in the production of the degeneration of the neurone, and which frequently act in combination, affecting not only the nervous system of the individual but also of the offspring. Such are alcohol and syphilis.

THE CLOSE RELATIONSHIP IN THE ETIOLOGY AND PATHOLOGY
OF GENERAL PARALYSIS AND TABES.

Syphilis is the best example of a poison—probably, though not proved to be, of microbial origin—which has a selective influence upon the nervous system, with a remote effect; it is the most important factor in the production of two progressive degenerations of the nervous system, one affecting especially the exogenous afferent spinal neurones, namely, *locomotor ataxy*—the other affecting especially the association neurones of the frontal and central convolutions of the cerebral hemispheres—namely, *general paralysis of the insane*.

A striking instance of the selective action of the syphilitic poison is shown in the fact first pointed out by Sir William Gowers that only in persons affected with acquired or inherited syphilis is the symptom known as the Argyll-Robertson pupil found; indeed, it is sometimes the only symptom. Seeing that this is the most common objective phenomenon in the two diseases mentioned, it strengthens the presumption, based on experience, that the syphilitic poison is the cause of the disease in the majority of instances. It is the opinion of many authorities—and I may say that my experience supports it—that locomotor ataxy and general paralysis are one and the same morbid process, affecting different parts of the nervous system. They are, in my opinion, both a primary and a progressive decay of the nervous elements, and are, etiologically, clinically, and pathologically, very closely related.

At a discussion held at the Pathological Society I supported the view that tabes and general paralysis are one and the same disease, affecting different parts of the nervous system. It may be asked then, if this be so, how do you explain the fact that in general paralysis it is the brain, and especially one particular part, which is affected, while in locomotor ataxy it is the cord? Let us consider the effects of poisons like alcohol, lead, ergot, lathyrus, and diseased maize (pellagra). They may produce both peripheral nerve and cord changes, together with brain changes, in the same individual. It is the *individual*, his occupation and habits which determines the seat of the morbid process. In some cases, however, the cord symptoms, on the one hand, predominate, and the brain symptoms may be slight, or even absent; on the other hand—and these are the cases of lead and alcoholic poisoning which come into the asylums and are not seen in the hospitals—we have the brain symptoms predominant, and the paralytic symptoms often less defined, overshadowed by the brain affection or even absent. So it is with general paralysis; cases come into the hospitals with Argyll-Robertson pupils, marked paresis, and speech affection, but with the mental symptoms only comparatively slightly developed. Likewise numerous cases of tabes attend the hospitals for a considerable time, and then marked mental symptoms develop, when the case is certified as tabetic general paralysis. In all these degenerative diseases we have more than one factor in operation; and I quite agree with Edinger in his opinion that *stress* will determine the initial localisation of the degenerative process. I do not know that we can learn very much about these primary degenerations from experi-

ments upon animals; however, much valuable knowledge undoubtedly has been obtained by the effects of poisons in producing acute or subacute degeneration of the neurones. Certainly animals have not been inoculated with syphilis. Tuczek, who first described the changes in the nervous system in ergotism and pellagra, was unable to produce these degenerative processes in animals by long-continued feeding with diseased maize or rye, nor have other experimenters been successful with injection of ergotin and sclerotic acid. Likewise alcohol and lead administered to animals do not produce the characteristic clinical and pathological conditions found in man. Moreover, many other poisons, the products of micro-organisms, produce different effects in man to those produced in animals.

The close association of tabes and general paralysis is to my mind clearly shown by the fact that there are a considerable number of cases in which it is difficult to say whether they should be classed from their clinical symptoms and morbid changes found *post mortem*, as tabes with mental symptoms, or as cases of tabetic general paralysis. I have seen cases in which the diagnosis of general paralysis has been made, because the patients were suffering with mental symptoms indicating that disease; namely, maniacal or melancholic symptoms, and delusions associated with ataxy. After a time the mental symptoms have cleared up, and the case has then been called tabes. Again, I have frequently seen cases of tabes which begin with all the characteristic phenomena of this disease, and then terminate in progressive dementia and paresis, dying in an asylum from general paralysis. Symptoms which are looked upon as characteristic of tabes, such as grey atrophy of the discs, are not at all uncommon in general paralysis, and I have met even with symmetrical perforating ulcers and Charcot's joint. I have recently examined 12 cases

Fig. 1.—Symmetrical perforating ulcers from a case of tabetic general paralysis.

of the tabetic form of general paralysis, in which the changes in the brain—naked eye and microscopical—were characteristic of general paralysis, and the cords showed the characteristic lesions of tabes. My experience would point to about 10 per cent. of the cases of general paralysis being associated with tabetic cord lesions. The etiological relationship of the two diseases is almost identical; both are affections of men in the prime of life, of townspeople, of men of all grades of society, but women of the lower and lower middle class only; moreover, juvenile general paralysis and juvenile tabes occur in the subjects of congenital syphilis, and affect the sexes with equal frequency. I have met with 1 case of the latter and 30 cases of the former with 24 *post-mortem* examinations. In 80 per cent. of the cases of juvenile general paralysis, a definite

history, or signs of syphilis, were obtained. A considerable number of cases have now been recorded of married couples being affected with general paralysis. I recently saw a man who had well-marked signs of syphilis suffering from the tabetic form of general paralysis, from which he subsequently died; his wife, who had healthy children by the first husband, none by the second, is now dying of general paralysis. Dr. T. Buzzard related a similar case at the same discussion, previously referred to.

SOME FACTS CONCERNING THE ETIOLOGY AND PATHOLOGY OF GENERAL PARALYSIS.

There are two types among the juvenile general paralytics: (1) In which the syphilitic poison seemed to have produced an arrest or impaired development of the higher centres, so that the child was weak-minded or imbecile; (2) in which the child was mentally capable, in some cases highly intelligent and active-minded.

Fig. 2.—Section of ascending frontal convolution from a case of general paralysis, showing engorgement of vessels, disappearance of Meynert's columns from displacement of the nerve cells and overgrowth of glia cells.

Fig. 3.—Section of occipital lobe from the same case, showing practically normal appearance of cortex. The Meynert's columns are distinctly seen, and there are no vascular changes.

The cause of the degenerative process in most of these cases seemed to be associated with the increased *psychical activity*, which must of necessity develop after puberty, when new emotions, objects, and ambitions are awakened by the sexual instinct, and the struggle for existence. That psychical activity plays a very important part in this disease, as affecting adults, is clearly shown by the following facts: the sufferers are nearly all townspeople, with a quick reaction time, ambitious and energetic, and the first symptom of the disease may be undue mental activity, approaching now and then to that of genius. It might be argued that a large number of these people are from the lowest and least educated classes; still, I am convinced that they belong to the mentally active class. Not only do we find the people affected possess mental activity, but also usually, sexual proclivity; and it is very difficult to decide whether the increased sexual activity so frequently met with in the early stages of this disease is a

cause or an effect. But all forms of mental excitement are associated with fatigue, and too often the *neurasthenic* condition, which precedes the more definite symptoms of the organic brain affection leads to alcoholic excesses; and it is often very difficult to decide whether a case is one of *mania a potu* or of general paralysis. The two are frequently combined, and if so the disease runs a more rapid course. The researches of Bonhofer and Trömmner have shown that acute degenerative changes may occur in the cortical cells as a result of acute alcoholism; and I have found, and can therefore agree with Jolly, that in cases of alcoholic dementia there exist organic changes affecting the superficial layers of the cortex, and causing atrophy of the tangential and super-radial fibres. It is then probable that although alcohol will not of itself produce general paralysis, it will materially increase the rapidity of the progress of the disease. Krafft-Ebing sums up the etiology of this disease in two words—Civilisation and Syphilisation; and he brings forward very strong arguments in support thereof. It has been argued that in Mohammedan countries, where syphilis is rare, general paralysis is unknown. The recent report by Dr. Warnock from the Egyptian hospital for the insane, states that during 1899, 57 general paralytics were under care out of a population of 500. The large towns furnished nearly all the cases of this disease, and syphilis was known to be the cause in 29 of the 35 cases admitted; 24 of them were native Egyptians. These facts upset the above argument.

Why should general paralysis be associated especially with atrophy of the frontal and central convolutions? It has already been pointed out that in these regions venous stasis is most likely to occur. Psychical activity is associated with hyperæmia of the brain and congestion; those portions of the brain in which the mechanical conditions favour this congestion in the most marked degree would be more likely to suffer from the effects of the congestion. The whole cerebrum and spinal cord waste in advanced general paralysis, but certain regions are earlier and more markedly affected than others—namely, the frontal and central convolutions. These are the regions

Fig. 4.—Case of juvenile general paralysis from which these preparations were made. The photograph shows Hutchinson's teeth and rhagades round the mouth.

whose veins drain into the longitudinal sinus, and in which, therefore, for reasons previously mentioned, congestive stasis is more liable to occur. If it be admitted that owing (in the majority of cases) to the influence of the syphilitic poison the durability of the nervous system has been lowered, increased psychical activity will tend to exhaustion and disturbance of the normal nutritional equilibrium of the neurones. But psychical activity will cause hyperæmia and congestion of the brain, and in regions where there is a tendency to stasis the congestion may persist, especially if it leads to insomnia. A vicious circle becomes established by conditions which tend, on the one hand, to perpetual venous congestion in certain regions, on the other hand to increase excitability of the neurones; these factors mutually interact.

Venous congestion (according to the researches of Waller, who has shown that CO₂ increases the excitability of nerve), may lead to hyperexcitability of those regions in which the stasis occurs. Likewise there is probably an impaired supply of arterial blood to the brain, for the following reasons: The experiments of François-Franck show that excitation of the Rolandic area of the cortex causes contraction of the arterioles and rise of blood pressure; observations which I have made upon the blood pressure in general paralysis by Hill's sphygmo-

meter¹ entirely accord with the results obtained by Leonard Hill and Craig. There is a considerable rise in the arterial pressure above the normal, and this is increased markedly during the occurrence of seizures, whether congestive or epileptiform. The blue condition of the skin and the coldness of the hands and feet of patients suffering from general paralysis, suggest a small amount of blood in the arterial system and a large amount in the venous. Although we find this high arterial pressure, there is seldom marked hypertrophy of the left ventricle, and I have found that if a patient has a great number of epileptiform seizures the arterial pressure falls, right heart distension and sometimes a condition of asphyxia arise with great engorgement of the veins, and death in consequence. The heart muscle in these cases exhibits early and often extensive fatty degeneration, due to a combination of causes—insufficient oxygenation of the blood, autointoxication probably from fatigue products, and increased destructive metabolism owing to the much greater resistance to be overcome. Not only the heart, but also the striated muscles show this change; I could not find evidence of degeneration of nerves to account for this change, neither do I believe this to be the effective cause, seeing that exactly the same changes in heart, diaphragm, and other striped muscles have been found by me in seven cases of *status epilepticus*.² Some of the latter patients, prior to the fits, were in perfect health. In connection with this, I may mention that the venous congestion of the brain, caused by the *status epilepticus*, produced marked changes in the cells of the cerebral cortex, changes which corresponded with the appearances presented by many of the large pyramidal cells in general paralysis, and not unlike those found in experimental anæmia with convulsions. There was great swelling of the cell (œdema), disappearance or disintegration of the Nissl granules, often eccentric position of the nucleus, and dilatation of the perineuronal and perivascular lymph spaces. Moreover, epilepsy frequently ends in dementia, and we find in such cases atrophy of the tangential, super-radial and inter-radial association fibres, a condition which is always found in general paralysis even in the earliest stages, frequently before any fits have occurred. Dr. George Watson, who has looked over a large number of my specimens, reports that in 20 cases which he has examined he found the tangential fibres, the super-radial and inter-radial fibres atrophied in all the 16 cases of general paralysis; but that of these 16 none showed any recent changes by the Marchi method, consequently we must suppose the atrophy was of some considerable standing, and probably years before the patient comes to the asylum a regressive change has commenced in these latest morphologically-developed structures.

Occasionally I have been able to show that the tangential fibres of Broca's convolution are more atrophied on the left than the right side when the left hemisphere has weighed less than the right. The four cases in which he did not find atrophy of the association systems mentioned were primary degenerations of projection systems, namely, two of amyotrophic lateral sclerosis, one of combined sclerosis, and one of universal syphilitic arteritis. In a considerable number of the cases of general paralysis there was recent degeneration of the radial fibres, especially in those cases where there had been epileptiform seizures. The perivascular lymphatics frequently contained the fatty products of degeneration.

We can thus understand that a number of contributory factors may arise to establish a vicious circle, which is continually enlarging, until a fatal termination occurs. Such factors may not only lead to rapid destruction of the neurones or nervous elements, but by irritation lead to a proliferative formation of the neuroglia cells, and we can account for the ependymal granulations almost invariably met with in this disease by the irritation caused by an altered cerebro-spinal fluid. Although the most constant, naked-eye changes are not found exclusively in general paralysis, but sometimes in other wasting diseases of the brain.

GENERAL PARALYSIS A PRIMARY DEGENERATION.

The morbid process in general paralysis has been considered by Mendel and many other authorities to be a primary-meningo-encephalitis with secondary atrophy. I would advance the following reasons for considering it a

primary degeneration of the neurone with secondary meningo-encephalitis:

1. Its relation to tabes dorsalis, and the probability of its being the same morbid process due to the same cause (syphilis) commencing in a different part of the nervous system.

2. The existence of the Argyll-Robertson pupil in the majority of cases.

3. The existence of grey atrophy of the discs in a number of cases—much more frequent than can be explained by mere coincidence. The last two symptoms cannot be explained except by a primary atrophy.

4. The evidence of a wasting of the whole nervous system, affecting some parts more than others, but out of proportion to the evidences of inflammation. This wasting must be primary in the nervous system and not secondary to bodily disease, for in no cachectic disease, nor even in starvation, do we find extensive wasting take place.

5. The thickening of the pia-arachnoid membrane is proportional to and corresponds with the degree and locality of the atrophy; so it is with tabes.

6. In many cases of tabes, especially those with mental symptoms, atrophy of the tangential and super-radial association fibres of the brain are found, quite similar to but in different situations to general paralysis.

7. In diseases with well-marked meningo-encephalitis—about which there can be no dispute that it is primarily an inflammatory process—we do not find this extreme atrophy.

In illustration of this I would call attention to two cases of African lethargy which I had the opportunity of examining, and of describing for the first time the histological changes in the central nervous system. Throughout the whole central nervous system in both these cases there was evidence of a profound and widespread chronic inflammatory process. The whole of the perivascular lymphatics were choked up with mononuclear leucocytes. The pia-arachnoid membrane was similarly infiltrated, indicating the existence in the cerebro-spinal fluid or blood of an irritant poison, the nature of which I was quite unable to discover, although the most painstaking efforts were made by me and Dr. J. E. Bulloch, both *post mortem* and during life, to discover a micro-organism. The only abnormal condition that was found in the blood of these negroes, as also in a previous case of Dr. Stephen Mackenzie's (the tissues of which by his courtesy I was able to examine, and observed similar histological changes), was the existence of the embryo *filaria perstans*. The evidence of this being the cause of the symptoms, or of the morbid process found in the nervous system, is wholly inadequate. Although there was this chronic inflammation, yet throughout the nervous system there was far less cellular atrophy and nerve-fibre destruction, even in the most advanced case, than one meets with in quite the early stages of general paralysis. In fact, the brains showed little or no atrophy or change to the naked eye; and microscopically there was very little disarrangement of Meynert's columns in one case. The weight of the brains showed little deviation from the normal in one case, none in the other, whereas the bodies were extremely emaciated in both cases. I think this evidence tends to show that there is a primary atrophy in general paralysis, and that the inflammatory and vascular changes are secondary complications.

Primary degeneration of the neurones may affect the afferent, efferent, or association systems singly or combined; and in the tabetic form of general paralysis all these may be affected.

PRIMARY DEGENERATION OF THE AFFERENT SYSTEM OF NEURONES.

In tabes we have an example of degeneration of the afferent projection system, which for reasons already mentioned is probably due to nutritional failure on the part of the posterior spinal neurone, by which parts most remote from the centre of nutrition undergo a regressive atrophy. The cells of origin seldom undergo marked changes, unless pigmentation can be considered evidence of degeneration, but there seems to be some reason why the cells of the posterior spinal ganglia should be able to maintain a trophic independence. Possibly it may be the existence of the nucleated capsule; or possibly the cells receive stimuli from the viscera

by sympathetic branches; or lastly, it may be that they have become more or less independent of the influence of stimuli by the impulses from the periphery travelling directly across the T-shaped process. Again, after section of the posterior spinal roots, I did not find any change in the posterior spinal ganglion cells. Moreover, we know that in amputation cases of long duration, although the nerves and posterior roots waste, the spinal ganglion cells undergo little change. It is particularly the central projection of the neurone that undergoes the degenerative process in tabes, and from the experimental evidence above adduced this would not suffice to cause changes in the cell. The peripheral portion of the neurone—namely, the sensory peripheral nerves—have been shown to undergo regressive atrophy in tabes and degeneration from the termination towards the centre. We know that the peripheral portion of the T-shaped process is ensheathed by the hollow mesoblastic cells forming the sheath of Schwann, which probably exercise an indirect trophic influence upon the long axis-cylinder process.

Again, in tabes the idea that a sclerosis of the posterior columns produced by an irritative proliferation of the glia tissue is the initial morbid process causing a secondary degenerative atrophy is the result of confusion of cause and effect. The overgrowth of the glia tissue is the result of, and proportional to, the primary progressive atrophy of the nervous elements, for we cannot suppose that the glia tissue would electively destroy exogenous fibres, leaving the endogenous intact. In support of this statement I show a photomicrograph (Fig. 5) of the sixth cervical segment of the spinal cord of a monkey, in which the third, fourth, fifth, sixth, and seventh cervical, and first, second, and third dorsal posterior spinal roots were cut on the left side. The eighth cervical, which especially supplies the hand, was not cut. This animal was kept alive six months, and it was after a time very difficult to determine upon which side the operation had been performed, as it used each hand equally well, thus behaving entirely differently to the animals which had had all the roots cut.³ The result of this operation is shown in two bands of sclerosis in the posterior column on the side of the divided roots, with an area of normal fibres corresponding to the undivided root lying between.

Fig. 5.—Described in text.

It will be observed in this photomicrograph of the sixth cervical segment that fine fibres are passing across the area of sclerosis to the grey matter of the posterior horn; in not a single section of all the segments of the upper part of the cord could I find the absence of these fibres which could only be terminal branches of the undivided eighth root. This points to the probability of the overlapping of roots of spinal segments. It certainly shows that sclerosis does not cause atrophy of fibres, for here is a band of fibres lying between two definite bands of

sclerosis, with delicate fibres passing across the sclerosed area. Obersteiner has maintained that the degeneration of the posterior columns is due to a meningitis affecting the roots at their entry, thereby compressing the accompanying nutrient vessels; but there are so many facts against this theory which will occur to everyone upon consideration that I need not mention them. Suffice it to say that one does not find this same degeneration of the posterior columns in obvious cases of meningitis, syphilitic in origin. Obersteiner figures specimens stained by the Pal method, showing, as the fibres pass through the membranes to enter the cord, disappearance of the staining. This, however, must not be taken as indisputable evidence of degeneration at this particular point, because the anterior roots sometimes show a similar defect in staining upon their emergence from the cord. Moreover, the meningitis theory does not explain the changes in the peripheral nerves met with in this disease, nor does it explain the affection of the posterior roots as far back as the ganglion, leaving the anterior roots quite intact. That some anatomical condition of the circulation in the posterior columns may act as a contributory factor, as occurs in the frontal and central convulsions in general paralysis, is possible, especially when one takes into consideration the effects of cerebral tumour in the production of degeneration limited to the posterior columns (Hoche, Batten).

PRIMARY DEGENERATION OF THE EFFERENT SYSTEM.

In amyotrophic lateral sclerosis we have an example of a systemic degeneration affecting the motor efferent system of neurones, from cortex to periphery. I have had the opportunity of examining three typical cases of this disease; in all three I have found degeneration of the whole efferent system comprising the cortico-spinal neurone and the spinal muscular neurone; the degeneration being limited to these neurones alone. This was pointed out by Sir William Gowers in the first edition of his *Manual*. Certain groups of the motor-spinal neurones we know from clinical and microscopical observation are affected before others; for example, the postero-external group in the eighth cervical and first dorsal segments of the cord is especially proved to be the seat of the earliest and most severe change in a large number of cases. This is a group of neurones which presides over the small muscles of the hand. I am of opinion that the morbid process in these systemic degenerations commences at the periphery of the neurone and

Fig. 6.—Section of the corpus callosum from a case of amyotrophic lateral sclerosis showing large black degenerated fibres in transverse section.

extends back towards the trophic and genetic cells of origin finally, in prolonged cases, causing the destruction of the cells themselves. The arguments I would advance in favour of this view are that in some cases of amyotrophic lateral sclerosis degeneration could only be followed as far as the pyramids; in others, to the crus cerebri; while in other cases, published by Charcot and Marie, Kahler and Pick, and Kowjenikoff, the atrophy had extended to the pyramidal cells of the cortex. In the case referred to by the last observer there was even atrophy of the motor convolutions with thickening of the membranes; this I have also observed in one of the three cases I have above mentioned. In two of the three cases which I have examined there was not only degeneration discoverable by Marchi method of the whole cortico-spinal neurones, but of the lateral branches, which pass off from the axis-cylinder processes to enter the corpus callosum. This degeneration of the motor fibres in the corpus callosum strongly favours the primary degeneration theory of the origin of the disease being a nutritional degrada-

tion of the neurones themselves, independent of external vascular or supporting tissue changes. Moreover, in these cases, I have found that the tangential and super-radial and inter-radial systems of fibres were intact.

Fig. 7.—Section of the superficial cortex cerebri of the Rolandic area, stained by Marchi-Pal method, showing the super-radial and tangential fibres intact.

Now, if it were any external condition these neurones would have suffered with the motor neurones. Senator published a case of typical amyotrophic lateral sclerosis, in which there was no degeneration found in the pyramidal tracts; we can only explain the symptoms by supposing that there was interruption between the cortico-spinal and spinal muscular neurones, either a failure of junction between the two, or possibly, in view of the opinion of Von Monakow and of the recent interesting observations of Schäfer, an atrophy of intermediate cells (of Golgi). Schäfer is of opinion, based upon observations made by the Marchi method on spinal cords of animals on which he had performed hemisection of the spinal cord, that the fibres of the pyramidal tract do not end in the terminal arborisation around the anterior horn (spino-muscular neurones), but are in connection with intermediate cells situated at the base of the posterior horn; if this doctrine be true, a voluntary motor impulse will pass through three sets of neurones instead of two. There is always a considerable amount of cellular atrophy at the base of the posterior horn in amyotrophic lateral sclerosis, therefore the appearances presented by this disease do not negative this theory.

Fig. 8.—Section of lower portion of grey matter showing absence of large pyramidal cells and replacement by Deiters's cells. This occurred in little isolated foci of the motor area of the cortex.

DEGENERATION OF AFFERENT AND EFFERENT SYSTEMS.
Both afferent and efferent tracts of the spinal cord may

undergo degeneration, giving rise to the condition known as *combined sclerosis*, which is met with in various forms of grave anæmia, and in pernicious anæmia, first described by Lichtheim and Minnich; it may occur also in ergotism and pellagra.

This degeneration cannot be produced experimentally in animals, and we must suppose that some auto-intoxication occurs, by which a progressive degeneration affecting primarily the long tract afferent and efferent systems in the cord takes place. I have had the opportunity of examining microscopically 3 cases of combined sclerosis, with grave anæmia, and I found the process of degeneration was not limited to the spinal cord. In 2 cases, which I examined by the Nissl method, there were marked changes in the cortico-pyramidal cells, and by the Marchi method all these cases showed degeneration in the whole pyramidal system from the cortex downwards, although it was more marked and extensive in the spinal cord than in the pyramid and pons. Likewise, the cells of Clarke's column showed in 2 cases, examined by the Nissl method, degenerative changes, and both ventral and dorsal cerebellar tracts were extremely degenerated. The changes, however, in the posterior spinal ganglia were not marked, probably for the same reasons as I have mentioned in referring to tabes.

A valuable paper on subacute combined degeneration has recently appeared in *Brain* by Batten, Russell, and Collier. Twelve cases are narrated and seven necropsies with microscopical examinations. The authors are of opinion that the disease is a degeneration due to a toxic agent in the blood.

PERIPHERAL NERVE DEGENERATION.

Multiple polyneuritis occurs as the result of toxæmia; the poisons which give rise to the condition are numerous, but by far the most common is alcohol, and it is about this that I shall speak more particularly. Alcohol affects not only the peripheral nerves, but the brain too, where it produces degenerative changes accounting for the symptoms manifested by the patients during life. A consideration of the extent of surface of the motor and sensory neurones shows that relatively the portions covered with the myelin sheath and sheath of Schwann, as compared with the rest of the neurones, are enormous; for it is obvious that the neurones supplying sensation to the soles of the feet and the motor neurones supplying the muscles of the feet are 3 to 4 feet long, and if we admit that the trophic centres are in the cells of origin at the lower end of the spinal cord, then it is quite obvious that parts so remote from the trophic and genetic centres will first suffer from nutritional failure caused by the insidious action of toxic substances such as alcohol. As the effects of the poison become more marked, so the functional defect of sensation and movement travels up the legs towards the centres, so that we have in peripheral neuritis an anæsthesia progressing in the manner one puts on a stocking, and as sensation returns on recovery, it proceeds as one takes off a stocking, except that there is not a sharp upper border. This would quite accord with the fact that the parts most remote from the centres of nutrition are the first to be affected and the last to recover. Very probably, also, the parts most remote from the centre of circulation (the heart) are more liable to be affected. Thus the extremities of the limbs are most affected as regards movement and sensation, and it seems that mineral poisons, arsenic, lead, etc., and alcohol, which are taken into the system for some time before effects are produced, act more particularly on the peripheral nerves. There is very little evidence in these cases of the poison-producing interstitial inflammation, neither do we find changes sufficiently marked, as a rule, in the ganglion cells to account for the symptoms. The earliest and most obvious change is a proliferation of the nuclei of the sheath of Schwann; and this condition may frequently be found before microscopical evidence exists of the degeneration of the myelin sheath as revealed by the Marchi method. This does not, however, show that changes have not taken place in the myelin sheath, for the following reasons:—The products of degeneration, we know from experimental section of the nerves, are rapidly absorbed, and are by no means so obvious as in the central nervous system. Again, a chemical change may have taken place in the protogon, which has not advanced to a stage in which a non-

phosphoretted fat, essential for the Marchi reaction, has been produced. We know that for at least four days after section of the nerve the Marchi reaction is not given, and yet we have no reason to believe that protagon has not been undergoing some chemical change during that period. Again, the nerve fibres are not all affected equally and simultaneously, some fibres being affected more than others. It may be asked, If the poison, which has been accumulating in the system and producing its toxic effects on the nervous system, acts upon the whole neurone why are changes not seen throughout the whole neurone, and why should the poison not be the effect of irritation of the chain of tubular mesoblastic cells which surround the axis-cylinder process of the neurone? If it were so, there is no reason why it should not affect the nerves of all parts of the body equally. I conceive that this pro-

gs. 9, 10, 11, and 12 are microphotographs of cells of the anterior horns of the lumbo-sacral enlargement, from a case of a woman with severe alcoholic paralysis, muscular atrophy and degenerative changes in the nerves and muscles of the legs. (Magnification 600.)

Fig. 9 shows a cell with commencing chromolytic change.

Fig. 10 shows a cell with advanced chromolytic change and eccentric nucleus. Both these cells resemble the appearances presented by cells after section of a nerve, and the change may be due to the morbid process having caused destruction of their axis-cylinder processes. They, however, are capable of regenerating the axis-cylinder process, just as regeneration may occur after section of a nerve.

Fig. 11.

Fig. 12. (Figs. 11 and 12 show morphological changes indicating death of the trophic and genetic centre. We see in Fig. 11 a cavity on one side indicating rupture of the nuclear membrane; and in Fig. 12 there is so much vacuolation of the protoplasm of the cell as to indicate its destruction.)

liferation of the nuclei of the sheath of Schwann is due to a disturbance of the normal physiological nutritional inter-relationship between the neurone and the cells which ensheath its axis-cylinder process. It is a vital reaction on the part of these cells against the progressive nutritional failure of the neurone, which will eventually terminate in destruction of the essential conducting axis cylinder. In fact, we know that this takes place when a nerve is cut, and it is a provision for repair, therefore, it is wrong to look upon this proliferation of nuclei of the sheath as evidence of irritative effects of the poison, but rather as an attempt to repair the destruction caused by the poison.

In three cases of alcoholic neuritis which I have lately examined in conjunction with Mrs. Williams, M.B. (late Technical Scholar), it was found that many of the nerves did not show very marked evidence of degeneration by the Marchi method; there was, however, considerable nuclear proliferation of the sheath of Schwann, especially marked in the nerves of the lower extremities. In one case in which there was complete paraplegia the ganglion cells of the lumbar-sacral spinal cord showed well-marked chromolytic changes; the Nissel granules in many of the cells of the anterior cornua

had entirely disappeared; the nucleus was eccentric and the processes broken off; some of the cells were vacuolated, and degenerative changes were observable in nearly all the nerves of the limbs by the Marchi method. The changes in most of the cells resembled the condition which one would find after section of a nerve, the reaction phase mentioned in Lecture II; in fact, when we consider it, the condition is really very much the same as that produced by section, for the axis-cylinder processes of the sensory and motor nerves have in such advanced cases died for a considerable part of their extent; but under favourable circumstances, especially if the poisonous influence

Fig. 13.—Section of the external popliteal nerve stained by Marchi method. The black degenerated myelin is not very abundant because it has in great part been absorbed, but other stains, for example, Stroebe, show that hardly any healthy fibres exist. This preparation is from the same case as the cells described above. (Magnification 200.)

be removed, and the nutrition of the muscles be maintained by appropriate treatment, there is no reason why, the same as in section of a nerve, regeneration should not take place. The great thing to remember is that the joints should not be allowed to become stiff nor the muscles inactive. Passive

Fig. 14.—Section of the vagus nerve from a case of acute alcoholic neuritis with hæmorrhagic encephalitis and dementia. The patient suffered with very marked signs of cardiac failure, and died comparatively suddenly. Marked fatty degeneration of the heart was found *post mortem*. The section, stained by Marchi method, shows fine medullated fibres undergoing degeneration. (Magnification 600.)

movements, massage, and galvanism will stimulate the neurones and hasten regeneration, for we have already had abundant evidence to show the important influence stimulus

exercises upon the metabolism of the neurones, and the degenerating and atrophic effects of non-stimulation. In two of these cases, in which there was marked fatty degeneration of the heart, we found fatty degeneration of the fine myelinated fibres of the vagus.

Examination of the brains of 2 cases showed a certain amount of atrophy of the tangential and super-radial systems of fibres, accounting for the dementia which existed. There were also changes revealed by the Nissl method in the cortical pyramidal cells, but seeing that there was no degeneration discovered by Marchi's method in the spinal cord, we cannot assume that these were more than of a functional nature. In one case there were marked congestion and microscopical intracerebral hæmorrhages. The condition of the cortex could not be mistaken for general paralysis, for there was not the same overgrowth of glia cells or atrophy, nor was there the same disappearance of Meynert's columns so characteristic of the latter disease.

RELATION OF STRUCTURE TO DEGENERATION OF THE NEURONE.

Structure and function are mutually reciprocal and interdependent, and we know that a structure which is not used will gradually lose its function, while its nutrition will also suffer, and in time atrophy may occur. Consciously and unconsciously a continuous stream of impulses pours into the nervous system from without by the sensory channels, which are the avenues of experience and intelligence, and our bodily and psychical life depends on the existence of such stimuli.

Excess of normal stimulation of itself is seldom the cause of organic disease, although we have examples of psychomotor paralyses in the palsy affecting scribes, typewriters, pianoforte players, violinists, hammermen, etc.; but whether this is due to an actual degeneration or to a functional depression is not known. If, however, by excessive exercise such a disturbance can take place without any other apparent cause, then undoubtedly stress, acting upon structures in a state of nutritional deficiency, will lead to a disturbance of the normal physiological equilibrium and a progressive degeneration of those structures which are most remote from the centre of nutrition. But increased functional activity of a part is associated with increased blood supply, and if the blood contains a toxic substance, a larger amount of that toxic substance will be carried to the functionally active part, so that whatever benefit might arise in the way of repair from the additional amount of blood will be neutralised by the excess of poison. Numbers of instances have occurred in my experience in which stress seemed to determine the seat of the degenerative process. I will give a few illustrations:

1. A policeman, who was affected with tabes commencing in the arms, turned out to be a mounted policeman, and when I pointed out to the students the unusual situation, he immediately volunteered the information that the pains began in the arm in which he held the reins.
2. A case of amyotrophic sclerosis affecting a cooper began in the muscles of the right arm, with which he wielded a 4 lb. hammer.
3. A man, who had alcoholic dementia, paralysis, and wasting of the muscles of the upper extremities, the lower being unaffected. This man was shown to me as a case of progressive muscular atrophy. I found that he was a porter at Covent Garden Market, and the symptoms he presented were determined by his occupation of carrying boxes of potatoes all day on his shoulders. This patient completely recovered.

I will not detain you with a number of further examples; but asylum experience only too well demonstrates the importance of undue mental excitement in causing degeneration of the higher structures of the brain, as in general paralysis. Professor Edinger has emphasised the important influence of stress in determining the seat of nervous degeneration, and his philosophical writings on the subject are worthy of careful consideration; he has, too, endeavoured to prove it experimentally.

Voss was unable to produce degeneration in the spinal cord in rabbits, guinea-pigs, and dogs by injections of pyridine sufficient to produce a severe anæmia; but Edinger repeated these experiments, varying them by inducing stress upon the nervous system by various means, one of which was to place the animals (rats) in a wheel cage. He claims then to have shown:

1. That abnormal stress can produce in animals a degeneration of the posterior columns.
2. That it is possible to produce a predisposition by artificial anæmia, by which the influence of stress of much less degree and of much shorter duration can cause this posterior column degeneration.

3. That this disease stands in close relationship, both as to localisation and cause, to the tabetic degeneration of the posterior columns in man.

Fig. 15.—Case of tabetic form of juvenile general paralysis, which died, aged 20, 3 months after onset of symptoms. The photograph shows characteristic teeth.

RELATION OF HEREDITY TO DEGENERATION OF THE NEURONE.

Of all the causes of nervous disease, hereditary predisposition stands pre-eminently first. It may be paternal, maternal, convergent, from grandparents, or according to Weismann's theory of the continuity of the germinal plasma there is no limit to the remoteness of the origin of a neuropathic taint. This doctrine must have been known to the high-born Romans, who carried the masks of all their ancestors upon public occasions. In fact, in *Lucretius*, vol. i, p. 207, it is stated: "Sometimes, too, the children may spring up like their grandfathers, and often resemble the forms of their grandfather's fathers, because the parents often keep concealed in their bodies many first beginnings mixed in many ways, which, first proceeding from the original stock, one father hands down to the next father, and then from these Venus produces forms after a manifold chance, and repeats not only the features but the voices and hair of forefathers; and the female sex equally springs from the father's seed, and males go forth equally from the mother's body, since these distinctions no more proceed from the fixed seed of one or other parent than our face, and bodies, and limbs. Again, we perceive that the *mind is begotten along with the body*, and grows up together with it and becomes old along with it." The history of the Roman Emperors from Julius Caesar, one of the greatest geniuses the world has seen but an epileptic, shows how the endeavour to keep the sacred Julian blood for the dynasty culminated under the influence of a depraved environment in the criminal madness of Tiberius, Messalina, Caligula, and Nero.

Strictly speaking, it is the tendency to nervous disease rather than the disease itself which is inherited, and this is frequently spoken of as neuropathic or neuropsychopathic taint. There are, however, a number of inherited diseases, which although rare, are of great interest, inasmuch as they affect members of a family, the disease frequently commencing in each individual at about the same age. These

are termed *family diseases*, and include hereditary ataxia (Friedreich's disease), hereditary chorea, amaurotic idiocy, paramyoclonus multiplex, an interesting family of cases of which I have recently seen. Two boys and two girls were affected with epilepsy, and this clonic choreiform spasm of the muscles; in each it commenced at the age of 15; there was no direct hereditary history in the parents of any nervous affection, but an uncle suffered with epilepsy. Presumably, therefore, ancestral germinal plasma possessed the neuropathic predisposition, which possibly under some influence which I was unable to ascertain, for example, some acute specific fever affecting the members of the family, or possibly alcoholism or syphilis in the parents, had supplied the contributory factor to develop the disease.

In a healthy nervous system, we must suppose that the balance of potential is high, and that the sense of fatigue is the natural indication for sleep and repose by which nervous energy may be recuperated. The neuropath may be conceived to possess in some portion of his nervous system communities, groups, and systems of neurones either of defective durability or with an inherited *low potential* readily becoming exhausted, and especially liable to functional depression, and which under the influence of contributory factors such as *toxic conditions* of the blood or *undue stress*, undergo premature degeneration. To explain the inherited neuropathic tendency morphologically, we may suppose that there is an inherent defect in the germinal plasma, which is concerned in the formation of the neurones.

Certain acquired conditions in the parents, affecting them especially at the time of conception, are liable to produce this defect in the germinal plasma; they are acute and chronic *alcoholism*, *syphilis*, and *tuberculosis*. Statistics by Mr. Tredgold relating to 40 cases of congenital imbecility, although not numerous, are valuable because reliable; and in course of time, when he has completed the investigation of this question in all the London county asylums, as he has done in Claybury, will be of still more value. As far as they go, they show that the most important cause of *congenital imbecility* is *inherited neuropathic taint*, 70 per cent. generally in some form of insanity, but that *alcoholism*, *tuberculosis*, and *syphilis* are important contributory factors.⁴ My own researches on juvenile general paralysis, of which I have now had the opportunity of examining 30 cases, show:

1. That the disease affects both sexes equally.
2. That it may commence at any age from 8 to 23 years (according to my statistics).⁵
3. That in 80 per cent. of the cases there were either undoubted signs or history of congenital syphilis, and that in 20 per cent. it could not be excluded.

Therefore we may assume that the effect of syphilis on the germinal plasma on one or both of the parents is the essential cause. In the greater proportion of the cases I was unable to obtain a history of insanity or nervous disease in the family; although it was remarkable that in four of the cases and also in one hereditary case of tabes the fathers suffered with general paralysis; but the notes of their cases give no evidence of their having acquired syphilis, yet in four out of the five cases there were distinct and well-marked signs in their offspring. From a very careful study of the family histories of these 30 cases I was led to believe that the germinal plasma of the parents, particularly of the father, may be very unequally affected by the syphilitic poison, and it seemed to me that the inherited syphilis was not infrequently the result of spermatic infection only. Many of the mothers never had any illness that they knew of, yet some of their children showed syphilitic teeth, chorio-retinitis, rhagades, and other characteristic signs, while other children appeared perfectly healthy. Generally, however, the history was miscarriages, stillbirths, syphilitic children, and healthy children in succession. In one family there were three children; the eldest had no external signs of congenital syphilis, but a syphilitic liver was found *post mortem*. He was an able-bodied seaman, but at the age of 20 broke down with general paralysis. I consider that this was induced by stress, for he was on duty in the Mediterranean just at the Fashoda crisis, when the disease commenced by a fit. The next brother had a characteristic syphilitic nose and teeth, but was earning his living as an artisan. The youngest boy is an imbecile in an asylum with characteristic objec-

tive signs of congenital syphilis. Another family was interesting in this respect, that the eldest daughter of a mother who gave a history of infection showed no signs of syphilis on the body, yet died of general paralysis. The next daughter presented well-marked external signs, but at present is healthy otherwise. The majority of the 30 cases gave some interesting details bearing upon this question. Another factor which seemed to have an important bearing upon the occurrence of general paralysis in children of parents suffering with syphilis was the existence of chronic alcoholism in one or both of the parents. Thus, we see impaired vitality of specialised structures may result from devitalising influences acting upon the germinal plasma of one or both of the parents. Inherent defect in the germinal plasma as the cause of juvenile general paralysis is supported by the fact that very frequently the reproductive organs in both sexes never come to maturity, the genitals in the males being of infantile proportions, with absence of or very scanty hair on the pubes. Menstruation may never occur in the females, and if it does it is scanty as a rule and soon ceases. The ovaries and uterus are often of infantile proportions. In fact, Fournier regards infantile development of the genital organs as strong presumptive evidence of hereditary syphilis. If we admit the Weismann doctrine of the continuity of the germinal plasma, it is probable that the syphilitic poison has had a devitalising influence, which may cause arrest of development in the offspring of infected parents. With regard to the toxic influence of alcohol on the nervous system of individuals with an inherited neuropathic or psychopathic tendency, I have been particularly struck with this fact that, although at least 20 per cent. of the people admitted into the London County Asylums yield a history of intemperance as a result of their mental symptoms, yet I only once remember seeing in the *post-mortem* room of the asylums a case of well-marked cirrhosis of the liver with ascites, and that was in a person celebrated in the police courts, who was convicted nearly 400 times of drunkenness before she was found to be certifiable as incapable of taking care of herself. One must suppose, therefore, that these people who came into the asylum are susceptible to the toxic influence of alcohol, and long before they could drink sufficient to produce cirrhosis of the liver, symptoms of alcoholic poisoning of the nervous system arise. In fact, it would rather show that a person who could drink sufficiently long to get a hobnailed liver has inherited a nervous system of unusual stability. To the mentally unstable alcohol is a poison, and I have been particularly struck with the fact that it acts even in moderate quantities as a poison on women at the climacteric period when potential is low in the nervous system. Another class of individuals of low potential to whom alcohol is unquestionably dangerous is the neurasthenic. The sense of fatigue, whether of mind or body, is physiological and protective. It should be responded to by rest, but the active-minded town dweller who is suffering from nervous exhaustion takes spirits to enable him to make up the deficient energy. "He draws, so to speak, a bill on his health which must always be renewed at a higher rate of interest."

My own observations and those of Mr. Tredgold, the Technical Scholar, entirely agree with the observations of numerous authorities, who have shown that epilepsy, insanity, imbecility, idiocy, mental weakness, and loss of moral control and will power are frequently the heritage of children born of drunken parents and chronic tipplers. I am convinced that the two most important *extrinsic* (and therefore in some measure remediable) causes of the degeneration of the neurone are syphilis and alcohol.

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NOTES AND REFERENCES.

¹ *Archives of Neurology*, p. 192. ² *Ibid.*, p. 493. ³ Mott and Sherrington, *Proc. Roy. Soc.*, 1895. *It is very interesting to note that two of the cases of imbecility with congenital syphilis have become juvenile general paralytics, and in neither of these cases was there a family history of insanity, which is independent corroboration of my observations, as neither of these cases is included in my 30 cases. ⁵ A patient died in Banstead Asylum who was under Dr. Percy Smith in Bethlem for general paralysis. She had well-marked signs of congenital syphilis, but the dementia did not commence till after 25. It is possible, therefore, that cases occurring in adults in which no history can be obtained may owe the disease to an inherited syphilitic taint. It is not necessary that they should show external objective evidence of syphilis, for many of the cases which I have recorded were proved to be born of syphilitic parents, although manifesting no external signs of the disease.

MEMORANDA:

MEDICAL, SURGICAL, OBSTETRICAL, THERAPEUTICAL, PATHOLOGICAL, Etc.

SCHOOLS AND DIPHTHERIA INFECTIVITY.

CASES in which the infectivity of diphtheria patients is unduly prolonged appear not uncommon; but in view of their great importance amongst children returning to school, the following case may be instructive.

Early in February I was called to a boy in a boarding school said to be suffering from a severe cold. A nasal discharge had been noticed staining the bedclothes from the first day of term. Correlative symptoms led me to suspect diphtheria, and bacterial test confirmed the suspicion. Other boys were suffering from nasal catarrh, but in no case was the Klebs-Loeffler bacillus found. Every boy, master (except one), and servant about the school was inoculated with antitoxin, with the result that no one else contracted the disease except one master, the one who was not inoculated. He had a not severe faucial attack.

In the case of both master and boy the bacillus was found to linger for three months, in throat and nose respectively, in spite of energetic and constant disinfection.

Five weeks before the summer term and after disinfection had been stopped some days, both were tested with negative result, and the test was again repeated two days before term. In the case of the master the bacillus was again found to be present, and he was kept away from school altogether; but the test was again negative in the boy, and his nasal passages were quite clean. It was, therefore, looked upon as quite safe to let him return. Both cases were treated at the beginning with diphtheria antitoxin.

Three weeks after the beginning of term, another boy was found to be suffering from a severe type of the disease, to which he subsequently succumbed. The original case was, of course, immediately tested again, and the Klebs-Loeffler bacillus once more found to be present. Antidiphtherial inoculation was again practised throughout the school; and bacterial tests showed that three other boys were going about with the bacillus in their throats, two of them being quite well, while the third had only a slight rise of temperature for one night.

It should be mentioned that a small epidemic was present in the town during the whole of the winter 1899-1900, as to the origin of which local medical opinion was not in doubt.

Cases such as these seem to me to make it urgently necessary to modify the instructions issued by the Medical Officers of Schools Association in their code of rules. They run as follows:

A pupil may.....rejoin the school after diphtheria. In no case in less than four weeks, provided convalescence is completed, and that there is no longer any sore throat, or any abnormal discharge from the throat, nose, ears, or eyes, and no albuminuria; and that bacterioscopic examination of the pharyngeal (or nasal) mucus for the specific bacillus has been attended with negative results, this examination having been made in not less than three days after the discontinuance of local antiseptic precautions.

I would suggest that:

1. In the case of every boy returning to a boarding school, two or three days before the beginning of term, both throat and nose should be bac-