ticular industry to which the laboratory belongs, but that original research of every kind in chemistry is encouraged. The cost of such laboratories is extremely large, for the salaries of the workers are said to be on a very liberal scale. And some of the researches (which occupy weeks or months of the time of the workers) and of the space and accessories of the laboratory, are of no direct use to the industry. Yet the industry, which is proprietary, and not the property of the State, or founded for the advancement of chemical science, derives so much advantage from a certain percentage of the discoveries and applications made in the laboratories, that the funds expended on them are well laid out. Those Englishmen who are familiar with these establishments tell me that this investment of funds in scientific research has served to place the German colour industry far ahead of our own.

We want something of the same kind for the advancement of medicine and surgery, a direct and organised scheme for research and the application of pathology to our art. Of the advantage which may be derived from it I have no doubt. And if we fail to obtain it is because our forces are too divided and our views are not sufficiently in harmony. To those who think that the necessary funds would not be forthcoming, the answer must be that very considerable sums of money have, during the last few years, been devoted to medical research, and that the public mind is gradually becoming alive to the advantage to the nation of good health and the preservation of life.

NOTES AND REFERENCES.

- ¹ *Cours d'Opérations de Chirurgie*, Brussels, 1708. ² *Traité des Hernies*, etc., par Pierre Franco de Turriers en Provence, demeurant à présent à Orange. A Lyon, par Thibault Payan, 1561. ³ London, 1779. ⁴ London, 1782. ⁵ *Mémoires de l'Académie Royale de Chirurgie*, t. i, 1743; Préface, p. xlv; "Le plan que se propose l'Académie est d'élever la chirurgie sur les observations, sur les recherches physiques et sur les expériences." ⁶ Address on the Jubilee of the Pathological Society of London, October 20th, 1896, *Pathological Transactions*, vol. xlviii. ⁷ *Faraday as a Discoverer*, by John Tyndall, London, 1870. ⁸ *The Chirurgival Works of Percivall Pott*, a new edition, London, 1779. ⁹ Hey began to practise in Leeds in 1759. ¹⁰ *Triumphs of Invention and Discovery in Art and Science*, London, 1881. ¹¹ *The Collected Works of Sir Humphry Davy, Bart., LL.D., F.R.S.*, vol. vi, London, 1840. ¹² Evidence before the Committee of the House of Commons in 1833, *Smiles's Life of George Stephenson*, fourth edition, 1857. ¹³ The rushing of the fire-damp from fissures in the strata of coal is called a "blower."

THE LIFE-SAVING SOCIETY.—We have received the annual report of the Life-Saving Society, which is now in the ninth year of its existence, and are pleased to see that it is in a flourishing condition, and extending its useful work. It is, we believe, the only Society that organises systematic teaching of the various methods of rescuing the drowning and resuscitating those who are apparently drowned, and it has been the means of inducing many swimming organisations to make life saving an important element in their courses of instruction. By its instrumentality the subject has been introduced and successfully carried on by the aid of honorary teachers into many public and elementary schools and other educational bodies, and classes have also been formed in connection with the police, dock labourers, and Her Majesty's forces, the instruction given being theoretical and practical, on land and in the water. Another important branch of its work is arranging public demonstrations in various baths and docks, when large numbers of people, sometimes amounting to thousands, witness the graceful swimming and diving exercises practised, as well as the various modes of succouring and bringing safely to land the apparently drowning. This has perhaps done more than anything else to awaken a general interest in the work, and increase the demand for information and instruction. The Society, which has its central office at 8, Bayley Street, Bedford Square, London, W.C., is supported by voluntary subscriptions, and is well worthy of being brought into greater prominence.

REGISTERED MEDICAL PRACTITIONERS IN THE UNITED STATES.

—According to the *Medical Record*, the average number of registered physicians in the United States to the whole population is about 1 to 647. The proportion in the States varies greatly; California appears to be the State which is most liberally supplied, the proportion there being 1 physician to 420 inhabitants, while in Iowa nearly the same conditions prevail. On the other hand, in North and South Dakota and New Mexico, the proportion was respectively 1 to 1,285, 1,296, and 1,391 inhabitants.

THE CROONIAN LECTURES ON DEGENERATION OF THE NEURONE.

Delivered at the Royal College of Physicians of London

By FREDERICK W. MOTT, M.D. LOND., F.R.S.,

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LECTURE II.

MR. PRESIDENT AND GENTLEMEN,—In my last lecture I briefly referred to the present position of the neurone theory. I gave some examples of its practical application, and I dwelt at some length upon a method which has been used for studying the bio-chemical changes which occur in the protoplasm of the nerve cell. Moreover, I pointed out the important evidence afforded by the development of the myelin sheath in proving correlation of structure and function: and that the formation of myelin depends upon three fundamental biological principles:

1. An acquired inherent tendency the result of evolutionary differentiation of structure and function for certain systems, groups, and communities of neurones at successive periods of time to ensheath their axis-cylinders with an insulating and protecting structure, the myelin sheath, which in the case of the peripheral nerves is contained within, and partially formed by a chain of tubular mesoblastic cells.
2. Phylogenetically and ontogenetically stimulus from without is the determining factor in the bio-chemical change associated with the deposition of myelin.
3. Absence of stimulus as occurs from long disuse occasions a regressive metamorphosis back to the embryonic type.

THE EFFECTS OF INJURY OF THE NEURONE.

Section of the axis cylinder or destruction of the nerve cell (speaking collectively), whether produced by direct trauma or by morbid processes occurring in the vascular and supporting structures of the nervous system, causes a simultaneous death change of a characteristic chemical nature affecting the myelin sheath and axon extending from the point of injury to its terminal fibrils. This is Wallerian degeneration, or secondary degeneration of Waller and Türk. Ranvier showed that the sheath of Schwann consists of a series of tubular mesoblastic cells wrapped round the axon, and that when a nerve is cut there is degeneration of the myelin and axon above the lesion as far as the next node. Each internode, therefore, represents a cell; and the fact that the degeneration does not extend upwards beyond the node allows the presumption that these tubular cells have some metabolic interaction with the contained axon and its surrounding myelin. But whatever that reciprocal metabolic interaction of the axon and its ensheathing structures may be, secondary Wallerian degeneration conclusively proves that it is controlled and determined by the nerve cell and its contained nucleus; indeed, it is possible to conceive that the metabolic activity of the nucleus is the mainspring of this trophic influence, by the production of some bio-chemical or biophysical stimulus which pervades the whole complex neurone even to its far distant prolongations. The Nissl method has shown that section of an axon causes changes in the nucleus and cell protoplasm; these may be temporary and recoverable or permanent and irrecoverable, the result apparently depends very much upon the degree and extent of the injury. When a peripheral nerve fibre is cut through, the trophic influence of the cell is removed from the axon and myelin sheath which it generated. These die; not so, however, the independent tubular cells of the sheath of Schwann, for these, soon after the death change has commenced in the myelin, show signs of active proliferation; whether, as some authorities would have us believe, they can lead to regeneration of the nerve, or whether, as seems much more probable, they prepare the way for the down-growing axon, I shall not here enter into; but that they have an important function in regeneration is undoubted, seeing that regeneration in the central nervous system, where the sheath of Schwann is absent, does not occur. Tuckett has shown that when a non-medullated sympathetic nerve is cut, the nuclei and sheath

like structures remain unaltered, while the axon alone degenerates; it would thus appear that the degenerating myelin may act as a formative stimulus, causing nuclear mitosis and cellular proliferation.

THE EFFECTS OF INJURY OF A NERVE UPON THE CELLS OF ORIGIN.

Only since the introduction of the Nissl method of staining has it become known that changes occur in the ganglion cells almost immediately after section of the nerve. Nissl, who first studied this, called it "*primäre Reizung*"; and Marinesco, who has made a special study of this subject, has shown that section of the hypoglossal nerve on one side is followed by three stages of change in the corresponding nucleus of origin.

Fig. A.—Hypoglossal nuclei of two sides. In the upper part of the figure are shown the swollen cells of the nucleus on the side of section during the phase of reparation (after Marinesco).

The hypoglossal nucleus is especially favourable for the study of this question, the nerve being purely motor. From the close proximity of the two nuclei, comparative observa-

tions of the nuclei of the two sides make very evident changes, which occur as the result of section of the nerve on one side.

Marinesco divides these changes which occur in the nucleus into three phases. The *reaction phase* occurs during the first month, and is characterised by a dissolution of the chromatophil elements, and a displacement of the nucleus towards the periphery of the cell. This change has also been recognised by many other observers—namely, Nissl, Ballet et Dutil, Lugaro, Flatau, Van Gehuchten, Sano, Erlanger, and others. The condition is not necessarily one of degeneration, as I shall show later on. It is important to bear this in mind, for a similar condition may be found affecting the anterior horn cells in peripheral neuritis, where disease has led to a destruction of the axis-cylinder process. In the *reparation phase*, the cell body increases in volume, the nucleus resumes its original position, and the cell shows a distinct pyknomorphic condition (abundance of stainable substance). About ninety days after the injury, the process of reparation has proceeded so far that the nuclear group of the injured side is only distinguished from the uninjured side by the increase in size of the cells and their processes. A little later the cells return to their normal appearance, in point of time corresponding to the regeneration of the nerve. We may consider this cell-hypertrophy as evidence of the increased physiological activity necessary for regeneration. If now the hypoglossal nerve be torn out, according to the method of Von Gudden, or if a large piece of the nerve be resected, or any other condition arise so severe that the regeneration process in the nerve is prevented, then the reaction phase proceeds rapidly, and instead of a reparation phase of hypertrophy, the cells undergo atrophy, and a *degenerative phase* ensues. The accompanying diagram (Fig. A) shows the changes in the cells of the hypoglossal nucleus which result from section of the nerve in which regeneration is possible. It differs from tearing out the hypoglossal nerve, in which regeneration is impossible. In the former case the return of the cells to normal is coincident with regeneration and return of function; in the latter, the degeneration and subsequent atrophy of the cell group is brought about by such an injury as to render repair impossible, and resembles, therefore, the effects of amputation of a limb. Recently, Schäfer has shown that hemisection of the spinal cord produces chromatolytic changes in the cells of Clarke's column and subsequent atrophy, substantiating thereby the theory that these cells give origin to the dorsal and ventral cerebellar tracts; and Lloyd, a pupil of his, has also shown that the cells of Deiter's nucleus undergo similar changes, thus tending to support the observations of Risien Russell, Ferrier and Turner that the cells of this nucleus give origin to descending fibres in the antero-lateral region. We can thus see that this method has proved of the greatest value in determining the cells of origin of tracts of fibres. Some observers, Bregmann and Darkschewitz, have even found, after tearing out cranial nerves, a degeneration recognisable by the Marchi method, and demonstrating the course of the nerve in the medulla or pons by the black-stained myelin. I have, by the kindness of Mr. Victor Horsley, the opportunity of exhibiting a lantern slide of the medulla showing degeneration back to the nucleus after an injury made just at the point of emergence of the nerve.

Marinesco, in his admirable work on the effects of amputation, describes slow progressive changes in the myelin sheath, and says the normal refraction of the fat disappears, the colour reaction of the same tends to disappear, and following the changes in the myelin there is a change in the axis-cylinder. In addition, there appears a considerable nuclear proliferation of the sheath when the myelin has disappeared, the atrophied fibres bearing resemblance to non-medullated fibres. A recent observation by Noll, which I shall refer to later on, showed that the protoplasm diminished in the central stump of a nerve after section, though of course, not to such an extent as in the peripheral.

Barker, after referring to the above experiments, as well as to the studies of Von Gudden and his pupils, and the observations upon the nervous system following amputation, remarks: "We have seen that these observations have partially at least annulled the validity of Waller's doctrine of the trophic relations of the nerve cells, for after injury to an

axon, in addition to the degeneration in the axon, peripheral to the lesion there are demonstrable alterations in the cytoplasmic end of the axon, and especially in the cell body of the neurone itself." The changes which occur after the amputation of limbs are probably, however, due to regressive atrophy from lack of stimulus from the structures over which the neurones presided. The changes which occur in the cells of origin of a nerve after section undoubtedly prove that the whole neurone had suffered by the injury, but there is no evidence to show that a degeneration occurs (in the sense of the chemical change to be referred to later) except in the peripheral portions of the cut nerve, and in the central portion as far up as the next node of Ranvier, unless the injury is so severe as to cause such a shock to the neurone that it dies as a whole.

DISEASES OF THE NERVOUS SYSTEM AS DISTINGUISHED FROM DISEASES WITHIN THE NERVOUS SYSTEM.

The histological elements which make up the nervous system may be divided into two groups; (1) the nervous units or neurones; (2) the supporting, protecting, and nutrient tissues. Organic diseases may start in a primary degeneration of the nervous units or neurones, or the neurones may be affected secondarily by diseases starting in the supporting, protecting, and nutrient tissues; such are essentially diseases within the nervous system, and include diseases of the blood vessels, lymphatics, membranes, and special nerve connective tissue (neuroglia). These give rise to secondary degeneration, either by direct injury, inflammatory compression, or by cutting off the blood supply. The causes of pathological processes occurring in the nervous system may be considered under two headings, external and internal, but it may be remarked that in all cases except direct injury the two groups are more or less combined. The external causes depend upon the condition of the blood and lymph, by which the neurones are nourished, and the excess or deficiency of normal stimulation, or existence of abnormal stimulation. The internal causes depend upon the inherent vitality of the neurones themselves. In considering, therefore, the causes of degeneration of the neurone, it will be necessary to point out the result of (1) failure of the blood supply; (2) toxic conditions of the blood; (3) the effect of excess or deficiency of stimulation; (4) inherited defects in the nervous system as a whole, or in some particular groups or systems of neurones. To do this, however, in a satisfactory manner would necessitate my referring in a very superficial manner to all the diseases affecting the nervous system. I shall, therefore, limit myself especially to personal observations relating to some few causes of the degeneration of the neurone in each of those groups which I have studied.

EFFECTS OF TEMPORARY OR PERMANENT FAILURE OF THE BLOOD SUPPLY UPON THE NEURONE.

The effects produced by complete anæmia for varying periods of time upon the nervous elements of the spinal cord have been the subject of numerous experimental inquiries, but I am unaware of any systematic series of observations upon the effects produced by ligation of the cerebral arteries. Many clinical facts show that this is a subject worthy of attention, for the sudden loss of consciousness which results from syncope is explained by a failure of activity on the part of the nervous elements of the cortex cerebri, in consequence of default in the circulation in the hemispheres. Again, the sudden loss of consciousness in epilepsy, followed immediately by tonic spasms and then clonic spasms, has recently found a possible explanation in the series of very valuable experimental observations by Dr. Leonard Hill. He has found that artificial cerebral anæmia in cats and monkeys produced by ligation of the four cerebral arteries produces tonic spasm. If absinthine be injected, instead of causing clonic spasm, it increases the tonic spasm. Then, if the clamp or ligature be loosened on a carotid so that blood flows back to the hemisphere, clonic spasms almost immediately occur. This will again give place to tonic spasm on closing the artery: and again, on removing the clamp and allowing the blood to flow to the hemisphere, the clonic spasms supervene. He has, moreover, shown that if all four arteries in an animal be ligatured, in the dog recovery takes place; the explanation is that collateral circulation is restored soon enough

to prevent destructive changes occurring in the nervous elements. With two carotids and two vertebrals tied the dogs are for some days paretic and demented, very much in the condition of the dogs which Goltz showed after having removed the cerebral hemispheres; however, as Sir Astley Cooper and numerous other observers have shown, these animals recover completely. Dr. Hill has been good enough to send me portions of the brains of twelve such animals operated upon, which, after ligation of the four arteries, were allowed to live for varying periods of time. I have examined the nervous elements with a view of determining the condition of the nerve cells when the dog is in a state of paresis and dementia, and when it has recovered so completely as to pass for a normal animal. The methods which I have adopted have been for this and all other experiments and observations referred to, the Nissl method, the Marchi, the Marchi-Pal, and rapid Golgi methods of staining. The changes observed in the brain by the Nissl method, are shown in the accompanying photomicrographs of the sections (Figs. 2, 4, 5). Before, however, speaking of the pathological changes, I will again call your attention to the appearances of the pyramidal cells of the cortex, medulla, and spinal cord of a normal animal, when examined by this method, for it is the most reliable we have at present for studying pathological changes by comparing the appearances presented with the normal cells (Figs. 1 and 3). You will observe that, first of all, the cells have changed their shape, they are swollen up, their edges have not straight or incurved sides, but are curved outwards, the nuclei are swollen and often eccentric, and in some few of the cells may actually be extruded; when this has happened, of course the cell has practically been destroyed, and with it the nerve fibre which contains its axis-cylinder projection. Another obvious sign of change, although not necessarily a destructive change, is the appearance presented by the chromophilous (stainable) substance. It no longer presents those definite figures which have received the name of Nissl bodies; sometimes it appears as a fine dust, sometimes arranged in long threads separated from one another. One of the earliest changes to be observed is the absence or diminution of the chromophilous substance of the dendrons; moreover, the edges of the cells and the processes present a ragged instead of a clear-cut outline. Generally speaking, the changes in the chromophilous substance only do not denote destruction, but should the swelling be so great as to produce an extrusion of the nucleus, the cell must necessarily die; and we can, if the animal be kept alive over ten days, determine how many psychomotor cells have been destroyed by the temporary anæmia occasioned by the ligation of the arteries. We can do this by examining sections of the pons, medulla, and spinal cord by the Marchi method; the number of black degenerated fibres will indicate the number of pyramidal motor neurones which have perished as a result of the anæmia. These are usually comparatively few; we may consequently say that mere swelling of the cells, with very marked chromolytic changes, does not mean more than functional disturbance. Mere hydration—for thus I explain the swelling—without dislocation of the nucleus from the cell, even though the chromolytic changes are very intense, does not mean death of the neurone. This is an important fact in view of the association of pathological symptoms with changes in the nerve cell. Such microscopical changes are, for the most part, illustrated in the special plate by Figs. 2, 4, 5, 12. I would add in connection with this series of experiments that the tangential fibres were found in most cases intact in animals that had completely recovered. We must suppose, therefore, that collateral circulation in dogs is restored very shortly after ligation of four arteries. The experiments of Ehrlich and Brieger in 1884 proved that anæmia of the lower portion of the spinal cord could be produced by ligation of the abdominal aorta, and that if the circulation was cut off for not longer than a quarter to three-quarters of an hour, only a temporary paralysis of the hinder extremities resulted; but if for one hour permanent paralysis and destruction of the nervous elements were invariably the result. Numbers of other experimenters have produced anæmia of the lumbar spinal cord by this method; and Sarbo has given a full account of the changes which occur in the cells as a result of complete anæmia lasting for one hour to one hour and a half

after ligation; and the changes which he describes as occurring in the motor cells of the spinal cord as the result of complete occlusion of the circulation coincide very closely with the changes which I shall describe in other animals, especially monkeys and cats; also in dogs, which have died as a result of ligation of cerebral arteries, and in which collateral circulation was not soon enough established to prevent destructive changes. Sarbo found that ligation of the aorta for one hour in the rabbit caused a cell degeneration, which was manifested by a granular destruction of the stainable substance of the cell protoplasm, and a progressive homogeneous atrophic process, affecting the cell nucleus. The appearances presented by the degenerating cells, depended upon the time which was allowed to elapse between the ligation of the aorta and the killing of the animal—the longer the time the more evident was the cell destruction. He found no vascular changes indicating inflammations and no hæmorrhages.

The subject of cerebral anæmia is of clinical importance, as it is well known that in man, ligation of a carotid for aneurysm has been followed by hemiplegia, and I have examined the brain in one such case. Dr. Hill sent me a piece of the cortex from similar situations in both hemispheres, and asked me to decide by microscopical examination upon which side the patient was paralysed. This I correctly determined by the difference in the appearances of the cells of the two sides. We can understand also, how temporary loss of motor or psychical function, for example, transitory aphasia, monoplegia, hemiparesis, stupor, and dementia, or even hemiplegia, may occur in syphilitic disease of the arteries; for if collateral circulation be restored within an hour or so after the blocking of the artery, providing a thrombus does not spread to the small branches, the circulation may be restored in the part, and function may return in the course of a few hours or days.

In connection with the experimental anæmia of the spinal cord, produced by clamping the abdominal arteries, it is of interest to note two points. The exogenous fibres of the posterior columns, together with the pyramidal tracts—tracts, the fibres of which have their trophic and genetic centres respectively in the spinal ganglia and the cerebral cortex—do not undergo degeneration, whereas tracts which have for their trophic and genetic centres cells in the grey matter of the spinal cord, undergo degeneration. Munzer's and Wiener's experiments showed this, and recently I had the opportunity of examining a case of acute anterior poliomyelitis in an infant fourteen days after the onset of the disease; in this case also the degeneration was limited entirely to those tracts, the fibres of which arise from cells in the spinal cord, and I cannot help thinking that this case was of vascular origin. [A full account of this case is given in the *Arch. of Neurol.*, vol. i, p. 365.] Ballet and Dutil found from their experiments that complete anæmia of the lower end of the spinal cord for a few minutes (by clamping the aorta) produced chromolytic changes in the anterior horn cells. I have also found that swelling of the cells previously described with chromolytic appearances may come on within less than ten minutes after ligation of the four cerebral arteries, for occasionally one of Dr. Hill's dogs or cats has died from the effect of the anæsthetic very shortly after the four arteries have been ligatured. It may be said that this was due to the anæsthetic; it was not, however, so, for occasionally I have had the opportunity of examining the brain tissues of animals which have died from the anæsthetic before any of the arteries were tied, and these showed no changes (Fig. 3). We may therefore consider that the changes noted are due to the cessation of the circulation. Dr. Hill has shown that the cortex of these animals is readily excitable, and in some cases even hyperexcitable to electrical stimulations, epilepsy being produced; consequently this change in the appearance of the cells can be associated with increased electrical excitability, or perhaps more likely, increased tendency of stimulus to spread, a fact of considerable importance when put beside another fact, namely, that I have found in status epilepticus the cells presenting in many instances this swollen dropsical appearance, with marked changes in the chromophilous substance (Fig. 13). In general paralysis of the insane epileptiform seizures are of frequent occurrence, and when they do occur in the progress of the disease I have found invariably that in proportion to their frequency and severity, there is a large number of recent degenerated fibres

in the pyramidal systems. Consequently we may assume that epileptiform seizures in this disease are associated with death of the cortical pyramidal motor neurones, due in some instances (I believe in great measure) to vascular disturbances of the cortex (Fig. 9). The disease itself is, I consider, primarily a progressive decay of the nervous elements, but owing to the establishment of a vicious circle numbers of neurones are destroyed by circulatory disturbances.

I will now pass on to the effects of experimental anæmia, produced by ligation of arteries in which collateral circulation was not restored soon enough to prevent destructive changes in the nerve cells. If cats or monkeys have all four arteries ligatured, or if instead of ligaturing both vertebrals and both carotids in dogs, a subclavian be tied instead of one of the vertebrals, a sufficient collateral circulation cannot be restored soon enough, and the animal dies in a period varying from a quarter to twenty-four hours. The time variation no doubt depends upon the effect produced upon the medulla by the anæmia. The changes observed in the cells of animals which have thus lived some hours are different entirely to those which have been previously described. There is not merely a physical change due to hydration; this may or may not be present, for sometimes the cells are not swollen, but are even shrunken. The staining reaction is also different, showing a bio-chemical as well as a bio-physical change; sometimes the whole cell stains uniformly, but not with a brilliant coloration (Fig. 7). If a double stain has been used, for example, methyl blue and saffranine, the whole cell may be stained a uniform dull purple, the processes, as well as the body of the cell, having a homogeneous instead of a differentiated action to the dyes, a condition which is similar to that met with in hyperpyrexia, and to the appearances described by Sarbo in the motor spinal neurones of the lumbar-sacral region after clamping the abdominal aorta. These animals prior to death, according to Dr. Hill's notes, generally had epileptiform convulsions. One animal—a monkey—presented the most instructive changes, because after ligation of both carotids and one vertebral it was paretic and demented, took no notice of anything, and behaved exactly like an animal with its higher cortical centres destroyed, which, indeed, they were. It was killed on the fifth day, and examination of the brain of this animal exhibited the following changes, which are shown in the photomicrograph (Fig. 8). The nerve cells and all their processes were uniformly stained a diffuse dull purple, and were readily discerned on account of the dilatation of the lymph space in which the neurone lies; scattered through the protoplasm of the cells was a fine dust of coloured particles; the apical processes of the cells were either destroyed or twisted like a corkscrew; in many the dendrites had disappeared, but in some of the cells the axis-cylinder could be traced with unusual distinctness, probably due to some swelling; and one cell was observed which is of interest, because the axis-cylinder process could be traced some distance, giving off lateral twigs that seemed to merge into a general network, supporting therefore the diffuse nerve network theory of Golgi (Fig. 6). Many of the cells were swollen up, as shown in Fig. 8, others were shrunken. Some could be seen with phagocytes sticking to them and devouring the dead cells. Although one observed these very marked changes in the cells by the Nissl and Weigert iron methods, yet by the chrome-silver method the cells appeared normal, showing the gemmules on their processes with unusual distinctness (photomicrographs 10 and 11). The brains of other animals, dogs and cats, were examined by similar methods with the same results. It may be that the chrome silver only stained those cells which had not undergone disorganisation; but none of the cells when examined by the methods I have alluded to exhibited normal appearances as regards their biochemical condition, nor was the animal physiologically normal. I have, therefore, come to the conclusion that the rapid silver method of Golgi, which stains only a few cells, although undoubtedly of the greatest value for anatomical purposes, yet for acute pathological findings is unreliable. Many of the statements which are made with regard to the effects of drugs, anæsthetics, and acute disease as represented by the appearances of the gemmules on the processes of the cells, as made evident by the chrome-silver method, are therefore open to serious objections. It is very probable that the method of Cox might be found of value in determining changes in the cells of

the cortex in chronic disease, and possibly also in acute disease. I have not mentioned that in most of these experimental brains a striking naked-eye feature was the distension of the veins of the cortex with blood, and frequently there was subpial hæmorrhage; also the perivascular lymphatics were usually distended with fluid; no doubt both the increase of blood in the superficial veins, the increase of fluid in the perivascular lymphatics, and the general cedema of the brain itself were proportional and compensatory to the diminution of the arterial blood; the arteries were generally empty, likewise the capillaries. In some cases the perivascular lymphatics and membranes were the seat of a marked cellular infiltration, resembling the condition found in general paralysis. Collateral circulation to the medulla, by which the respiratory centre is kept going, is essential to life. Such collateral circulation when established (and if the animal lives it must have been established) would be accompanied by blood supply to the choroid plexus; and the cerebro-spinal fluid, which functions as the lymph of the brain, would consequently be secreted in abundance and soon compensate the diminution caused by the failure of the arterial circulation; thus the increase of cerebro-spinal fluid would account for the cedema of the brain, the dropsical condition of the cells, and the dilatation of the perivascular lymphatics.

Some experiments which I made five years ago with Professor C. S. Sherrington, and which we have never found opportunity to continue and develop, are (although only few in number), I think, of sufficient importance to mention with this subject of anæmia. We found that compression of the spinal cord in the dorsal region, even enough to produce indentation, would not stop the passage of the impulses, generated by faradic excitation of the cerebral cortex, to the lower spinal motor neurones. Whereas in two animals—monkeys—upon compression with an eye removed from a rat immediately after death, fixed at the end of a glass tube attached to a horizontal lever in such a way that compression of the lumbar spinal cord could be made by this living tissue, and the pressure measured by means of a sliding weight—we found that extremely light pressure upon the lumbar spinal cord was sufficient to abolish conduction in one minute to a minute and a-half after the pressure was applied; and upon removing the pressure conduction, in a minute or two returned, because faradic excitation of the cortex was responded to by an appropriate muscular contraction. The experiment was repeated a considerable number of times, and I have no doubt that in these two animals we managed to produce an anæmia of the grey matter of the lumbosacral spinal cord by compression of the large artery that comes in about the third lumbar root, causing a physiological block in the synapsis formed by the terminal arborisations of the axons of the cortical pyramidal neurones with the dendrons of the spinal motor neurones.

Effects of Hæmorrhage.—Large quantities of blood may be lost to the body from hæmorrhage without producing any appreciable changes in the nervous elements. Voss has done a number of experiments on animals, endeavouring to produce degeneration of the spinal cord, by injections of pyridine sufficient to produce a severe anæmia, but without results. Likewise, numbers of cases of pernicious anæmia, leucocythemia, and exhausting blood disease, are not found associated with any noticeable change in the neurones. I have examined the nervous system in several cases of pernicious anæmia, in one of which the corpuscles had sunk to 500,000 per c.mm.; cases of very severe anæmia from hæmorrhage and exhausting disease; leucocythemia, in which the red corpuscles were reduced to one-fourth, and in which the whole of the brain and vessels showed congestive stasis and hæmorrhages; and yet the nerve cells of these cases of extreme anæmia showed little or no bio-chemical change, the Nissl granules appearing quite normal (Fig. 1); nor did sections of the nervous system in these cases show any degenerative changes by the Marchi method. It is therefore more than probable that those cases of combined sclerosis of the spinal cord, sometimes met with in pernicious anæmia, but more often accompanied by grave anæmia, are due to some other cause than the deficiency of red corpuscles; probably in the blood there is some neurotoxin which produces this primary systemic degeneration of neurones, with long axis cylinder projections, forming the long tracts in the spinal cord—or it possibly may be that those

individuals who suffer from this nervous affection have an inherent defective vitality or lowered durability of the nervous system, which, in combination with the defect of the blood supply in quantity and quality, leads to degeneration. The fact that inanition, even extreme inanition, produces little or no loss of weight in the nervous system, and hardly any changes of importance in the microscopical appearances of the nervous elements, is of considerable importance, for it seems to show that the metabolic exchange that goes on in the nervous system, is either especially protected by the metabolism of the whole body being subservient to it, or that, however important the metabolic exchange in the nervous system may be, in amount it is not considerable. Those primary wasting diseases affecting systems, communities, and groups of neurones, associated one with another by functional relationship rather than by anatomical or vascular supply, insidious in origin and progressive in course, cannot be ostensibly due to anything else than a metabolic failure on the part of the neurones themselves (which, after all, are but complex differentiated cells) to assimilate from the blood the necessary materials to maintain their specific vital energy. They die in a manner the reverse of their evolution; the most distant parts of the tree, namely, the terminal twigs (collaterals) being the first to go, then the branches, and last of all the trophic and genetic centre itself, the cell body and its nucleus.

Dr. Watson in my laboratory has carefully compared the sections of experimental anæmic brains with a large number of sections of general paralysis; he has made drawings of cells which he considered presented similar appearances in the two conditions, and the result of his observations appears to show that whilst a large number of the cells exhibit changes indicating chronic atrophy, a considerable number of cells in general paralysis present acute destructive changes similar to those met with in cases of experimental anæmia from arterial occlusion, but they are not due to the same cause, for the arteries in this disease are seldom occluded, but congestive stasis in the arterioles, capillaries, and veins, even thrombosis in the latter is common, and this congestive stasis probably takes part in the destruction of the nervous tissue.

It is curious how general it is to find the brain atrophy in this disease limited particularly to the frontal and central convolutions, whereas the occipital and temporal lobes escape in great measure. Over the atrophied regions the pia-arachnoid membrane is thickened and adherent. Many observers, including Flechsig and Mickle, consider that the region of atrophy corresponds particularly with the area of distribution of the internal carotid arteries. I think, however, the area of atrophy and pia-arachnoid thickening more closely corresponds with the distribution of veins which open into the longitudinal sinus, and from a large number of observations made by myself and my assistants, I have come to the conclusion that venous congestive stasis in that portion of the brain plays an important part in the symptomatology and pathology of general paralysis. I shall, however, have occasion to refer to this more fully later on.

Mendel and many authorities believe that general paralysis is a primary inflammatory condition of the vessels and meninges, with secondary destruction of the nervous elements. In 1884, Mendel, who believed that the necessary factors were (1) diseased walls of vessels allowing transudation of plasma and leucocytes; and (2) hyperæmia of the brain, claimed to have produced this condition artificially by rotating dogs upon a table with the heads outwards. Fürstner repeated these experiments over a considerable period of time, causing degenerative changes in the cortex, with secondary descending changes in the cord. There are many reasons, however, which will be alluded to later, for considering general paralysis to be a primary progressive decay of the nervous elements, with secondary changes in the vessels and membranes.

ALTERED STATES OF THE BLOOD.

Hyperpyrexia.

The study of the lesions of nervous centres due to hyperpyrexia is of great interest from a theoretical as well as from a practical point of view; from the former, because the exact knowledge of the nature of the lesion might be able to throw some light upon the nature of the pathological process and the clinical symptoms which accompany hyperpyrexia; from the latter, because it would indicate the direction of treat-

Fig. 1.

Fig. 2.

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Fig. 12.

Fig. 13.

Fig. 14.

Fig. 15.

Fig. 16.

Fig. 17.

ment. Goldscheider and Flatau, who for the first time described lesions of the nerve cells in the rabbit, caused by experimental hyperthermia, came to the following conclusions:

1. If the temperature remained about 106.7° F. (42° C.), the cells of the spinal cord examined by Nissl's method presented no appreciable modifications.

2. If the temperature exceeded 109.5° F. (43° C.) the lesions of the nerve cells of the spinal cord were very definite, extending throughout the whole of the grey matter.

3. The duration of the experimental hyperthermia they showed to be a very important factor in the production of the lesions; for if the animal be kept for some hours between 107° and 108° F., the same effect on the nerve cells is produced as occurs in a much more rapid manner when the temperature is raised to 109.5° F.—namely, swelling of the cell and its processes, diffuse staining of the whole neurone with disintegration of the chromophilous substance, and around the nucleus the chromophilous elements may still persist to some extent as if the outer portions of the cell were more affected than the central. The nucleus has an irregular and often an angular appearance.

Marinesco has also done some valuable work on this subject. He found that if artificial hyperthermia in animals be produced, so that the temperature is raised to 116.6° F. in the rectum, the animal died in thirty minutes with characteristic changes in the nerve cells. He also remarked that these changes occur at a lower temperature when the duration is increased. In five cases of hyperpyrexia occurring in the human subject, which I have examined, and in which the temperature reached 109° F. or more, I have found the same bio-chemical change revealed by the Nissl method in all the cells of the central nervous system. I have, however, met with cases of status epilepticus in which the temperature was 107° to 107.5° F. for a short time without showing this change. Again, I have seen in one case a moderate degree of chromatolysis and diffuse staining in prolonged pyrexia, varying from 105° to 106.5° F. This was a case of typhoid fever, and it might very well be that the change was due to the influence of the toxin; in fact, in most of the human cases the changes could be ascribed to the conditions which produced the fever and not to the influence of the increased temperature of the blood; but some of the cases which I have examined were so sudden, for example, one was probable sunstroke, another was a case of hæmorrhage into the spinal canal and the base of the brain in general paralysis, another was a case of Congo sickness.

The photomicrograph shows three anterior horn cells from the last case. You will observe the diffuse staining of the processes and of the body of the cell (Fig. 14). Another case of Congo sickness, in which the temperature never went above 103.8° F., showed no change in the Nissl granules, and the cells presented a fairly normal appearance. I have examined the nerve cells in many cases of septic poisoning and other diseases, but I have never seen this change unless there was either hyperpyrexia or prolonged high fever. The fact that experimental hyperthermia in animals produces this bio-chemical change in the protoplasm of the cell indicates that it is the altered temperature of the blood which is the cause in the human subject of these changes. Another point is that if the sections are stained with methylene blue and saffranine, the protoplasm is stained a uniform dull purple, instead of being differentiated. Now we have seen that the healthy cell shows a differentiation of staining; the Nissl granules, which have been shown to be a nucleo-albumen, are no longer visible in hyperpyrexia; and there is no longer the differentiation of a stainable and an unstainable substance with basic dyes; there must, therefore, have been produced by the fever a profound modification of the protoplasm of the cell. There are two points to be considered in this—namely:

1. The fact that a temperature of 109.5° F. can bring about rapidly this coagulation process and death of the protoplasm, also that it affects first and most markedly the periphery of the cell.

2. That prolonged high temperature of 107° to 108° F. will produce this same coagulation process.

Halliburton has shown that there are three proteids in nervous matter—namely: (1) a neuroglobulin which is coagulated at 116.6° F. (47° C.); (2) a nucleo-proteid which is coagulated at 132.8° F. (56° C.); (3) a neuroglobulin which is precipitated at 167° F. (75° C.); and that these three bodies can be separated out by fractional coagulation. We see, then, how it is that Marinesco found that animals in which the temperature is raised to 116.6° F. (47° C.) died almost immediately with changes in the cells indicating coagulation in the protoplasm. No doubt this neuroglobulin is precipitated at once, and it occurred to me that if a solution of neuroglobulin were subjected to long heating, it would coagulate at a much lower temperature. I mentioned the matter to Dr. Halliburton, who was of the same opinion, and we have therefore made experiments upon this subject, and we find that prolonged heating for four hours, for example, will cause coagulation of the neuroglobulin at a temperature of between 107.6° and 109.4° F. (42° and 43° C.) Brodie and Richardson have shown that in frog's muscle the tissue loses its irritability at that temperature, at which coagulation is induced first in one of its constituent proteids. We have thus a chemical explanation of the cause of death of the protoplasm, also of the changes manifested by it as regards staining.

Goldscheider and Marinesco have shown experimentally that a certain degree of this coagulation change may take place without death of the cells, for if they produce artificially hyperthermia in animals for only a short time and then kill them, they find a commencement of this coagulation process to have taken place; but these animals would have lived had they not been killed for the purpose of examination, consequently we may suppose that a certain degree of bio-chemical change, associated with coagulation of neuroglobulin, may take place without destroying the protoplasm to such a degree as to render it incapable of recovery. I think this entirely coincides with and explains the remission of symptoms, the return of consciousness and the recovery, which often takes place in some forms of hyperpyrexia, when the cold-bath method is resorted to without delay.

It is matter of speculation whether structures later developed and functionally more highly differentiated, as the cells of the cerebral cortex, are more highly susceptible to fever, and succumb more readily under it. Possibly high temperature of the surrounding blood and lymph is more readily felt by the small cells of the superficial layers of the cortex on account of the increased surface exposed, and delirium followed by coma may be the result of this; although the vital centres in the medulla may still be able to perform their functions.

The diffuse staining of the cells indicates a diffusion of the nucleo-proteid through the substance of the cell body and its processes. We may suppose, therefore, that the essential achromatic fibrillary substance is killed, and that the nucleo-proteid which is normally contained in the reticulum of the cell in solution has soaked into the achromatic substance, and given the protoplasm the uniform staining, which when once general is quite characteristic of hyperpyrexial death, as I have been able to verify in several instances. These facts, pointing to an actual bio-chemical change involving the death of the protoplasm, when the temperature remains for some hours above 109° F., support Dr. Osler's view that cases of paradoxical temperature occurring in women, and termed hysterical hyperpyrexia, are frauds as a rule, although he states that other cases have to be accepted, the explanation of which is impossible under known rules; in fact, it is quite conclusive that temperature above 114° F. is incompatible with life, even for a short time.

TOXIC CONDITIONS OF THE BLOOD AND LYMPH.

The primary degenerative changes occurring in the neurone are usually the result of poisonous conditions of the blood and lymph. The poisons may be produced:

1. Within the body by perverted functions of the organs or tissues (auto-intoxication).

2. By the action of micro-organisms upon the living fluids and tissues of the body, whereby various toxic substances are produced either locally or generally, and by their escape into the blood cause degenerative changes.

3. The poisonous substance may be introduced into the body from without.

Just as we know that various alkaloids used in medicine have a specific affinity for particular portions of the nervous and muscular systems, so we find certain

poisons which produce degeneration and disease have a special selective influence. We know that strychnine, for example, has a special selective influence upon the spinal cord, increasing reflex excitability. Goldscheider and Flatau have shown that strychnine poisoning produces changes in the motor anterior horn cells, closely corresponding to those observed in tetanus poisoning; these changes may be observed as commencing three minutes after injection of the poison, if a sufficient dose be given. As in tetanus poisoning, there is no close relationship between the morphological change and the degree of functional disturbance. They have also shown that acute cell changes occur as a result of malonitril poisoning ($\text{NC-CH}_2\text{-CN}$); injection of sodium hyposulphite neutralises the toxic effects of this poison, and prevents the changes in the nerve cells.

Experiment has shown that curare poisons the motor end plates, and recently, in an interesting communication, Dr. Waller showed how a very slight difference—a molecule of water—will alter the action of an alkaloid. Thus he has shown that veratrin has a special selective toxic action upon muscle, while proto-veratrin acts especially upon nerve. These facts, together with others which I will cite in connection with degenerative changes produced by the selective action of poisons in the production of disease, indicate a special chemical affinity of certain protoplasmic structures for certain particular poisons, and the corollary is that probably the protoplasm of every nerve structure having a different function varies in some slight degree. There is a difference which is not to be detected by chemical methods, but the varieties of which are clearly shown by the difference in their physiological reaction to an altered environment. Perhaps one of the most striking demonstrations of this selective affinity of protoplasm for particular chemical compounds is shown by the *intra-vitam* methylene-blue method introduced by Professor Ehrlich, and which, in the hands of many investigators, has produced such marvellous revelations into the minute structure of the nervous system. Ehrlich found that only those aniline dyes which contained sulphur in their composition were suitable for yielding the reaction.

Examples of the special selective influence of the various poisons which produce disease are numerous. There is a whole class of poisons which affect specially the peripheral nerves; and it is a debatable point whether in peripheral neuritis the whole neurone suffers, or whether the changes which have been found in the cells of origin of the peripheral nerves, in the spinal cord and ganglia, are due primarily to the action of the poison; or whether they are secondary to the destructive effects of the poison upon the outgrowths of the cells—namely, the axis-cylinder processes of the peripheral nerves. Again, there are a number of poisons—diphtheria, botulismus, etc., in which the fatty degeneration of the muscle is in excess of what could be reasonably attributed to the changes found in the nerves. Probably the vulnerable point of the neuro-muscular mechanism is at the junction of the nerve with the muscle. Comparative studies, however, which would show degenerative changes in the motor end plates, are extremely difficult; and it is rather by inference than direct observation that we must believe the poison to act upon this structure.

The effects of a poison in producing degenerative changes may be immediate or remote, even distantly remote. Thus some poisons on entering the system may produce sudden, or almost sudden, effects—for example, strychnine and absinth. Others produce more or less remote effects—for example, rabies, tetanus, diphtheria; others produce distantly remote effects—for example, syphilis. Again, many poisons, in order to be effective, must accumulate in the system—namely, the mineral poisons lead and arsenic. Dixon Mann states that lead may exist in the brain in appreciable quantities in encephalitis saturnina.

SELECTIVE INFLUENCE OF POISONS.

The most remarkable example of selective influence which I can cite is tetanus. The bacilli are found only in the wound; they must therefore be comparatively few in number, yet they elaborate a virulent poison which affects particular groups of neurones. The fact that lockjaw in man nearly always occurs first shows that the poison selects the motor

nucleus of the fifth nerve. This, however, is not the case in animals when poisoned by the tetanus toxin. We do not know whether this selection is due to some anatomical condition which favours the absorption of the poison, or whether it is the result of a bio-chemical affinity of that particular group of neurones for the poison. It is remarkable that experiment has shown that the tetanus toxin, if mixed with an emulsion of nervous matter before injection into an animal, loses its toxicity, showing thereby its affinity for nervous matter. Goldscheider and Flatau, who have studied the changes in the nerve cells of animals that have been injected with the tetanus toxin, describe conditions which they consider characteristic of the action of this particular poison. Examination of the cells of the anterior horns of the spinal cord shows enlargement and pallor of the nucleus, swelling and crumbling of the Nissl bodies, and fine granular disintegration of the Nissl bodies, associated with swelling of the whole cell.

Marinesco maintains that in nerve cells subjected to the action of the tetanus toxin, two independent phenomena can be distinguished; one, the result of the chemical combination of the poison with the cellular protoplasm, and the other the wearing out of the cell from excessive functional activity. He agrees with the conclusion of Goldscheider that there is a chemical transformation exalting the excitability of the motor neurones. There is a general consensus of opinion among authors who have worked at this subject, including those named, that the injection of tetanus antitoxin retarded these cell changes, and caused a more rapid return to normal; it is only right to say that Courmon, Doyen, Poirot (ref. Ford Robertson), from experimental results of their own, deny that tetanus toxin produces any alteration in the cells of the anterior horns, and certainly, specimens of the medulla and pons from two cases of tetanus in the human subject, which I have had the opportunity of examining, showed no certain noteworthy change.

Another poison, probably of microbial origin, rabies, has a special selective influence on the medulla, although the whole nervous system is charged with the poison; pointing, therefore, to the fact that there is some special affinity of the neurones in the medulla for the poison. I have had the opportunity, through the kindness of Dr. H. Durham, of examining the medulla of a child, who died of hydrophobia in Guy's Hospital six weeks after having been bitten by a mad dog. The greater number of the cells of the motor nuclei of the medulla showed marked degenerative changes indicating a slow process of coagulation necrosis, namely, uniform diffuse staining with absence of Nissl granules; there was also a great deal of nuclear proliferation in the glia substance, denoting an irritative as well as a degenerative process. He was also kind enough to give me the nervous systems of three animals which had been poisoned with the toxin of "bacillus botulinus," a disease first described by Ermenghen, who discovered the organism in unsound meat and fish eaten by people who had died with a characteristic group of symptoms. Such a condition in this country would probably have been called "ptomaine poisoning." The changes which I have found in the nerve cells are similar to those described by Marinesco, who has specially studied this subject. There is a marked chromolytic change, some cells being much more affected than others; the poison is extremely virulent and, if a minute dose is given, so that the animal does not die before the end of a week or so, the changes in the nerve cells are not more marked than in an animal which died within 24 hours (Fig. 16). The most noteworthy change, however, which I have found in an animal which survived seven days, was the extreme fatty degeneration of the heart and striped muscles of the body (Fig. 17). The liver also had undergone extreme fatty degeneration. Seeing that the peripheral nerves showed no degenerative changes, one may conclude that the poison acted more particularly upon the muscle, or the nerve endings in muscle. As I have already had occasion to point out, chromolytic changes of themselves do not indicate death of the nerve cell, but rather functional depression; seeing that there were no changes in the peripheral nerves or in the cord, observable by the Marchi method, it is probable that the changes in the nerve cells were mostly related to functional depression rather than actual destruction, and might have arisen from circulatory failure in the central nervous system, due to paralysis of the heart. Marinesco noticed that the

chromatolysis generally occurred first, at the periphery of the cells; as the morbid process advanced there was destruction of the achromatic fibrils and formation of vacuoles. I have not observed vacuolisation, only extreme chromatolysis. Kempner and Pollak have found similar changes in the nerve cells, and have further observed the slow restoration of the cells to normal under the action of specific antitoxin. Somewhat similar changes have been described by several authorities in the anterior horn cells of the spinal cord and medulla of animals injected with diphtheria toxin. Sidney Martin separated the chemical toxin of diphtheria, and produced by its injection into animals marked fatty degeneration of the muscles, which he attributed to an associated change in the nerves. In 4 cases of diphtherial paralysis in man which I have examined I was able to find fatty degeneration of the heart muscle in all; in only 1 case could I find Wallerian degeneration of the peripheral nerves, and in only this one case could I find any chromolytic changes in the motor cells of the medulla.

Abrin and Ricin-Toxic Proteid Bodies.—Sidney Martin long ago showed that the seeds of jecquirity contained a proteid body, which, if injected into an animal, profoundly modified the blood and caused its death. This body, abrin, together with a similar body, ricin, obtained from castor-oil seeds, were made the subject of a most valuable research by Ehrlich. Very small quantities of these poisons, injected into animals, cause profound modifications in the appearance of the nerve cells. The Nissl bodies disappear, the cells are stained uniformly, and show a fine, coloured dust all through the protoplasm of the cell and processes. All the nerve cells are affected, and the cause of these altered appearances would indicate a changed condition of the blood and lymph. By the kindness of Dr. Durham I have had the opportunity of examining the nervous system of two guinea-pigs, one which died forty-five hours after injection of 2 milligrams of abrus-globulin; the other after immunisation received in the course of a week an amount equal to 60 fatal doses. The former showed a marked change (shown in photomicrograph Fig. 16) in all the cells of the spinal cord and medulla; the latter showed marked chromolytic changes, but many of the cells showed Nissl granules and much less abnormal appearance. Although two observations are not of much value, it would point to the poison acting upon the nerve cells. Berkeley has studied the changes produced in the nerve cells by ricin.

Absinthe.—Dr. Hill, while making his experiments upon the cerebral circulation, had occasion to inject animals with absinthe. He sent me the nervous tissues of these animals, and I was greatly surprised to find that changes were discoverable in the cortical pyramidal cells of animals that had died in fits within ten minutes of the injection of 5 minims of the poison. The cells were, however, not all equally affected; some groups of cells showed marked chromolytic change, while others showed no change. Animals that had lived two hours after the injection of a smaller dose (2 minims) likewise showed unequal effects. The cortical pyramidal cells were, however, always more affected than the motor cells of the anterior horns of the medulla and spinal cord, and one therefore naturally asks, Can we account for this by supposing that the cells have each a specific vital resistance? That this may be so is perfectly clear from the fact that such poisons as abrin, botulin, ricin, etc., produce when injected much more marked effects on some cells of the same function than on others. In the case of absinthe, it must be remembered that we have to do with an oily fluid, and it is possible that really the fits may have been due to irritation caused by minute capillary emboli of an acrid and poisonous nature becoming lodged in the minute vessels of the cerebral cortex. The capillaries in the cortex are extremely small, and would favour such lodgment. Such an explanation seems possible, for if absinthe be injected subcutaneously, even in large quantities, fits are not produced (Hill). I am also indebted to Professor Horsley for the nervous system of a cat, which had received 2 minims of absinthe intravenously injected. The animal had three fits and survived two hours. The changes in the motor cells of the brain and cord corresponded to those above described.

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DESCRIPTION OF PHOTOMICROGRAPHS.

- 1.—Normal pyramidal Betz's cell cortex cerebri, stained by Nissl method, preparation made from the brain of a man who died from an obscure septic affection after eight weeks' illness. Towards the end of life he suffered with severe hæmorrhages producing the most extreme anaemia, the blood containing a large number of nucleated corpuscles. There was a remittent pyrexia during the whole period; the fever, however, never surmounted 103° F. The body was extremely emaciated at death. He remained conscious to the end, and it is interesting that this combination of factors was insufficient to produce bio-chemical changes in the nerve cells. Magnification, 700 diameters.
- 2.—Section of the motor cortex of a dog after ligation of both carotids and both vertebrals. Magnification, 250.
- 3.—Section of the motor cortex of a cat that died under the influence of an anæsthetic prior to ligation of arteries. Normal appearance of the cortical pyramidal cells, stained by Nissl method. Magnification, 300.
- 4.—Pyramidal cell of a dog after ligation of two carotids, one vertebral and one subclavian. Great swelling of the nucleus, advanced chromatolysis most marked at the periphery of the cell. Magnification 700.
- 5.—Pyramidal cell of a dog after ligation of arteries showing extreme chromatolysis with commencing extrusion of the nucleus. Magnification 700.
- 6.—Axis-cylinder process from a large pyramidal cell the lymph space around which is distended and showing the collateral side branches apparently forming a diffuse nerve network. Magnification 1000.
- 7.—Pyramidal cell with diffuse staining from a cat after ligation of four cerebral arteries. Magnification 500.
- 8.—Pyramidal cell from monkey five days after ligation of two carotids and one vertebral, referred to in lecture, showing swelling in pyramidal cell, diffuse homogeneous staining owing to stainable substance being scattered through the protoplasm of the cell as a fine dust.
- 9.—Section of the cortex of a case of general paralysis, showing acute cell changes. Magnification 250.
- 10.—Cell of Purkinje from the cerebellum of a dog twelve days after ligation of four arteries showing absolutely normal appearances.
- 11.—Pyramidal cell from cortex of monkey referred to in lecture stained by rapid Golgi method, showing gemmules on the dendrons, and all the external appearances of a normal cell. Magnification 150.
- 12.—Section of pyramidal tract of spinal cord of monkey ten days after ligation of two carotids and one vertebral. A few scattered degenerated fibres are revealed by the Marchi method. These were more numerous on the side opposite to the hemisphere on which the vertebral was ligatured, but altogether not more than 60 in number, so that only an inconsiderable number of the psycho-motor cells had perished as a result of the anaemia. This quite conforms with the fact that the animal had returned to the normal physiological condition when it was killed with chloroform. Dogs with four arteries ligatured and kept alive over ten days frequently showed that a certain number of the psychomotor neurones had perished, but the numbers were inconsiderable.
- 13.—Swollen oedematous cell from the top of the ascending frontal convolution, with diffuse staining and absence of Nissl granules from a case of status epilepticus. Magnification 700.
- 14.—Section of the spinal cord of a case of Congo sickness with hyperpyrexia in which the temperature reached 105° F. prior to death. The whole of the cells throughout the central nervous system showed a diffuse homogeneous dull staining. The Nissl granules had entirely disappeared from the processes and the body of the cell, and the stainable substance had a fine dust-like appearance. The processes are unusually distinct on account of the diffuse staining, the nucleus is clear and swollen, faintly stained, and the nucleolus deeply stained. Magnification 400.
- 15.—Anterior horn cell of spinal cord from a guinea-pig which died 45 hours after injection of 0.2 mg. of abrus-globulin. All the cells showed this diffuse staining and absence of Nissl granules. Magnification 400.
- 16.—A section of the anterior horn of the spinal cord of a rabbit, 21 hours after injection of 0.005 c.c.m. of botulism toxin, which killed the animal, the whole of the cells throughout the central nervous system showed more or less a marked chromolytic change as indicated in the photomicrograph. Magnification 250.
- 17.—Section of the diaphragm of guinea-pig, which died on the eighth day after injection of 0.005 c.c.m. of botulism toxin, containing 2 per cent. of

solids. The muscle was stained by Marchi method, and shows that quite one half of the fibres have undergone acute fatty degeneration. The dense black masses are fat cells; but the degenerated muscle fibres are indicated by the diffuse black staining. The musculi papillares of the heart showed even more marked fatty degeneration.

Figures 1, 2, 3, 4, 5, 7, 8, 9, 13, 14, 15, 16 are photomicrographs of preparations stained by the Nissl method. Figure 6 was stained by the Weigert iron method. Figures 10 and 11 were stained by the rapid Golgi method. Figures 12 and 17 were stained by the Marchi method.

ON LEAD ENCEPHALOPATHY AND THE USE OF DIACHYLON AS AN ABORTIFACIENT.

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In the following paper I propose to record three cases of cerebral disease due to lead poisoning, two of which were caused by diachylon taken to procure abortion, and some other cases in which diachylon taken with the same object produced a different set of symptoms:

CASE I.—A youth of 17 was sent into hospital for cerebral tumour.

History.—For three weeks he had suffered from headache, vomiting—chiefly after food—colicky pains in the abdomen and dimness of vision. The patient was a carriage painter who for 2 years had been engaged on fine work, but for the last three months had taken to coarse work in which much red lead was used.

Condition on Admission.—He was found to be well nourished but anæmic, lethargic, but complained of intense frontal headache. No paralysis, spasm, or anæsthesia, pupils and reflexes normal. Well marked double optic neuritis and a large retinal hemorrhage in the left eye. Heart somewhat dilated, blowing murmur at the apex; soft, regular pulse. Urine: specific gravity 1012 to 1016, free from albumen and sugar. Bowels open, tongue moist, furred and tremulous. Slight blue line on the gums.

Treatment.—The bowels were kept open and potassium iodide and bromide, with an occasional dose of antipyrin, ordered. A fortnight later he was no better, and then digitalis was added to his medicine. Within a week he was better, and all his symptoms left him five weeks after admission. The vision improved and the optic neuritis became perceptibly less, but some yellow striæ developed round each macula lutea. A trace of albumen was found four times in the urine, the daily output of which increased under the use of digitalis from 30 to 50 ounces, while its specific gravity decreased to 1006 to 1010, with urea only 1 per cent. The blue line was not quite gone when he left the hospital.

In this case the brunt of the disease fell on the brain, but clearly the kidneys, alimentary tract, and heart also suffered. I am sorry not to have been able to trace the further history of this patient, who was under my care eight years ago.

CASE II.—In April, 1899, I saw in consultation a married woman, aged 39, for brain disease.

History.—She was said to have had severe nervous symptoms and a mysterious abdominal pain a year ago, but these abated when it was proposed to send her into hospital. She had had two live children, the youngest 15 months old, and six miscarriages, but there was no history of a syphilitic rash. Apparently she had not been really well for a year, but had for four or five months suffered severely from headache and vomiting without relation to food. She had had three fits within the previous three months. A month ago she began to be unsteady on her feet, and had been confined to bed for three weeks. For a week she had been semi-delirious, having visual hallucinations, and for two days had had diplopia. No information as to her menstrual history could be obtained, either then or during her stay in hospital.

Anamnesis.—Only an imperfect examination was possible in the small dark room of her home, but we noted no paralysis, ataxy resembling that of cerebellar disease, and double optic neuritis. A week later she came into hospital, where in the well-lit ward I at once observed on her gums the most intense blue line I have ever seen. The notes say: "Patient is a stout, florid woman; intellect and memory poor, but she can answer some questions fairly; has some visual hallucinations at night; complains of severe headache on the vertex. She can sit up in bed, but can hardly stand or walk alone, tottering with the head craned forward and swaying from side to side. The ataxy is not worse when the eyes are shut. No muscular wasting or tremors, and no local paralysis of the limbs, though all are weak. No anæsthesia. Knee-jerks well marked. The pupils are of medium size, the left a shade the larger; they react normally. There is some convergent strabismus, as the left eye cannot be moved completely outward. There is occasional diplopia; no facial or lingual paralysis; speech normal. She can read ordinary type with ease; hears a watch at 5 inches from left ear, at 15 from right ear. The ophthalmoscope shows double optic neuritis, swelling of disc = 1.5 D. in each eye. There are hemorrhages on and around each disc; no choroiditis or sign of syphilis. The urine contained a trace of albumen for the first two days only. The uterus showed no distinct sign of a recent miscarriage and was not enlarged.

Treatment.—The patient was put upon potassium iodide (gr. xv daily) and magnesium sulphate, and improved with wonderful rapidity. Within three weeks the headache had gone, she was quite rational, and could walk well and steadily. She left the hospital a month after admission with the weakness of the left rectus externus muscle nearly gone and the optic neuritis diminishing. The blue line had also nearly gone.

This patient admitted having taken diachylon in pills for the purpose of checking the course of pregnancy, but we could not ascertain from her exactly when or what quantity she had taken, or what the effect had been on the uterus. I called,

however, to see Mrs. C. on March 20th, 1900, and found her in perfect health, and the proud mother of a three weeks old baby. There was neither blue line nor squint, she could read the local newspaper with ease, and the ophthalmoscope showed nothing abnormal but the faintest haze over the origins of the vessels in the optic discs. She must have conceived immediately on leaving the hospital, and did not repeat her experiments on ecobolics. The baby is, however, a puny creature, said to have "consumption of the bowels," but is not hydrocephalic, as the children of lead workers are at times. On interrogation, she now asserted that she had taken diachylon for a fortnight a year before I saw her, being then six weeks pregnant. Abortion took place at the end of the third month. She adhered to the statement that she had taken none since, although the symptoms of poisoning steadily increased up to her admission into hospital. I have no means of testing the truth of this statement.

CASE III.—H. W., an unmarried girl, aged 22, was admitted in June, 1899, for pains in the stomach and head, of three or four months' duration.

History.—She had been treated outside for gastric ulcer and kept on milk diet, as solid food caused acute pain. There had also been some vomiting and some severe colicky pains. For the last month she had suffered from intense headache chiefly in the frontal and right occipital regions. On interrogation, the patient admitted that in the March previous, having gone a week beyond her proper menstrual period, she had taken one day a half-pennyworth of diachylon, which she had made into two pills. She was positive that she had never taken any more. The period soon came on, and her menses had been regular since, but she began to feel weak and dizzy within a week of taking the pills.

Anamnesis.—After admission she was found to be a pale and rather thin girl with features drawn with constant pain in the head. A distinct blue line on the gums. She is drowsy, and occasionally a little delirious. She can sit up, but not stand alone, the knees doubling under her, and the feet being dragged. Knee-jerks absent; plantar reflexes well marked. Arms rather weak, but not paralysed. Pupils, eye and face movements normal; no anæsthesia; well-marked double optic neuritis. Her vision was unfortunately not properly tested at this time, but she could recognise the doctors and nurses, and I think read large type.

After-History.—During the first fortnight after admission she was frequently sick independently of food, and paresis of the left external rectus muscle was observed. For a month she suffered from intense headache, and remained drowsy and apathetic. On August 28th the optic neuritis had subsided, and the discs were atrophic. She was blind, and hardly able to point to the direction of the window. The paresis of the left external rectus had gone, and the general muscular tone and balancing power were much better. On September 10th she could walk well, and had the complete use of all her limbs, was free from headache, sickness, or abdominal pain, and was plump and rosy. The eyesight was, however, unaltered. I visited this patient at her home in March, 1900, and found her in excellent general health, but still blind. The medicinal and general treatment was the same as in the last case.

These three cases illustrate most of the usual symptoms of lead encephalopathy, and show how closely this affection resembles cerebral tumour. One symptom only of this disease was not prominent in these cases, namely, epileptiform attacks, which Dr. Oliver states are a frequent and early symptom. The woman had had three fits, but the other cases had none. One satisfactory feature of the cases was that all recovered, only the poor girl being left seriously injured. The fact that the married woman was said to have shown severe hysterical symptoms a year before is of interest, for a "toxic hysteria" has been found in other cases to sometimes precede the severe and even fatal form of the disease, and to have obscured the diagnosis. Possibly some cases diagnosed as hysteria which have ended fatally may have been due to undiscovered lead or other poisoning.

It is very remarkable that such acute, severe, and prolonged disease should have been produced in the girl by a single dose of lead—namely, one halfpennyworth of diachylon taken at once. To get some idea of the amount of lead taken by this girl I bought a pennyworth of diachylon at a chemist's, and had it analysed by Mr. Trotman, the city analyst. The diachylon, which was in the form of a ball about the size of a walnut, contained 86 per cent. of oleate of lead and 46.7 grs. of lead, so that we may suppose the girl to have taken about 23 grs. of lead.

This case proves that the excretion of the metal must be very slow, as does also that of Mrs. C., if her story be true.

The treatment of these cases in addition to rest, milk diet, and good hygienic conditions, consisted mainly of moderate doses of potassium iodide with Epsom salts. It is curious that the iodide should have obtained such a reputation in the treatment of lead poisoning, for Dr. Dixon Mann's researches seem to prove that it does not increase the elimination of the metal, the greater part of which escapes by the fæces and not by the urine. It should be noted, however, that in the first case improvement did not occur until the heart had been