ON THE ACTION OF TOXIC SUBSTANCES

and especially of

DIPHTHERIA TOXINE

on the

SPINAL STICHOCHROME CELLS.

Thesis submitted by -

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April 1899.

C O N T E N T S.

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PART I. INTRODUCTORY.

The following Thesis contains the record of a series of experiments which were undertaken by the author with the view of determining whether the paralysis which is known to follow poisoning by ~~by~~ various toxic substances of bacterial origin, and especially that which results from the action of the bacillus of diphtheria. is associated with alterations in the motor cells in the anterior cornua of the spinal cord; and if such alterations were found to exist of determining their nature and the relation which they hold to the changes found in the motor nerves.

At the time when the research was commenced (1894) the prevalent opinion, in this country at all events, was that diphtheritic paralysis was a form of peripheral neuritis, and Ross and Judson Bury in their book on this subject accepted the ordinary view ~~of others~~ without much demur. It is, however, manifestly open to objections, and a study of the cases recorded by the authors already mentioned, and of such other cases as I could avail myself of, suggested to me that at/

at least in many instances one had to deal with a central and not with a peripheral lesion. Of course in that group of cases where the paralysis only attacks the structures in immediate proximity to the seat of the disease, and occurs during or just after it, the most probable explanation is that the phenomena result from the direct action of the absorbed toxine: But on the other hand there is a series of instances where it affects distant parts of the body (the lower limbs for instance) some time after the disappearance of the local process, in which the mechanism of its production is manifestly different from that of the former group.

The research which I have thus been led to conduct is still in many respects incomplete, but so many other workers have now entered the field, and so many papers have been published on this and cognate subjects that I have thought it best to record the results which I have up to the present obtained, even although many of my investigations are still unfinished.

It is unnecessary in this Thesis to recount the history of the gradual increase of our knowledge of the normal anatomy of the nerve cell, especially as/

as this is given in the more recent Text Books, amongst which may be mentioned Lenhossèk (1), van Gehuchten (2); and in many compilations such as Goldscheider & Flatau's Anatomie der Nervenzellen, Bühler's Bau der Nervenzellen and others whose titles will be found in the appended bibliography. The broad conclusions to which these researches have led are :-

1. The nerve cell is bounded by a special investing membrane which sometimes appears to be continuous and homogeneous, but at other times has the aspect of closely apposed delicate scales, or of fine reticulum with regular meshes which can be traced for a considerable distance along the protoplasmic processes. (Golgi 80).

2. The substance of the nerve cell consists of at least two elements - (a) The chromatic or "tigroid" (Lenhossèk) which becomes aggregated into small masses known as Nissl's bodies whose structure will be subsequently detailed.

(b) The achromatic or ground substance which is by most writers, however, divided into a "formed" and a "structureless" part. Opinion is still divided as to the exact nature of the formed substance. The following/

following authors consider that it is fibrillar - Flemming (30), Benda, (20) Dogiel (22), Becker (19), Lugaro (36), Levi (34,35), Nissl (48), Robertson (82) Dehler (21), Kronthal (26) Bühler (6), and Bethe (54). The methods which the various ~~experimentors~~ observers adopted differed greatly, and if one may judge by their figures, the fibrils seen by them were not identical. (See Figs. 14, 15 and 16.) The following writers regard the formed achromatic substance as consisting of a reticulum and not of fibrils - Lenhossèk (1), van Gehuchten (2), Ramon y Cajal (38), and Held (25). (See Fig. 17.) Marinesco occupies an intermediate position considering that there is a reticulum which is continued into the fibres of the axis cylinder process.

3. Lenhossèk (33) describes Centrosomes in some nerve cells, but Bühler (6) has, I think, conclusively shown that these centrosome structures had their origin in a misinterpretation of certain appearances which can be easily explained on the assumption of a fibrillary element in the achromatic substance. Bühler himself has, however, described what he/

he designates a "microcentrum" with very fine radiating fibrils passing from it to the bounding mesh-work of the cell, corresponding, with very considerable precision, to Heidenhain's (3/) centred system. Golgi (loc. cit.) has described a delicate net-work in the interior of the cell consisting of flattened fibres which unite in nodal points.

4. The nucleus is bounded by a delicate nuclear membrane which is not infrequently obscured by the surrounding Nissl's bodies. It contains mostly an "acidophil" chromatic reticulum, but is not wholly destitute of Basichromatin which is ~~which is~~ much more abundant in the earlier stages of development than in the adult cell. Within the nucleus is found one, sometimes two or more sharply defined nucleoli, which may have granules of basichromatin closely apposed to them. See Fig. 1.

Of those various constituents of the nerve cell, Nissl's bodies are the most labile, and so are conspicuously affected by changes in the cell's vitality. On this account they are very appropriate structures to observe when the action of various noxae is being studied. It is, ~~however~~ therefore, important to review what

is/

is known of their structure, composition, and function. Whether they are preformed in the living cell, or only appear after death as artifacts, is a question which has been much discussed; but a good deal of the difference of opinion seems to have arisen from lack of correspondence in the sense in which the term artifact is employed. Their pre-existence is denied by Trezebinski (10), Kronthal (26) Fisher, (14), Held (25,41) and some others. Held thinks that they are formed as post-mortem products whenever the protoplasm of the cell becomes acid. Probably, however, a substance really exists in the living cell which closely corresponds to Nissl's bodies and occupies a position similar to that in which the latter can be demonstrated after death, although in the living state it is optically indistinguishable from the rest of the cell. Regarding the structure of Nissl's bodies as seen after careful fixation and in very thin sections, the most probable view is that they consist of fine granules associated with a ground substance staining violet by Held's method. This ground substance is perhaps identical with the achromatic reticulum of van Gehuchten (2) and Ewing (5). The chemical composition of/

of the granules seems to be that of a nucleo-albumen. They are according to Held insoluble in dilute or strong mineral acid, in acetic acid, in boiling alcohol, in cold or boiling ether and in chloroform. He also states that they are left intact by pepsin (a most unreliable test), that they are soluble in alkalies and that they react slightly to Lilienfeldt's test for phosphorus. More recently, much better evidence has been adduced regarding their composition by Dr A. B. Macallum (68) who finds that they are of the nature of a nucleo-proteid. He has demonstrated indubitably the presence of phosphorus by a modification of the older method, in which the hydro-chlorate of phenyl-hydrazin is used instead of pyrogallic acid as a reducing agent, after first treating the tissues with an acid solution of ammonium molybdate. As a preliminary he had extracted all lecithin from the sections. In addition to phosphorus he also succeeded in demonstrating the presence of iron. The same author has investigated the origin of Nissl's bodies by the aid of embryological methods, and considers that they are derived from the nuclear chromatin.

On the function of Nissl's bodies, very divergent/

divergent views have been expressed - that they are associated with cell metabolism, is certain from all that is known of their behaviour; - Lugaro* (81.), Cajal* (81) and van Gehuchten* (81) regard them as a reserve alimentation for the cell, and therefore essentially of a nutritive function. This, in the writer's opinion, is improbable, as the extreme complexity of their chemical composition makes it unlikely that they are in any immediate sense food stuff for the cells, whilst the observations of Bühler (6) Goldscheider and Flatau (7) and Ballet and Dutil* (81) indicate that they are not necessary either for the life or functional activity of nerve cells. Bühler states that they are absent in the cortical cells of the lizard (Eidechse). Goldscheider & Flatau employed malonnitril on rabbits, and when they became paralysed through its action, quickly restored them by the administration of sodium hyposulphite ($Na_2S_2O_3$), which proves a perfect antidote, and the use of which restores the powers of movement within a very brief period. A rabbit killed shortly after its powers of movement had been recovered showed that Nissl's bodies had become disintegrated, the power of movement returning some hours before the cell resumed its normal aspect. They also raised the/

*Quoted by Marinesco.

the temperature of rabbits to a height of over 43° centigrade. This also led to paralysis and disintegration of Nissl's bodies but if the temperature was lowered by the removal of the animals from the hot chamber they frequently recovered and it was found that in this case also power of movement reappeared earlier than Nissl's bodies were reconstituted. Marinesco has expressed opinions which differ in several respects from those of other investigators. The following is a brief summary of his most important positions as expressed in his latest paper (81). - Nissl's bodies he regards as sources of energy but not primarily of nutrition, considering that their irregular distribution and variability preclude the latter function. He says :- "Je pense que ces derniers "constituent une substance à haute tension chimique "qui est le siège de phénomènes d'intégrations et de "désintégrations continues." The convulsions which follow certain poisons, such as strychnine and that of tetanus, he explains by pre-supposing the existence of an affinity between them and Nissl's bodies, which is productive of a sudden discharge of energy when the two are brought into relation with one another. Following/

ing up these views he has suggested that Nissl's bodies are ordinarily traversed by the nerve impulses which reach the cell, and that during their passage energy is liberated by these structures so as to send a reinforced nerve current into the axis cylinder process. For the material of which Nissl's bodies are composed, he suggests the name "Kinetoplasm." He lays stress in discussing the above mentioned results of Goldscheider & Flatau on the fact that one must discriminate between the total destruction and merely the disintegration into smaller portions of these bodies,- the former he considers would be necessarily associated with absolute paralysis, the latter might only lead to less efficiency and therefore to weakness of the affected muscles. The achromatic substance as has already been indicated is in his opinion divided into an amorphous and a figured element - the figured element in the cell being of the nature of a reticulum, which, however, seems continuous with the bundle of fibres entering the cell through the axis cylinder.

Nissl has suggested an elaborate classification of nerve cells based exclusively on the appearance and situation of the chromatic substance in the cell/

cell body. This classification has from time to time varied in detail. The latest is as follows :-

I.* Small ganglion cells divided into (a) Karyochrome with a small nucleus and a small amount of surrounding chromatic substance (b) Cytochrome whose nuclei never exceed in size those of neuroglia cells.

II. Somatochrome. This group includes most ganglionic cells and is subdivided according to the distribution of the chromatic granules. His present classification is as follows :-

(a) Stichochrome where the Nissl's bodies form spindles parallel for the most part to the boundaries of the cell. This type probably occurs in motor cells only and is characteristic of them - being found in the motor cells of the anterior cornua, in the cells of the motor nuclei in the medulla, and in the cells of the motor cortex.

(b) Gryochrome. In this Nissl's bodies constitute irregular granules variously aggregated together.

(c) An indeterminate group in which a considerable variety of unclassified cells are provisionally associated.

(d)/

* In former classifications the whole of group I was named Karyochrome, and was stated to contain all the chromatic substance in the nucleus.

(d) Arkyochrome, Where the Nissl's bodies seem to be arranged so as to give the impression of a network. This group is composed of numerous sub-groups whose limits have not yet been very precisely defined.

Under certain conditions Nissl's bodies stain with great intensity, on other occasions the staining may be moderate or the cell may present a very faintly tinted aspect. When deeply stained, owing to Nissl's bodies being closely drawn together, the cell is described as pyknomorphic, when moderately stained as parapyknomorphic, and when faintly stained, as apyknomorphic.

A number of authors, including Nissl*, Lenhossèk, and Lugaro, have sought to prove that resting nerve cells are pyknomorphic, whilst those which are exhausted after passing through a period of activity are apyknomorphic, and evidence in support of their view has been also adduced by Vas, Lambert, Hodge, Mann and others. Most of the experiments are, however, inconclusive; as stimuli have been applied directly to the neuron under investigation, whereas, as Goldscheider has pointed out conclusive results can only be arrived at if the stimulus reach the neuron whose cell/

* At least in some of his earlier papers.

cell is under examination through the ordinary channels of nerve stimulation. This he points out can readily be done for the lower motor neuron by stimulating the upper neuron. Jacobsohn who examined the nerve cells of the hedge-hog during its hibernation found no marked change from the aspect which they present during the summer.* (97)

Some very important work has been done within the last few years with regard to post mortem changes which occur in nerve cells and as this has a very direct bearing on the appearances which have been described in many cases where death was due to diseases associated with paralysis it is necessary to refer to them here. Colucci finds that post mortem changes do not begin in ordinary circumstances until 20 hours after death. At that time alterations may ~~make themselves~~ appear in those parts of the brain which are most dependant. The character of the changes are, - first a granular disintegration of the cell body which becomes powdery, or homogeneous and diffusely stained; all elements of the cell may be affected - the last to become implicated is usually the nucleus; secondly, the protoplasmic processes stain irregularly and/

* Levi, on the other hand, found the chromatic bodies absent during hibernation (96).

and so on cursory observation may be regarded as broken or fragmented; thirdly, as the changes advance, complete rupture may actually occur in the processes, and, fourthly, black droplets in the cell itself or in its processes may be demonstrated by Marchi's method.*

Neppi (85) observed the spinal stichochromes of a dog. For 6 hours after death their appearance was absolutely normal: 24 hours after death, Nissl's bodies were still normal, some cells, however, exhibited a slight nuclear chromatophilia. In 48 hours he observed obvious staining of the whole cell body - many of Nissl's bodies still remained sharply defined: they seemed, however, to be scarcer than usual in the protpplasmic processes. The nucleus was also less regular in outline and had sometimes become eccentric. Thereafter the changes advanced with moderate rapidity, and in 96 hours the cell was extremely ragged and its structures were visible for the most part with difficulty.

A very elaborate study of the post mortem changes occurring in the spinal cord of the rabbit was conducted by Barbacci and Campacci (86). They employed Nissl's, Golgi's, and Marchi's methods. The first of/

* The appearance of black droplets is not always of pathological import, in cells from Marchi's method. (cf. Rosin. Berl. Klin. Woch. 1895. p. 903)

of these methods indicated that the chromatic elements stained less readily, became irregular; their outlines growing indistinct and eventually fusion or disintegration occurring. Frequently the change was much most distinct at the periphery of the cell. Vacuoles were not uncommonly present: the nuclei became irregular, first swelling and then shrinking; - the nucleolus seemed the most resistant structure of any. Golgi's method revealed erosion of the protoplasmic processes. Levi (88) found that in the cord changes only occurred after 60 hours. His method, however, was unsatisfactory in this respect that the spinal cord was not left in situ but was removed shortly after death and thereafter remained exposed to the air until fixation was performed at varying intervals.

Ewing conducted a series of experiments to check the above results. He also, however, allowed the spinal cords to decompose in contact with air. The alterations which he observed appeared to fall into three distinct periods. The changes of the first period were, he states, marked within 24 hours. They were chiefly confined to the cerebral cortex where there was a granular disintegration of the chromatic substance/

substance. In the spinal motor cells the outlines of the chromatic bodies were only slightly irregular, and the granules were larger than normal; whilst the dendrites exhibited an irregular network of fine granules, and the chromatic spindles appeared more coarsely granular than in the fresh specimens treated by the same methods. The nucleus also appeared to be affected. The second period was well marked at the end of 48 hours. In the spinal motor cells the nuclear changes were still moderate, but diffuse staining of the achromatic part of the cell body and dendrites had occurred, whilst Nissl's bodies were still more irregular and coarsely grained. In the third period the tissues became invaded by bacteria and rapid destruction supervened. The cells in the spinal cord were attacked at a later period than those of the brain, and Nissl's bodies were amongst the last structures to disappear entirely.

The changes which are said to occur during fatigue, and to which reference has already been made on pages 12 and 13, afford a natural transition to the more profound alterations which are the result of disease. Whilst much still remains to be learned regarding this/

this department of the subject, yet, within the last 5 years a vast amount has been added to our knowledge of at least the microscopic anatomy of the nervous systems as influenced by it. The following classification although purely provisional will facilitate a rapid review of the most important results that have been obtained. Morbid processes may affect the nerve elements in one or other of two ways, either the nervous system may suffer simply as a part of the organism which has fallen under the influence of disease - no selective action of the noxa being apparent; or, these structures may become specially implicated through the toxic products of the disease possessing a special affinity for them. Only the more important results will be referred to in the text. Further information is to be found by consulting the bibliography which is appended. The writer would also direct special attention to Ewing's recent paper (5) in which a very fair abstract of recent work is embodied.

I. Morbid conditions which affect the nervous system along with the other systems, but which are apparently devoid of any selective affinity for it.

(a.) Fatigue.(90 to 101) This, when extreme/

extreme, must be regarded as a pathological condition. Experimenters have attempted to demonstrate the effects of fatigue on the nerve cells in various ways. In one, electrical stimulation was applied to the cervical sympathetic ganglion on one side. and the appearance was compared after death with that of a control ganglion on the other side. Others kept animals in motion up to the stage of extreme fatigue, or to complete exhaustion. In other instances peripheral nerves were stimulated and the effect on the corresponding cells in the spinal cord was noted. An ingenious device was adopted by Magini and Valenza who caused a torpedo to yield a rapid succession of electric shocks, and then examined the nerve cells which regulate the action of its electric organ. Perhaps a still more satisfactory method is that adopted by those who have stimulated the cerebral cortex and observed the changes in the anterior cornual cells which by that means were subjected to a normal form of stimulation. In spite of all this work, the results are by no means conclusive.. Nissl, discussing the question in 1896, felt bound to, state that the morphology was still unknown, and that the evidence adduced was inadequate to prove whether

pyknomorphic/

pyknomorphic cells indicated a state of rest, and apyknomorphic cells one of activity. About the same time, Lugaro arrived at the following conclusions - "Activity "of the nerve cell is accompanied by a state of turges- "cence of its protoplasm, while fatigue produces a pro- "gressive diminution in the size of the cell body, In "moderate degrees of fatigue, while the cell body "swells, the nucleus does not change its volume. The "shape of the nucleus always remains uniform, nor is its "position changed, marked eccentricity being just as "common in ganglia in repose as in fatigue. When "activity is much prolonged, the nucleus undergoes the "same changes in volume as the cell body, but less "markedly, and more slowly. The quantity of chromatic " substance in the cell body varies as an individual "character, and in relation to the size of the cell. "During the swelling of the cell in activity, there is "perhaps an increase of chromatic substance, and in the "stage of fatigue, perhaps it fades a little and be- "comes more diffuse, but it is certain that the "great differences in staining power and content of "chromatic substance that one sees in cells of the "same ganglia cannot be attributed to differences in "the physiological state. Activity and fatigue may "cause/

"cause changes in the staining capacity of all sorts of "cells but do not change a pyknomorphic into an apyk- "nomorphic cell. Activity determines in the nucleolus "an increase of volume which yields slowly to the "contrary action of fatigue."

(b.) Hunger, inanition, and anaemia. (102 to 112). Many observers have described vacuolation of the cells and disappearance of Nissl's bodies in cases of gradual starvation. It is, however, an open question whether during the process abnormal products have not been absorbed from the alimentary tract - in fact, the results described might be interpretated as arising from auto-intoxication. More satisfactory evidence of the results of mal-nutrition is to be sought in cases where from vascular changes the blood supply of the cells has been cut off. Experimentally the conditions have been fulfilled by ligature of the aorta and by the production of emboli through the introduction into the circulation of lycopodium powder. Clinically it has been observed by Ewing in a case of basilar thrombosis and in cases of pressure following intra cranial haemorrhage. In general terms the most noteworthy lesion was chromatolysis, which as a rule was very marked, and uniformly present in the compressed/

compressed or anaemic areas. Cell changes have also been found associated with ordinary and pernicious anaemia. Here, however, there is always the possibility that other toxic influences were present and formed a common cause of both the anaemia and the cellular changes.

(c.) Changes of temperature. (113 to 119). Very notable results have been obtained by Goldscheider & Flatau, Marinesco, and Ewing as the result of experimentally induced hyperpyrexia. Nissl's bodies are found disintegrated and this disintegration may reach the most extreme degree of chromatolysis. Changes, in many respects closely analagous, have been observed by Ewing in cases of sunstroke, and in the high temperature of many fevers somewhat similar conditions have been described. When the hyperpyrexia is rapidly induced, Nissl's bodies exhibit granular sub-division before disappearance. Where the process is slower they seem to fade out without much evidence of sub-division having occurred.

(d.) Asphyxia. (5 & 120.) Very little seems to have been done in this department which, however, is one of considerable importance. One case

where/

where asphyxia came on gradually in the course of acute bronchitis is described by Ewing who found that in the nucleus of the tenth cranial nerve the chromatic bodies were usually limited to a narrow peripheral ring, the remainder of the cell showing a more or less distinct chromatic network often infiltrated with yellowish pigment. Towards the termination of the disease the patient's temperature rose to 103·5 and therefore the temperature ~~affected~~ may have had some influence in the appearance presented.

II. Morbid conditions where the nervous structures are specially implicated, through the toxic products of the disease exhibiting a definite affinity for them. In some cases the nerve cells may be directly affected, in others, the affection is secondary either to a lesion of the nerve or of the upper neuron. Marinesco and certain other writers have attempted to distinguish between the effects produced on the nerve cell according as it is directly affected or only secondarily influenced through its peripheral nerve. In the former case they describe chromatolysis as commencing at the periphery of the cell - the nucleus remaining central and the achromatic substance showing at an early period changes such as vacuolation/

vacuolation and rupture of the processes. In the latter they describe partial or complete perinuclear chromatolysis and migration of the nuclei to the periphery of the cell, whilst the dendrites are not ruptured. It is, however, more than doubtful whether so sharp a line can be drawn between the two groups.

A. Secondary involvment of the Nerve Cell.

(a.) Section of peripheral nerve, or amputation of limb. (121 to 131). In such cases changes are stated to occur in the nucleus and nucleolus which both may shrink and migrate towards the edge of the cell. The chromatic bodies gradually break up and may largely disappear. van Gehuchten states that the changes which occur in motor nerve cells affect the chromatic substance only,- the achromatic reticulum remaining intact, the nucleus showing no marked degeneration, and the changes being of such a nature as to permit of subsequent return to normal conditions. Dr Warrington has recently given an account of some [redacted] investigations which he has conducted on this subject. He showed that marked changes occured in the anterior cornual cells of the spinal cord after cutting off the afferent impulses which normally impinge upon them. The affected cells were chiefly found/

found in the postero-external group and in that segment of the cord ~~usually~~ whose afferent and efferent roots were specially concerned with innervation of the foot. He also mentioned, in the case of the spinal cord, that after section of an anterior root almost every cell on the side of the lesion of the affected segment gave evidence of a distinct change in its structure. Changes corresponding to those occurring in section of the peripheral nerve are also reported as being found in cases of peripheral neuritis.

(b.) Removal of control from upper neuron by section of spinal cord. (132 to 135).

Lugaro has found that under these conditions most cells near the point of section show chromatolysis, but that the anterior cornual cells, unless actually implicated in the injury, escape entirely.

B. Nerve cells directly affected. - A very extensive series of observations has now been accumulated in connection with this part of the subject. They may be tabulated as those following the administration of chemical poisons, those resulting from faulty metabolism, and those due to the action of toxines/

toxines which are produced by bacteria in the course of disease. (136 – 152)

(a.) Chemical Poisons. (153 to 178)

Metallic.- Observations have been made on the effects of lead, arsenic, silver, and antimony.

Non-metallic. Phosphorus, Hydro-chloric acid, potassium bromide, carbolic acid, alcohol, strychnine, morphine, veratrin, trional, atropin, and cocaine, have been experimentally employed. In all of them, alterations in Nissl's bodies have been a prominent feature, although different poisons act on different cells, and the changes introduced in each case are more or less characteristic of the various drugs employed. Thus in an important paper published in 1897 by Nissl, in which in the course of 107 pages he discusses much of the more recent work and also records his own experiments on 24 different poisons which he administered to the dog and rabbit, he states that arsenic causes swelling and dissolution; silver, retraction and a kind of atrophy; and strychnine a pyknomorphic appearance. He lays considerable stress on the method of administering the poison and advocates what he calls a sub-acute maximal intoxication, by which he means the administration on repeated occasions of doses insufficient/

insufficient individually to cause the death of the animal but sufficiently large to maintain a constant action of the drug on the nervous system.

Animal products.- Experiments have been made by Uhlenhuth and Moxter on the toxicity to rabbits of the serum of beef and human blood. They state that they uniformly found in the stichochrome cells a certain degree of peripheral chromatolysis and swelling of the remaining chromatic bodies. They also found that many of the animals died in convulsions. The writer has been unable to verify this observation. In one case a rabbit received on five successive days 30 cubic centimetres daily of ox's blood serum without manifesting any symptoms whatsoever. It seems not impossible that the recorded results may have been due to septic changes. Several observations have been made on the action of snake-venom, & many changes have been recorded, including parenchymatous neuritis, myelitis, and destruction of the chromatic elements of the nerve cells and of their protoplasmic processes. (179 to 183)

(b.) Perverted Metabolism.- Ewing has recorded marked changes in cases of uræmia and eclampsia (loc. cit. pages 351 to 358). (184 to 187)

(c)/

(c.) Toxines. (188 to 225) Changes have been described in typhoid fever, in pneumonia, in septic disease, in hydrophobia, in plague, in leprosy, in malaria, in influenza, and numerous other conditions. References to these will be found in the bibliography. Two groups, however, demand special attention, viz, those occurring in cases of Tetanus, and those following diphtheria. By far the most important series of observations on tetanus are those recorded by Goldscheider & Flatau who experimented on nearly 100 rabbits. They found at an early stage, swelling of the nucleolus which, however, subsequently resumed its normal appearance. The swelling of the nucleolus was followed by considerable increase in size of Nissl's bodies which subsequently became irregular in outline, grew granular and eventually disappeared, - ~~the~~ changes also occurring in the other elements of the cell at a later date. Marinesco has found somewhat similar changes, but his observations were conducted on a much smaller scale, and the details are less conclusive. Courmont, Doyon and Paviot have reported in several papers on a limited number of experiments which they conducted. Their results are not very satisfactory and their conclusions seem to me/

me somewhat untrustworthy. The writer has conducted observations on two cases in which toxine was injected and the symptoms of tetanus supervened. These will be recorded in a subsequent part of the thesis, and, so far as they go, tend to corroborate the contentions of Goldscheider & Flatau. In the recently published Volume of Twentieth Century Medicine (Vol.17) Babes, in the article on tetanus, states that Nissl, Marinesco and himself have all found changes in the cells of the anterior horns and in certain commissural cells; that they have especially noted degeneration of axis cylinder processes and of Nissl's bodies, with increasing homogeneity of the basement substance.

Diphtheria. (226 to 306) It will be necessary to enter on the changes found in diphtheria in somewhat greater detail. Valuable references to the earlier literature on the subject are to be found in Dr Paul Meyer's Anatomische Untersuchungen über diphtheritische Lähmung published in Virchow's Archiv for 1881; and in Crocq's Recherches expérimentales sur les alterations du système nerveux dans les paralysis diphtéritiques, published in 1896. The former especially contains a very exhaustive bibliography up to/

to the date of its publication. In 1862 Charcot and Vulpian described degenerative changes in some of the fibres of the palatine nerves. In 1864, Weber in two cases of post-diphtheritic paralysis was unable to find any changes in the brain or spinal cord. In 1867, Buhl, in one case, found haemorrhages in the brain and swelling with infiltration of the anterior and posterior cornua of the spinal cord. In 1868 Clos found in one case changes in the nerves similar to those produced by section. In 1869, Lorain and Lepine described changes analogous to those observed by Clos. In 1870, R. Maier in a post mortem examination on a child of six years old who died of diphtheritic paralysis, confirmed the observations of Buhl, especially with regard to the haemorrhages, and considered that these produced pressure on the nerve fibres and cells. In 1871, Oertil found capillary haemorrhages of the cerebral and spinal dura mater, and of the sheaths of the peripheral nerves. He also noted infiltration of nuclei and granulations in the anterior cornua. In 1872, Leyden observed peripheral and central lesions, - the latter he attributed to neuritis migrans ascending to the central nervous system. In the same year Bailly/

Bailly expressed the opinion that diphtheritic paralysis might be due ~~either~~ to a primary lesion, sometimes situated in the central nervous system, sometimes in the nerves, and sometimes in the muscles. In this year also Liouville noted slight degenerative changes in the phrenic nerves. In 1875 Roger and Damaschino, as the result of post-mortem examination of four cases, recorded alterations in the nerves, and particularly in the anterior nerve roots. In 1876, Pierret described a case where he found disseminated plaques of spinal meningitis, as well as perineuritis in the neighbouring nerve roots. In this case, however, as also in those of Déjerine and Barth (1880) the cases were not purely diphtheritic, but probably were suffering from an inter-current purulent meningitis. In 1876 Vulpian, in two of three cases, observed modifications in the anterior cornual cells, which he described as being more globular than usual. He also noted that their contents were unusually homogenous - almost concealing the nucleus - and thought that possibly the processes were unusually fragile. In 1877, Sanné, as the result of observations on several cases, failed to find any constant lesion. In 1878, an

extremely/

extremely important paper was published in the Archives de Physiologie by Déjerine. Besides changes in the nerves he recorded that the anterior cornual cells were globular, were deficient in processes, that their nuclei and nucleoli had become indistinct, and that some cells had entirely perished. He also noted lesions of the anterior roots corresponding to the paralyzed nerves. These lesions he considered constant. They seemed to vary in degree with the duration of the paralysis; they never affected the posterior roots, and they seemed to be secondary to changes in the grey matter of the spine. In 1879, Shech described slight degenerative changes in the vagus and recurrens. In 1880, Landouzy propounded the view that vascular changes might be primary ones. In the same year, Quinquand observed lesions analogous to those described by Déjerine. The grey matter of the lumbar region was the seat of marked hyperæmia and numerous cells were involved. Sinclair, also in 1880, directed attention to the presence of inflammation in the nerve sheaths, in the vessel sheaths, and in the lymph spaces of the cord; and suggested that the paralysis might be due to "meningo-"lymphite." In 1881, Gaucher contended that changes/

that changes only occurred in the anterior roots, and in the same year Abercrombie declared himself unable to corroborate Déjerine's observations, having only found a very slight diminution of the cells of the anterior cornua. In 1881 appeared the important paper of Paul Meyer which has been already referred to. His conclusions, based on a very typical clinical case, were that the diphtheritic poison acted on various points of the nervous system - equally in his case, on the peripheral nerves and spinal cord. In 1883, Kidd found congestion, increase of connective tissue and atrophy of the anterior cornual cells - the atrophy being most marked in the dorsal region. In 1884, Sanne concluded that the spinal lesions were primary ones and the changes in the nerves were consecutive to them. Mendel in 1885 found no change in the cells of a child who died of diphtheritic paralysis. In 1888, Bristowe noted a normal condition of the nerve cells, a degeneration of the third cranial nerve and a hyperemia with small haemorrhages near the base of the brain. Pye-Smith, in the second edition of Fagge's Principles and Practice of Medicine, notes the divided state of opinion but does not commit himself to any definite view. In 1889, Fuchs drew attention to the close

resemblance of post-diphtheritic and post-influenzal ocular paralysis. In the same year, Eustace Smith in the second edition of his Diseases in Children, notes the probability of nerve cells being primarily or at least early affected. In 1890, Babinski states that in diphtheritic paralysis one finds a periaxial neuritis, at the same time noting that the peripheral origin of diphtheritic neuritis is very dubious. In 1892, Gowers, in the second edition of his "Diseases of the Nervous System" says in one place "Diphtheria may cause acute changes in the nerve "cells and nerve roots," and in another place "diphther-"itic neuritis is not wholly peripheral." In the same year MacBride pronounced diphtheritic paralysis to be due to polyneuritis, and Osler was of opinion that the primary change was a toxic neuritis. Also in the same year, Déjerine modified his former view and expressed his concurrence with Leyden's view. Arnheim also adhered to this opinion. In 1892 Preisz recorded observations on two cases of death from diphtheritic paralysis. In the first case he noted atrophy of the anterior cornual cells, haemorrhages in the grey matter of the spinal cord, and changes in the peripheral nerves.

In/

In the second case, in addition to these facts, he records degeneration of the column of Goll in the cervical cord.

In 1893, Gay recorded in "Brain"a case of somewhat abnormal symptoms where post diphtheritic allocheiria supervened. In the post mortem on this case, marked degeneration was found in the columns of Goll. Stcherbak in the same year observed marked changes in the nerves of animals which had received injections of diphtheritic poison. In 1894, Vincent recorded the case of a patient, aged 24 years, who died on the 14th day of his illness from diphtheritic cardiac paralysis. The medulla, vagus and sympathetic nerves were normal, but a serious inflammation of the plexus cardiacus was found, consisting in destruction of the myelin sheath and inflammation of the axis cylinder. The changes of the heart muscle were deemed inadequate to lead to the fatal issue.

Bikeles (1894) contributed a paper describing changes which he, in association with Prof. Kolisko, observed in a very typical and extremely well marked case of post diphtheritic paralysis in a middle aged man. The nerves, which were examined by Marchi's method/

method as well as by the commoner procedures, exhibited absolutely no alteration from the normal. The spinal cord, stained haematoxylin and carmine, Likewise presented no great alterations, and he was unable to detect any abnormality in the motor cells. Marchi's method, however, as applied to the cord, demonstrated a very characteristic degeneration of the posterior roots where they enter the grey substance of the posterior cornua, and these changes he very reasonably suggests may account for the frequent ataxic symptoms which one finds clinically associated with cases of post diphtheritic paralysis. Enriquez and Hallion, as a result of the experimental injection of diphtheritic toxine under the skin of animals, observed very marked changes in the spinal cord. Those which they laid chief emphasis on, were, marked increase of vascularity - especially in the grey substance, in which numerous foci of haemorrhage were observed -; patches of myelitis were also noted. In 1895, Hochhaus found neither in the central nervous system nor in the peripheral nerves any trace of pathological change in a case which came under his observation. Vidal & Bezançon observed changes in the posterior columns of the spinal cord after the use of/

of streptococcus toxine, in the case of experimental investigations conducted in 1895. The importance of this observation is manifest, as many of the cases in which changes in the white matter of the spinal cord have been recorded were clinical cases where the possibility of a mixed infection must always be borne in mind. In this year, Crocq, Junr., published his first communication on the subject in the "Archives de Médecine "expérimentale," but as he published in the following year a very much more full account of his work, the statement of his conclusions will be reserved until that is noticed. In 1896, Pernici & Scagliosi reported an examination of the central nervous system. In the brain, many of the cells were normal; others were somewhat markedly implicated, and by Golgi's method were found to present varicose atrophy. The changes in the spinal cord were indefinite - many of the cells appeared smaller than normal, - a condition which the present writer has also observed - and their protoplasm was granular. The nuclei are reported as having often presented a shrunken aspect, whilst some of the cells were in a state of extremely advanced disintegration. In the same year, Manicatide published

a/

a paper in which he collated 19 cases of post diphtheritic paralysis. He divided the cases into 4 groups - (1) Cases where the lesion was purely muscular, with no nerve implication; (2) Cases of polyneuritis; (3) Lesions of the spinal cord which were either localised in the grey substance leading to atrophy of muscle, or involved the white matter of the cord in a manner such as is found in loco motor ataxia, or multiple sclerosis; (4) Central paralysis, chiefly resulting from changes in the circulation. He notes in his paper that Ceni established an experimental post diphtheritic primary encephalitis, but no clinical cases have been recorded of this condition. Courmont, Doyon, and Paviot conducted experiments of the action of the diphtheritic toxine on frogs kept in incubators, on dogs, and on a horse. Peripheral lesions alone were observed. The neuritis was associated with paralysis and atrophy of muscle. The functions of the sensory nerves seemed unimpaired. On one occasion only was the presence of myositis established. They further noted that the diphtheritic poison required, in cold blooded animals, that the temperature should/

should be raised to a point above that which they usually possess - in the case of frogs, 38° C.

Turning to English authors we find that in the same year (1896) Professor Kanthack writing in Clifford Allbutt's System of Medicine expressed the opinion that the primary lesions consist in a parenchymatous degeneration of the nerves and also of degenerative changes in the muscle. In support of his opinion he quotes Déjerine, Gombault, Meyer, and Sidney Martin - the latter of whom especially lays stress on the changes of nerve and muscle. Dr Gee in the same volume also seems inclined to account for the symptoms which one meets with in post diphtheritic paralysis by assuming the existence of multiple neuritis. The same view is expressed by Rotch in his treatise on Hygiene and Medical Treatment of Children.

In 1896, Crocq Junr., summed up the results of all his observations in a short monograph on diphtheritic paralysis. His conclusions will be given at some length as representing the general state of opinion in the year when his results were published. He says - "In the spinal cord the diphtheritic poison provokes "very marked alterations of the grey matter; the cells "become/

"become swollen, they stain badly, their nuclei and "processes disappear; the neuroglia and ependyma- "proliferate, the nerve cells atrophy or may dis- "appear altogether and be replaced by sclerosed tissue. "The white substance is but rarely affected. Thus, mye- "litis generally progress slowly. In some cases, "however, it may be rapidly evolved and end in softening.

"As regards the nerves, the diphtheritic poison "produces a degeneration which is first manifested by "irregularity in the contour of the nerve fibres, by "the segmentation of the myelin, and by the hypertrophy "or multiplication of the nuclei. Presently, the axis "cylinder breaks into segments, the myelin aggregates "into droplets, the protoplasm increases in amount. "Eventually the axis cylinder disappears; the proto- "plasm becomes still more abundant, and the nuclei still "more numerous, until at last the myelin is entirely "absorbed. This degeneration is most distinctly "visible at the anterior roots, whilst the posterior "roots remain almost normal. With regard to the medulla, "the diphtheritic poison only produces some swelling "of the cells at its lower part.- the middle and upper "parts remaining normal. The cranial nerves are not "affected/

"affected by the diphtheritic poison. The poison pro-
"duces in the rabbit a primary myelitis and secondary
"peripheral neuritis. Diphtheritic paralysis is dis-
"tinctly different in the man and in the rabbit. In
"the former it generally begins with involvement of
"the palate and throat,- with the rabbit, by weakness
"of the hind limbs. In man, diphtheria seems to
"produce two different kinds of paralysis in which the
"one remains localised in the mouth, nose, eyes, larynx,
"and pharynx, whilst the other is generalised and may
"affect the whole body, commencing with the lower
"limbs. It is reasonable to suppose that the former
"is due to a primary peripheral neuritis, whilst the
"latter depends in man, as in the rabbit, on a primary
"myelitis with secondary neuritis."

In 1897, papers appeared by Sharp, Katz, and Murawjeff, as well as others of less importance which will be recorded in the bibliography. Sharp applied diphtheritic toxine to the isolated heart. He observed that the beats were at first intensified the systole soon became weakened, whilst diastole was lengthened, arrest finally occurring with the heart fully dilated. He considers this result to follow from the action of the/

the toxine on the heart muscle, but beyond the statement of this experiment he offers no proof for his thesis. Katz examined the spinal cord of three children who had died of diphtheritic paralysis at ages of from 5 to 6 years. Golgi's and other methods were employed. In all three cases the anterior cornual cells were found partly necrotic and partly exhibiting fatty degeneration. In the peripheral nerves, destruction was observed of the axis cylinder and special note was made of the fact that the phrenic nerves were implicated in this process. The diaphragm is described as having been fatty. Murawjeff made a series of examinations of the spinal cord of Guinea-pigs which died in from 1 to 3 weeks after the injection of cultures of diphtheria. He found in the anterior cornual cells all degrees of chromatolysis, nuclear changes, and vacuolation. Many fibres in the peripheral nerve trunks were also degenerated, but this change he considered secondary to that of the cells. In the same year he also investigated the action of diphtheritic anti-toxine and came to the conclusion that it caused similar changes in the cells and nerves and that the intensity of its action depended directly/

directly on the dosage. He found further that, if the toxin and antitoxin were given simultaneously, [redacted] changes only occurred when the toxin was in excess, so that some of it remained free. He also noted that if the toxin were administered some time before the antitoxin, its effect on the cord varied with the interval between the administration of the poison and of the remedy. From this series of observations he concludes - (1) That antitoxin is a valuable remedy; (2) that it must be used early (3) that it is not an indifferent substance, and is therefore best used in small and repeated doses.

In 1898, a very considerable addition has been made to our knowledge of post diphtheritic paralysis. Thomas, reviewing the subject and basing his conclusions on the observations which he was able to make on 25 fatal cases states (1) That marked parenchymatous degeneration of the peripheral nerves is an ordinary condition, and that it is occasionally associated with hyperaemia, haemorrhages, and inter stitial changes; (2) that in the brain and spinal cord, acute diffuse parenchymatous degeneration occurs in the nerve-fibres, whilst little or no change was found by him in the nerve/

nerve cells; (3) that degenerative conditions are present in the heart muscle and other muscles of the body; (4) that some times one observes hyperaemia, infiltration, and haemorrhage in the brain and spinal cord but that these conditions are rarely severe enough to leave permanent effects; (5) that sudden death, during the disease or convalescence, results from the action of the toxin on the nervous apparatus of the heart. Murawjeff followed up his former observations by experiments on the action of the streptococcus. He injected under the skin or into the peritoneum of a guinea pig, 0·2 to 2·0 c.c. of such virulence that 0·1 killed a rabbit. This dose was repeated for 5 or 7 days - the only manifest result being that the guinea pig became thin. After 4 to 7 weeks it was killed by chloroform and the post mortem was made within two hours after death. The spinal cords and nerves were examined by his own formol methylene method and by Marchi's method. The cells showed no great change. The posterior columns of the spinal cord were very markedly altered in the dorso-lumbar region. The posterior nerve roots were also degnerated. A combination of streptococcus and diphtheritic toxin produced the/

the joint effects of both. Zeigler, in the 9th edition of his Lehrbuch der Pathologie states that diphtheria may cause spinal degeneration affecting the white matter, and he cites the analogous conditions which Tuczek and others have demonstrated in poisoning by Ergot and in pellagra. Donaggio, whose paper seems to be based on some joint work which he performed with Vasale, expresses the opinion that the nerve fibres are primarily affected; whilst the cells are not specially referred to. Babes has observed chromatolysis, vacuolation, loss of nucleus and nucleolus, vascular changes and increase of round cells. Enriquez and Hallion have recently made some experimental researches on the action of diphtheritic poison on the circulation and respiration. They conclude that the toxin paralyses the cardio-inhibitory centre, whilst in advanced stages the accelerans is stimulated. When the blood pressure is low, vaso-motor paralysis and weakness of the heart muscle occur, the irritability of the heart is also reduced. They think that the respiratory centre is also implicated. At the Meeting of the British Medical Association last Summer, Dr Woodhead introduced a discussion on post-diphtherial paralysis.

He/

He gave statistics of 7832 cases of certified diphtheria. Of these cases, 5068 had diphtheritic bacilli in the throat; 1362 suffered from paralysis. Of these cases, 1096 had been treated with antitoxin. In a smaller group, where the nature of the paralysis was carefully inquired into, [redacted] primary paralysis of the palate was recorded in 185 out of 494 cases. The eye muscles were primarily affected in 197; the muscles other than those of the eye, in 10 cases, the heart in 102 cases. The palatal cases occurred mostly between the 5th and 15th, the ocular between the 4th and 17th; the 10 muscular cases between the 10th and 14th; the cardiac cases mostly between the 5th and 10th, a few cases occurring as early as the second day: one as late as the 59th. And in reviewing these statistics he says- "It is evident then that in the human subject these "paralyses occur at a comparatively early date, although "in numerous cases they come on at very much later stages; "and one cannot help thinking that we have evidence of "the primary affection of the nerve cells, or of a "direct action of the poison on the muscular tissue in "the fact that cardiac paralysis occurs relatively at "so much earlier a period than other forms of paralysis."

Further/

Further on in the paper he states that he has examined two cords from experimental animals treated with full doses of toxine and that in one case the chromolysis and vacuolation of the cells was fairly distinctly marked, whilst in the other there was no perceptible deviation from the normal. In the discussion that followed this paper, Dr Mott stated that his opinion was that the poison acted on the whole neuron, especially upon the terminal arborizations of the dendron and the end plates. Professor Baginsky of Berlin announced that his assistant. Dr Katz, had examined the brain, spinal cord and peripheral nerves of cases of post-diphtheritic paralysis, and had found advanced degenerative changes in all parts of the nervous system - both nerve cells and nerve fibres.

During the present month (April 1899) Dr Judson Bury in his article in Clifford Allbutt's System of Medicine on "multiple neuritis," appears on the whole to pronounce in favour of his former view that the condition is primarily a a peripheral one. §Before passing ¶ to the question of the chemistry of diphtheritic toxin and antitoxin, it may be well to recapitulate very briefly, the changes which we have seen may occur in the cells of the anterior cornua/

cornua of the spinal cord. -

1. Chromatophilia and fragmentation of the protoplasmic processes may both be set down as a general rule to the imperfection of the methods employed in preparing the sections, and in fact wherever they are visible one must be on one's guard lest other associated appearances are also simple artifacts.

2. Physiological changes are probably expressed by alterations in the volume of the cells and the aggregation of Nissl's bodies,- the resting cell being described by Nissl as pyknomorphic, the acting cell as apyknomorphic. [see however discussion supra. p 18]

3. Pathological Changes. (a) Chromatolysis. The first stage in this process seems to be swelling of Nissl's bodies. Thereafter, either uniform diminution in their size occurs, or else the body fades irregularly and so assumes a condition of uniform sub-division. In severe cases the process may lead to very marked granular sub-division of Nissl's bodies. At a later stage, any of these changes may give place to an almost entire disappearance of the chromatic substance - this last being described as complete simple chromatolysis. The change may occur either throughout the whole cell, or, in certain regions. If it

begins around the nucleus one speaks of central chromatolysis, if the periphery of the cell is first affected, of peripheral chromatolysis, and if the condition occurs irregularly throughout the substance of the cell, of circumscribed chromatolysis. Diffuse staining of the achromatic substance which may occur along with chromatolysis is probably either the artifact (chromophilia) or is due to incomplete decolourization.

(b.) Vacuolation seems to be very characteristic of advanced structural changes in the protoplasm of the nerve cell. It is found as a late post mortem alteration, and also occurs from the action of certain toxins.

(c.) The nucleus and nucleolus may exhibit swelling, shrinkage with crumpling of the nuclear membrane, or eccentricity, as the result of morbid changes.

(d.) The cell as a whole may be swollen or shrunken when influenced by various poisons.

Recent views regarding Diphtheritic Toxin and Antitoxin.

It is not my purpose to enter fully into the chemistry of this subject, which indeed is so complicated that I am quite unable to do so profitably. My present/

present purpose is merely to recapitulate the views which have been expressed by several of the leading workers in this field.

Roux and Yersin in the Annals of the Pasteur Institute, and Professor Gauthier in his Treatise on Les toxines (1896) record a number of observations tending to show that the diphtheritic toxin is a diastase. It exhibits many of the reactions of these bodies, particularly so in the changes which heat effects upon it. Brieger and Fraenkel in the years 1890-91-92. published experiments which in their opinion showed that the toxin was an albuminoid body. Its toxicity, however, was 50 times less than that of the substance previously isolated by Roux and Yersin. In 1892, Guinochet communicated to the Society of Biology that he had cultivated the bacillus of diphtheria in urine which had been found free from albumen. From its culture he obtained an extremely toxic product which was perfectly free from all the albuminoid bodies. Within the last year, a most valuable paper has been published by Ehrlich, an abstract of which was given in the Journal of Pathology for December 1898,- in which he pointed out that diphtheria toxin is liable to a remarkable form of alteration on keeping, substitution products known as toxoids/

toxoids being largely produced. As these toxoids arise from toxins, and possess their combining powers, it is evident that they contain their combining elements in integrity, but that the toxic central nucleus has assumed an altered condition. Thus, toxoids may present an affinity for antitoxin either greater than, equal to, or less than that of the original diphtheria toxin. The result is that one has to reckon with those varied toxoids both in experimental work upon the toxin of diphtheria, and also in experiments with the antitoxin. Further details, however, of the paper must be sought in the original.

PART II/

PART II. EXPERIMENTAL.

It will be seen from the foregoing account that even now there is considerable variety of opinion as to the pathological changes in the nervous system which are attributable to the toxine of diphtheria; and when this research was commenced about five years ago, reliable information was still more scarce.

The following experiments have as their aim the determination of the changes, if any, which occur in the motor cells of the anterior cornua as a result of the action of the toxine and the antitoxine of diphtheria upon them. and incidentally of any other alterations which might occur in the spinal cord under their influence.

. It was from the first obvious that the problem which presented itself did not necessarily involve the securing of a picture of the state of the cells of the cord as they exist during life - which indeed is quite impossible to obtain.- The aim was rather to determine by the use of methods whose application would lead to constant end-products in the case of a living cell, firstly, the result of such a method on the healthy cell - paying particular attention to the amount of variation which exists within normal limits - and, secondly, the comparison/

comparison of these results with the appearances exhibited by diseased cells similarly treated. This principle has subsequently been insisted upon by Nissl who describes the result in either case as the "Nerve-cell-equivalent" of the corresponding condition. At the same time one is bound to consider that, other things being equal, the process which least alters the constitution or at all events the structure of the cell will best fulfil the requirements of the case.

In pursuance of this end a considerable number of methods were tried, some of which were found to be unsatisfactory and were soon abandoned whilst others seemed to meet the requirements of the case fairly well. Although even amongst the latter group one or two methods were distinctly superior to the others and were normally employed, reliance has not been placed exclusively upon them, the results yielded by the different procedures being used to check the conclusions which the normal ones seemed to suggest.

The following critique of the more important cytological methods employed may be of service to other workers -

A/

A. Fixation.

The importance of as perfect fixation as possible effected as soon as practicable after death is now recognised by all cytologists. With the view of determining the best process for the particular end in view - the fixation of the spinal stichochromes - the following were tried -

1. Mann's Method of fixation, by injection of the fixation fluid into the aorta.
2. Alcohol, as advised by Nissl.
3. Formalin.
4. Formalin and mercuride chloride.
5. Mercuric chloride.
6. Hermann's fixative.
7. Platinic chloride.

Mann's method, independently of the exact composition of the fixative fluid, proved unsatisfactory on three grounds, firstly, because during the necessary manipulation the spinal cord was dependent and therefore tended to become congested; secondly, even where the nerve elements were fairly well fixed it was impossible to draw any conclusions from the condition of the vessels, which were often dilated by the pressure of the injection fluid/

fluid; thirdly, whilst the brain was found well fixed in almost every instance it was practically impossible to secure uniform fixation of the spinal cord, as blood, or the saline solution which was used to drive the former from the vessels was seldom wholly got rid of. It therefore became necessary to abandon the method and to fix the structures after a preliminary dissection. 2. Alcohol as recommended by Nissl was tried but owing to the frequent occurrence of distinct shrinkage was dismissed as unsatisfactory. 3. Formalin in strengths of from 5 to 10 per cent was also tried, but was not wholly satisfactory, and so far as I can judge, after its use the staining tended to be less precise than that which was obtained by the use of mercuric chloride. 4. Ewing has recently recommended the employment of a mixture of formalin with mercuric chloride and his figures show that in his hands the method was successful for the most part. The writer has also used it with some success, owing to the penetrative power of the formalin; at the same time, the advantage which it can offer over simple formalin fixation is but slight as the mercuric chloride is very quickly decomposed and precipitated from the solution. 5. I was therefore led/

led to employ as the standard medium of fixation, a saturated solution of mercuric chloride in normal saline solution. 6. Occasionally, in order to check the results obtained by this, I employed Hermann's fixative mixture which contains 1 per cent platinic chloride, 15 parts; glacial acetic acid, one part; and 2 per cent osmic acid, 4 parts. This fixative I found extremely reliable - the chief objection being that the outer portions of the specimen tend to become blackened. Nissl's bodies after its employment, seemed rather smaller and more finely granular than when mercuric chloride was used. 7. On some occasions I also made use of a solution of platinic chloride. I found that its general effect was not unlike that of corrosive sublimate but the subsequent staining was less precise.

B. Imbedding and cutting. After fixation the specimens were very thoroughly washed in running water and carried with great care through a series of graded alcohols and chloroform, after which they were embedded in paraffin. Sections were cut of various thicknesses from two to eight teeth of the Rocker Microtome. The thinner sections are specially valuable in the determination of detail, but present a somewhat more variable appearance than those of greater thickness. After the sections/

sections were cut they were floated out on water, after Gulland's method; the very thin sections generally require colder water than those which are less delicate. When arranged on the slide the latter is left for from 12 to 24 hours in an incubator whose temperature is well below that of the melting point of the paraffin, thereafter the paraffin is melted by the application of further heat, and the slide dropped into a tube of Xylol which should be frequently renewed . The mercuric chloride is thoroughly washed out of the tissues by free supplies of alcohol containing a trace of iodine and the sections are then ready for staining.

C. Staining. The chief stains used belonged to the aniline group: (1) one of the best proved to be toluidin blue which I found extremely precise in its results and comparatively easy to work with, whilst it seemed fully as permanent as any of the others. The specimen as a rule was stained for about 10 minutes in ¼ per cent watery solution, it was then washed in water, decolourised in alcohol - this process being controlled by the use of the microscope,- cleared in xylol, and mounted in Canada Balsam, (2) Thionin blue was also used but was much less precise in its staining qualities. (3) Unna's Polychrome Methylene Blue, which

gives/

gives a most exquisite differential stain for the various structures of the spinal cord, often proved disappointingly evanescent, although fresh specimens of the stain were repeatedly obtained from Grübler; whilst the different samples were by no means uniform in their action. Bismarck Brown was occasionally employed but possessed no advantages over the stains mentioned. (4) A stain named Kernschwarz, although giving less brilliant pictures than toluidin blue or methylene blue, is fairly permanent and would probably prove better for photographic purposes than either of the former. It is, however, more diffuse in its action. (5) M. Heidenhain's iron haematoxylin, either alone or in combination with saffranin as recommended by Bühler was useful in determining some of the finer structural conditions in the nerve cells. (6) One of the best methods was a modification of Held's methylene blue and erythrosin double stain. I employed the methylene blue before the erythrosin instead of after it as recommended in the original paper, because a mixture of these two stains produces a granular precipitate which is insoluble in methylene blue, and soluble in erythrosin.

The following are the details of the process as/

as I have latterly employed it.

The sections, fixed to the slide in the usual manner, are covered with a fluid prepared immediately before use by mixing equal parts of a solution of methylene blue in distilled water (0·375%) and of 5% watery solution of acetone. This is carefully warmed until all odour of acetone has disappeared, it is then allowed to cool and the sections are washed in water. It is thereafter stained for 5 or 10 seconds in a solution containing 1 gramme of erythrosin in 150 c.c. of distilled water to which a couple of drops of glacial acetic acid have been added, and again washed in distilled water. Differentiation is effected by means of alcohol, the process being controlled under the microscope, and after clearing in xylol the specimen is mounted in Canada balsam.

As to Nissl's special method I have never found it necessary to use an alkaline soap as a mordant, nor do I think that the other troublesome technicalities with which the method is burdened, exert any appreciable influence on the precision of the results, and I would rather lay emphasis on care and experience in carrying out the ordinary details of the methods above enumerated.

In/

In addition to cytological methods those of Golgi and Marchi were employed. Their details are well known and need not be further described.

In considering the results of experiments on the action of a given toxin one must always remember, as has already been stated, that the limits of variation compatible with health must be determined before concluding that the changes which may be seen really result from the poison employed. In view of this it was necessary to determine the limits of variation which are found in the spinal cord of apparently healthy rabbits, and it also soon became obvious that as death not unfrequently occurred through the night or at times when the laboratory was closed, a preliminary study of the post mortem changes likely to occur under the precise conditions of the main group of experiments was indicated. The normal variation was determined by the examination of the spinal cords of seven healthy rabbits, and the series thus obtained showed - (1) That the motor cells found in the anterior cornua have when in health a characteristic and well-defined appearance. (Fig 1)

The chromatic substance stains sharply and is disposed in/

in oblong or spindle shaped masses tending to run parallel to the boundaries of the cell, and entering all the protoplasmic processes but being absent in the axis cylinder process and immediately adjacent portion of the cell body. The chromatic masses have well defined boundaries, which do not present an eroded aspect, and the granular structure of Nissl's bodies is usually invisible or at least indistinct except under high magnification and in the case of very thin sections. The achromatic substance when stained by erythrosin fails to show any definite structure even under high magnification.

The nucleus contains but little basichromatin, and is best demonstrated by an acid stain such as erythrosin, when the structural arrangements become distinct. The nucleus as a rule contains one nucleolus, but in some instances two or more are visible. In addition to the nucleoli some small masses of chromatin are occasionally visible within the nucleus. The nuclear membrane is often scarcely visible in the normal cell but quite evident when morbid processes have induced chromatolysis. The size of the anterior cornual cells varies in the rabbit, as observed by myself in a number of instances they ranged between 40 and 100 microns/

microns in their greatest length, the majority of them lying between 60 and 80 microns.

Chromophilia was rarely visible in any cells from normal spinal cords provided fixation had been satisfactory, and in my later work I was able to obtain good fixation in almost every instance.

(2) In addition to furnishing a series of standards with which to compare morbid cells, the "normal" series was also very useful as affording a criterion for the ordinary size and appearance of the blood vessels of the cord.

The specimens prepared to demonstrate post-mortem changes are in my opinion of considerable importance. Under this head, three groups of experiments were conducted. In the first group, which was the most important for the purpose of my subsequent research, 6 rabbits were killed and left in their cages at the ordinary temperature of the animal house, which is moderately warmed by hot pipes, for 6, 12, 18, 20, 24 and 30 hours respectively. Portions from the lumbar and cervical regions of the spinal cord, from the brain, and from the peripheral nerves, were then dissected out, fixed by mercuric chloride and stained

by/

by several of the various methods already enumerated. No changes of any importance could be detected in the first four specimens. In the fifth specimen, however, - in which death had occurred 24 hours before fixation - very notable alterations had manifested themselves. The achromatic substance tended to stain faintly, Nissl's bodies were slightly swollen, irregular, rather more granular than usual, and instead of their margins appearing sharp they presented an eroded aspect, whilst in many cells large clear vacuoles were distinctly visible. Since the first distinct alteration only occurs about 24 hours from the time of death, one may conclude that in all probability animals which have died through the night may safely be used on the following morning. [Fig 2]

In the second group, portions of the spinal cord were removed, placed in normal saline solution and kept either in ice or at the temperature of the room for varying periods. A test specimen was also prepared which showed that immediately after death the normal appearances of the spinal cord were present in this instance. Of the series placed in normal saline and kept in ice, a specimen which remained for one hour/

hour before fixation showed no distinct change; another which was left for two hours exhibited slight granular disintegration of Nissl's bodies in a few of the cells; a specimen which was left for four hours showed moderate granular disintegration of Nissl's bodies and very slight commencing vacuolation.: a specimen which was left for 8 hours showed the same type of disintegration and in addition more marked vacuolation. A specimen which had remained 24 hours before fixation showed advanced chromatolysis, (the granular disintegration having progressed to a very marked degree,) - pronounced vacuolation, and, apparently, disappearance of some of the cells. The specimens which were left in normal saline at the temperature of the room showed similar changes but the alterations progressed somewhat more rapidly.

The third series of experiments was conducted on a rabbit which after death was placed in ice for 12 hours after which, the lumbar portion of the spinal cord was removed with as little disturbance as possible of the upper portion of the vertebral canal. After 24 hours, the cervical portion of the spinal cord was removed. In the first specimen, no distinct change could be detected; in the second, granular degeneration was seen/

seen in some of the cells though the condition was only slightly marked: the achromatic reticulum showed a slight tendency to take on the stain but the unformed achromatic substance remained perfectly clear; no vacuolation was present. From this experiment it was obvious that any attempt to treat the spinal cord outside the body before fixation was liable to be fraught with the production of serious artifacts which would confuse the issues of the experiment. It also appeared that the appearance of post mortem changes was influenced to a certain degree by the temperature at which the spinal cord was kept - changes occurring in it more rapidly at highest temperatures, and being retarded when the temperature was near the freezing point.

Before commencing the main experiments on the action of diphtheria, I undertook some preliminary investigations on the effect of lead poisoning, - the lead being administered by the mouth, along with food - and also in two instances I had an opportunity of observing the effect of tetanus toxine on rabbits. In the cases where lead was employed, I found changes which closely correspond to those that have been described by Nissl. Chromolysis is well marked and, on the whole, appeared to affect the peripherally constituted Nissl's bodies earlier/

earlier than those which surround the nucleus. The nucleus remained central, it did not exhibit any very marked change, but owing to the disappearance of the surrounding chromatic elements, the nuclear membrane was seen with unusual clearness. It appeared in the course of the experiments that rabbits are peculiarly refractory to the influence of lead administered by the mouth; and it was only in one or two instances, after the administration of enormous doses for prolonged periods, that any symptoms of paralysis were detected. In the case of the rabbits which were subjected to tetanus toxine, the symptoms appeared in one case 5 days after the administration of the first, and two after the administration of the second dose of the toxine. The effect of the poison was most marked on the hind limbs of the animal. It was killed at an early stage of the disease. In the other case, the symptoms also occurred 5 days after the administration of the first, and 2 days after the administration of the second dose of poison. In both instances, the changes which were found corresponded to those referred to in the account of Goldscheider & Flatau. I was unable to discover any indication of increase in the volume of the nucleolus. This was probably due to the fact that the rabbits were not/

not killed at a sufficiently early stage of the disease. The nucleus also exhibited no marked alteration from its normal appearance - the principal change consisting in an early phase of chromatolysis. Nissl's bodies were swollen, and presented an eroded outline and granular aspect. They seemed in some cases to be particularly affected in the protoplasmic processes, but I was unable to identify any marked difference between their appearance in the peripheral and perinuclear portions of the cell body. See Figs. 8, 9, and 10.

My experiments on diphtheritic paralysis and subjects immediately related to it fall into 7 groups.-

1. In the first of these, 4 rabbits were injected subcutaneously with 4 emulsions of diphtheria bacilli of varying degrees of virulence. Three survived and manifested no symptoms whatever. The 4th died in 10 days, symptoms only occurring within a day of the fatal issue. No nerve lesion was observed before death, and the spinal cord was free from any marked appearance.

(D^a, D^b, D^c, D^d)

2. In the second group, which includes two series of injections, doses of toxine considerably below the lethal dose were given at intervals of several days.

It/

It was found that tolerance was established so that eventually a large dose could be borne. In these cases no paralytic phenomena were discovered during life, whilst after death no pathological change was detected in the cells or other structures of the spinal cord.

(D^2 D^3)

3. In the third group, the rabbits received one or two large doses of toxine. Death resulted in 4 cases in one day, in five more within two days, 3 cases died on the third day, three on the fourth, ~~1 on the fifth,~~ 1 on the 6th, 1 on the 7th, and one during the second week. One case survived altogether and several other cases are not included in the record because of circumstances which vitiated the experiment. In this group, none of the rabbits dying within the first three days exhibited any paralytic phenomena unless perhaps in the case of D33 and D10. Two at least of the three cases dying on the fourth day were observed to have a very slight degree of weakness of the limbs on that day but I feel uncertain whether this was anything more than the natural weakness which precedes death. The rabbit which died during the second week was not observed to suffer from any weakness of the hind limbs when the laboratory was closed on the previous evening. Beyond

a/

a slight swelling of Nissl's bodies in some of the above cases, which might be rather due to the general effects of the disease on the animal than to any special local influence which the poison exerted on the nerve cells, the microscope generally revealed little or no change in the spinal cord. In some instances, however, a few of the anterior cornual cells - especially those belonging to the commissural groups* showed some fading of the chromatic substance. This condition is occasionally seen in spinal cords removed from normal rabbits, but in the latter case I have never observed it occur to the same extent. In some of the later experiments the cells have also been examined by Golgi's method, but this process revealed no abnormality.

(D26, D27, D33, D38; D7, D28, D34, D35, D9, D8^{b}, D15; D37; D8^{a}, D5, D10; D4; D6; D1; D25.

4. The fourth group includes those cases where the toxine was administered according to the principle of sub-acute maxinal intoxication. So far this method has been adopted in three cases. The rabbits developed paralytic symptoms rather suddenly about the close of the first week and died soon after the paralysis had become well marked. The affection was most distinctly marked/

* See figures 7 & 13.

marked in the hind limbs, curiously enough the right side was more affected than the left in each case. An examination of the spinal cord yielded the following appearances :-

(a) Grey matter. Many of the cells in the anterior cornual group were abnormal and presented two types of morbid alteration. Some cells were slightly swollen, Nissl's bodies presented the appearance of somewhat advanced disintegration, the achromatic substance stained but faintly with erythrosin, the nucleus and nucleolus appeared to be normal, and the nuclear membrane which, owing to the disappearance of much of the chromatic substance of the cell body was often unusually conspicuous, was not crumpled. Some cells on the other hand were altered in a very peculiar manner. They were markedly shrunken, Nissl's bodies were not very much affected at first sight, but considering the reduced volume of the cell the amount of chromatic substance which it contained was probably diminished, the achromatic substance took on the stain with unusual intensity, whilst many of this group of cells exhibited vacuolation of the protoplasm in a most marked degree.*

I have been unable as yet to prepare specimens of these/

*See Figures 3, 4, 5.

these cells treated by Golgi's method, as sufficient time has not yet elapsed for their preparation.

(b) White matter. Marchi's method so far as I have been able to apply it up to the date of writing, has revealed no degeneration in the white columns of the cord. (see appendix)

(c) Vascular changes. In all these cases, the capillaries have appeared to be dilated. In one at least of them actual haemorrhage has occurred into the substance of the spinal cord.

(D42, D43, D45.)

5 In the fifth group will be found cases where both diphtheria toxine and diphtheria antitoxine have been administered. This series of experiments is still incomplete but so far the facts which I have observed have been -

(a) In three cases where the antitoxine was insufficient in strength to protect the rabbits from the full influence of a large dose of the toxine, death occurred within 24 hours without any paralytic symptoms. Microscopic examination of the spinal cord failed in these cases to disclose any abnormality.

(b) In one case where after the administration of antitoxine/

antitoxine in sufficient quantity to protect the animal, the latter was killed 24 hours after the injection. No symptoms occurred during life nor was any change detected in the spinal cord.

(c) In two cases in which under similar conditions the rabbits were killed 48 hours after injection, no symptoms had appeared during life, nor was any morbid appearance detected in the spinal cord after death.

Further experiments are at present being conducted, in which one or several doses of toxine, along with a sufficient amount of antitoxine to prevent its lethal action, are administered with the view of ascertaining whether paralysis may supervene at a later period. The observations are not sufficiently advanced as yet to permit of any report being submitted.

(D29, D30, D31, D32, D36, and D39)

6. Only one experiment has yet been made in the sixth group. In view of Murawjeff'sassertion that paralytic changes almost identical with those produced by diphtheria toxine may result from the employment of antitoxine, I have arranged for a series of cases in which large doses of the latter may be administered. In the one case which I can record, a rabbit received 1350 units of/

of Behring's antitoxine within four days during last March, and this month the same rabbit has within a week received as much as 6000 units of Burroughs Wellcome & Co.'s antitoxic serum. It is still in perfect health, no abnormal consequences whatever having been observed

(D44)

7. The seventh group has been devised to investigate the accuracy of Uhlenhuth & Moxter's statement regarding paralysis following the injection of ordinary serum. For this purpose I have injected a rabbit on five occasions within a week with from 20 to 30 c.c. of blood serum obtained from the Slaughter House, taking the precaution to render it sterile by filtration through a Pasteur-Chamberland bougie. Beyond some slight acceleration of the rate of breathing during and for a short time after the injection, absolutely no symptoms have occurred. The quantity of serum used being vastly in excess of that of the fluid employed in the toxine and antitoxine experiments one may assume that the phenomena observed in these did not result from any action of the serum itself apart from the influence of the toxic or antitoxic elements which it contained. (D47)

With regard to Uhlenhuth & Moxter's experiments, one cannot help thinking that the paralysis must either have/

have resulted from general changes of vascular origin, caused by an extravagantly large addition to the fluid circulating in the blood vessels, independently of the nature of the added fluid, or else to the presence of septic organisms and their products in the serums which these observers employed.

On Murawjeff's antitoxine observations I do not yet feel justified in expressing any decided opinion. My own limited observations have so far failed to confirm his statements, whilst the clinical opinion that since antitoxine treatment has been introduced, paralysis has become commoner (compare Lewin "Nebenwirkungen der Arzneimittel," 3rd edition, page 398) is obviously open to other interpretations than that which Murawjeff would suggest. It is, however, probable that, in cases of diphtheria, death may be warded off by the displacement of combined epitoxoids in the anti-diphtheritic serum by free diphtheria toxine from the patients blood, and the epitoxoid so liberated though less dangerous to life may still be able to set up changes in the nerve structures, and so may induce paralysis. It is even conceivable that substances may exist in the blood of persons who are not suffering from diphtheria at all, which/

which possess power to liberate some at least of these epitoxoids from their combination, and thus, indirectly, antitoxine might cause paralysis. This, however, is for the present, matter of pure speculation.

In the foregoing experiments I have repeatedly attempted to ascertain whether changes in the fibrillary structures of the nerve cells also occurred in consequence of the action of the toxines. So far, however, although various methods were attempted for their demonstration, I have been unable to see these fibrils most likely because the motor cells of the rabbits spinal cord are not favourable for this research.

Clinical Case.

I also had an opportunity a few months ago, at the Royal Hospital for Sick Children, of studying a case of post-diphtheritic paralysis which was under the care of Dr Playfair, and as the case terminated fatally I was able to examine the cells of the spinal cord also. The following is a brief account of the case :-

J. L. aged $2\frac{11}{12}$th years. [Fig. 6.]

History.- Patient caught a bad cold 4 weeks before admission. He coughed a good deal but was not confined to bed and did not complain of sore throat. Two weeks before admission his mother noticed that he stumbled

on/

on walking, and his knees seemed to give way below him. One week before admission, his speech became affected, its character was nasal and he spluttered when drinking.

State on admission.-December 5, 1898. The child is well nourished. There are no abnormal surface conditions. Nervous System.- There were no abnormal sensations. Sensibility normal, superficial reflexes present, knee jerks both absent. Motor functions.- No apparent atrophy of limbs, but some loss of power in lower limbs. Gait ataxic, & Slightly staggering, worse when his eyes are shut. Organic reflexes all normal, except swallowing which is impaired. Speech. nasal; soft palate, drooping; throat insensitive; eyes staring, ocular reflexes and fundus oculi normal. Ocular Muscles - External recti paralysed. Dr Argyll Robertson detected also slight deficiency of upward movement. Electric reactions. The faradic current was employed, and was found to yield perfectly normal reactions although the muscular power was evidently diminished. This indicated that either the paralysis was due to some lesion of the upper neuron, or else that the affection of the lower neuron was not uniformly affecting all the motor cells but at most producing destruction or injury to some of them in a scattered manner.

Post/

Post mortem examination.- The heart contained fluid blood, both lungs were congested, the upper part of the right being collapsed, the larynx was free from any membrane, the fauces showed nothing abnormal. Swabs taken from the larynx, on examination at the Royal College of Physicians Laboratory gave evidence of the bacillus of diphtheria. The brain was reported to have presented no abnormalities. At the close of the post mortem examination I had an opportunity of securing a portion of the lumbar cord which was alone available. Immediately after its removal from the body it was divided into thin portions and was fixed in the ordinary saturated solution of mercuric chloride in normal saline solution, and carried through the usual processes which have already been detailed. The sections were stained in various manners the most important stains being toluidin blue, and methylene blue with erythrosin. With the former, I failed to detect any conspicuous change in the motor cells. A condition, however, was observed in the cells of Clarke's column which differed greatly from the appearance presented in the rabbit. Here, they frequently exhibited a most eccentrically situated nucleus, whilst Nissl's bodies instead of being regularly distributed through the cell seemed to be few in number

and/

and were crowded into its extreme periphery. This not unnaturally suggested that one had to deal with a central chromatolysis, whilst the associated eccentricity of the nucleus led one to think of "Axonal degeneration" which results from a primary lesion of the nerve fibre. This conclusion, however, is erroneous. The condition described is common enough in Clarke's column cells in the human spinal cord, and it occurs quite apart from any disease of the nervous system. I am indebted to Dr Robertson of the Asylum's Laboratory for having directed my attention to this peculiarity of these cells, and for permitting me to examine some of his specimens which confirmed this view. The double stain, however revealed that in the motor cells of the anterior cornua vacuolation was occasionally present and in these specimens I also saw occasional early chromolytic changes such as occurred in the rabbits which died paralysed after the exhibition of diphtheria toxine. Slight haemorrhage into the cord was also noted. Still, a large number of the cells remained healthy, so far at least as microscopic examination could determine; and this may be the explanation of the persistence of response to faradism which was manifested during life at a period subsequent to the onset of very well marked paralysis. Unfortunately, material/

material was insufficient for the preparation of specimens by Marchi's method, the ataxic symptoms being such as to suggest that changes have been found in the white ~~motor~~ of the posterior columns of the nature which has been described by Bikeles.

RESUMÉ.

In conclusion, I may sum up the facts which I think may be asserted with regard to diphtheritic paralysis. Diphtheritic paralysis is associated not only with changes in the peripheral nerves but also with alterations in the spinal cord itself. Of the latter, cellular changes are the most characteristic. They may, however, be associated with vascular ones. The changes are very definite and consist in chromatolysis to a moderate degree, and in increased staining capacity of the achromatic substance for acid stains, and vacuolation of the cell protoplasm. In this connection I would be inclined to support Nissl's opinion that each toxic substance has a somewhat specific action on the nerve cells, and whilst it is probably impossible to tabulate the effects produced in such a way that one could/

could definitely argue back from them to the toxine which caused them, still, there are more or less marked divergence in the action of different groups of toxic agents. Thus with each of the three on which I have recorded observations in this paper,—lead, tetanus toxine and diphtheria toxine, the aspect of the affected cells differs in several respects. In diphtheritic paralysis the cell change is probably antecedant to the nerve change in the majority of cases. This, however , requires further investigation, and I am at present conducting experiments in the hope of elucidating the problem, but my results are not yet ready for tabulation.

RECORDS/

Records of Experiments.

I.

Injection of Cultures of Diphtheria.

Rabbit Nr. Da. — **Culture of very slight virulence.**

1895. Nov. 8. Inoculated with above culture. No symptoms. Rabbit survived.

Rabbit Nr. Db. — **Culture of slight virulence.**

1895, Nov. 8. Inoculated with above culture. No symptoms. Rabbit survived.

Rabbit Nr Dc. — **Culture of moderate virulence.**

1895, Nov. 8th. Inoculated with above culture. No symptoms. Rabbit survived.

Rabbit Nr Dd. — **Culture of decided virulence.**

1895, Nov. 8. Inoculated with above culture.

Nov. 18. Rabbit died. Before death it exhibited no paralysis. No alterations were observed in the spinal cord.

II/

II. Injection of Diphtheria Toxine.

Rabbit Nr D2. Weight 1700 g.m. Toxine No.1 Intervals.

1895.	April 26.	0·2 c.c. of Toxine injected.	
	May 2.	0.2 c.c. "	5 days.
	May 7	0.2 c.c. "	5 "
	May 14	0·4 c.c. "	7 "
	May 21	0.6 c.c. "	7 "
	May 29	1.0 c.c "	8 "

Animal showed no symptoms and became more or less immune. Weight risen to 2150 gm.

Rabbit No.D3. Weight 1500 gm. Toxine No.1.

1895.	Apl. 26.	0.1 c.c. of Toxin injected.	Intervals.
	May 7.	0.2cc. "	11 days
	May 14.	0.4 cc. "	7 "
	May 21.	0.6 cc. "	7 "
	May 29	1.0 cc. "	8 "

No symptoms. Weight risen to 1700 grammes.

Rabbit. Nr. D5. Weight 1850 gm. Toxine Nr 2.

1895	Dec. 17.	0.75 cc. of Toxine injected.
	Dec. 20.	Rabbit found dead in morning. No symptoms on previous evening. No abnormality in spinal cord.

Rabbit Nr. D7. Weight 2450 gm. Toxine Nr. 2.

1895. Dec. 17. 1.5 cc. of Toxine injected.

Dec. 19. Died at Midday. No paralysis.

No abnormality in spinal cord.

Rabbit Nr D 8a. Weight 1850 gm. Toxine Nr 2.

1895. Dec. 17. 10 cc. of Toxine injected.

Dec. 20. Died at midday. No paralysis. No

abnormailty in spinal cord.

Rabbit Nr D4. Weight 3170 gms. Toxine Nr 2.

1896. Jan. 16 0.75 of toxin injected.

Jan. 22. Died suddenly; no paralysis.

Spinal cord, normal.

Rabbit Nr D6. Weight 2800 gm. Toxine No.2.

1896. Jan. 16. 0. 5 cc. of toxine injected.

Jan. 23. Died. No paralysis; spinal cord, normal.

Rabbit Nr D 1. Weight 2010 gms. Toxine Nr 2

1896 Jany 16. 0.3 cc. of toxine injected.

Jany 28. Found dead. Not examined post mortem.

Rabbit Nr. D9. Weight 2020 gm. Toxine Nr. 3.

1897. May 31. 1·0 cc. of toxine injected.

June 4. Died. Very slight weakness noted in

hind limbs for a few hours before

death. Spinal cord normal.

Rabbit Nr. D8b. Weight 2010 gm. Toxine No.3.

1897. May 31. 1.0 cc. of toxine injected.

June 4. Died. Slight weakness in hind limbs for a few hours before death. Spinal cord, normal.

Rabbit Nr. D.10. Weight 2070 gms. Toxine No.3.

1897. June 21. 0.6 of toxine injected.

June 24. Died during night. Very slight weakness observed previous evening.

Rabbit Nr D15. Weight 1850 gms. Toxine Nr. 4.

1897. Oct. 6. 0.1.cc. toxin injected.

Oct. 10. Died during night: slight weakness perhaps present previous evening.

Rabbit Nr D.25. Weight Toxine Nr.5.

1898. June 2. 0.3 cc. of toxine injected.

No symptoms. Spinal cord normal.

Rabbit Nr. D.26. Weight 1742 gms. Toxine Nr.6.

1898. Sept. 6. 0.6 cc. of toxine injected.

Sept. 7. Died. No paralysis. Spinal cord, slight chromatolysis.

Rabbit Nr. D.27. Weight 1625 gms. Toxine Nr.6.

1898. Sept .6. 0.3 cc. of toxine injected.

Sept. 7. Died. No paralysis. Spinal cord, normal.

Rabbit Nr. D.28. Weight 1865 gms. Toxine Nr.7.

1898. Sept. 8. 0.4 cc. of toxine injected.

Sept. 10. Found dead in morning: no paralysis on previous evening. Spinal cord, slightly affected. [Fig 7.]

Rabbit Nr. D 33. Weight 1235 gm. Toxine Nr. 7.

1898 Sept. 27. 0.5.cc. of toxine injected.

Sept. 28. Died. Slight weakness of limbs shortly before death. Spinal cord, normal.

Rabbit Nr. D 34. Weight 2135 gms. Toxine No.7.

1898. Nov. 21. 0.5 cc. of toxine injected.

Nov. 23. Found dead in morning. No weakness on previous evening. Spinal cord, some cells slight chromatolysis.

Rabbit Nr. D 35. Weight 2230 gms. Toxine Nr. 7.

1898. Nov. 21. 0.5.cc. of toxine injected.

Nov. 23. Found dead in morning. No eakness on previous evening. Spinal cord, very slight chromatolysis?

Rabbit Nr. D. 37. Weight 2280 gms. Toxine Nr. 7.

1898. December 29. 0.5. of toxine injected.

December 31. Died. no paralysis. Spinal cord, slight changes.

Rabbit Nr. D.38. Weight 1760 gms. Toxine Nr.7.

1898. Dec. 29. 0.5 of toxine injected.

Dec. 30. Died. No paralysis. Spinal cord, very slight chromatolysis.

Rabbit Nr. D 42. Weight 1450 gm. Toxine Nr.7.

1899. Mar. 13 0·1 cc. of toxine injected.

" 14 0.1 cc. "

" 16 0.1 cc. "

" 17 0.1 cc. "

" 18 0.1 cc. "

" 20 0.2 cc "

" 22.

2.30 p.,m. paralysis in hind limbs

5 0.p.m. died (weight 1480 gm)

Spinal cord. Changes observed.

Rabbit Nr. D.43 Weight 1600 gms. Toxine Nr.7.

1899. Mar. 13 0.2 cc. of toxine injected.

14 0·2 cc. "

16 0·2 cc. "

17 0·2 cc. "

18 0·2 cc. "

20 0.4 cc. "

21 0.4 cc. "

22/

Mar.22. 0.4 cc. of toxine injected at 10.30 a.m.

2.30 p.m. No symptoms.

6 p.m. slight paralysis of hind limbs.

23. 10 a.m. Found dead (Weight 1500 gms) Spinal cord. Changes observed.

Rabbit Nr. D 45. Weight 1570 gms Toxine Nr. 7.

1899. Mar. 14 0.3 cc. of toxine injected.

16 0.3 cc. "

17 0.3 cc. "

18. 0.3 cc. "

20 0.6 cc. "

21 0.6 cc. "

22. 0.6 cc. " at 10.30 a.m.

2.30 p.m. paralysis in hind limbs.

4.45 p.m. died (Weight 1520gm.) Spinal cord. Changes observed.

Index/

Index to Toxines employed.

Nr.	Source.	Toxicity.
1	R.C.P.E.Laboratory.	0.2 cc.killed guinea pig of 580 gm. in 8 days.
2.	"	0.5 cc. " 540 gm. in 3 days
3.	"	0.4 cc. " 500 gm. in 2 days.
4.	"	0.5 cc. " 500 gm. in 4 days
5.	"	0.2 cc. " 560 gm. in 3 days
6.	"	0.2cc. " " "
7	Messrs Burroughs Wellcome & Co;	undetermined toxicity.

The last of these was much the best toxine, and appeared perfectly transparent, straw coloured, and free from all sediment.

III.

Injection of Toxine and Antitoxine.

Rabbit Nr D 29. Weight 2295 gm. Toxine No.7.

1898. Sept. 15. 0.6 cc. toxine injected at 11 a.m.

1.0.cc. antitoxine previously prepared in Laboratory of R.C.P.Ed. injected at 2 p.m.

The rabbit survived until 20th September when it was killed. No symptoms. Spinal cord normal.

Rabbit Nr D 30. Weight 2085 gm. Toxine Nr 7.

1898. Sept. 15 0.6 cc. toxine at 11 a.m.
1.6 cc. antitoxine (as above) at 5.30 p.m.

Sept. 16. Found dead in morning. Spinal cord normal.

Rabbit Nr. D 31. Weight 1872 g.m. Toxine Nr.7.

1898. Sept.27 0.5 cc. toxine at 10.30 a.m.
1.0 cc. antitoxine (as above) at 3 p.m. Survived : no symptoms. Killed in 48 hours. Spinal cord, normal.

Rabbit Nr. D.36. Weight 2190 g.m. Toxine No.7

1898. Dec. 29. 0.5.cc. toxine at 11.30 a.m.
60 units Behring's antitoxine at the same hour.

Dec. 30. Died in morning, about 21 hours after injection. No paralysis. Spinal cord, normal.

Rabbit Nr.D.39. Weight 2120 g.m. Toxine No.7.

1898 Dec. 29. 0.5 c.c. toxine at 11.30 a.m.

30 units Behring's antitoxin at 3 p.m.

Dec. 30. Died in 20 hours after injection

No paralysis.

Spinal cord, slight chromatolysis.

IV.

Antitoxine alone.

Rabbit Nr. D.44. Weight 1650 gm.

1899. Mar. 14. 500 units Behring's antitoxine

16 500 " " "

17 375 " " "

No symptoms. Weight 1640 grammes.

Apl. 8. 1500 units Burroughs & Wellcome's Antitoxine Series 79.

11. " " Series 78.

12 " " "

13 " " "

No symptoms. Weight April 8, 1950 gm.

April 12, 1930 "

V.

Blood Serum.

Rabbit Nr. D.47. Weight 1950 gms.

1899. April 6. 20 cc. Blood serum from Slaughter House.

8. 30 cc. "

10 30 cc. "

11 30 cc. " "

12 30 cc. "

No symptoms.

VI.

Tetanus Toxine.

Rabbit Nr.15 a. Weight 2380 gm.

1897. Nov. 19. 1 cc. of 1 in 50 dilution of Tetanus toxine.

22 1 cc. of 1 in 10 " "

No symptoms. Rabbit survived.

Rabbit Nr.16a. Weight 1950 gm.

1897 Nov.19 1.5 cc. of 1 in 50 dilution of Tetanus toxine.

22. 1.5 cc. of 1 in 10 " " "

24. Slight jerkings in hind limbs occasionally.

Nov/

Nov. 25. Distinct tetanic spasms in hind limbs when animal is moved.

Killed. Spinal cord;- changes observed in Nissl's bodies.

Rabbit N^{r}18a. Weight 1820 gms.

1897. Nov. 19. 2.0 cc. of 1 in 50 dilution of Tetanus toxine.

Nov. 22 2.0 cc. of 1 in 10 " " "

Nov. 23. Slight jerkings in hind limbs.

Nov. 24. Distinct tetanic spasms can be induced in hind limbs.

Killed. Spinal cord :- changes observed in Nissl's bodies.

ADDENDUM.

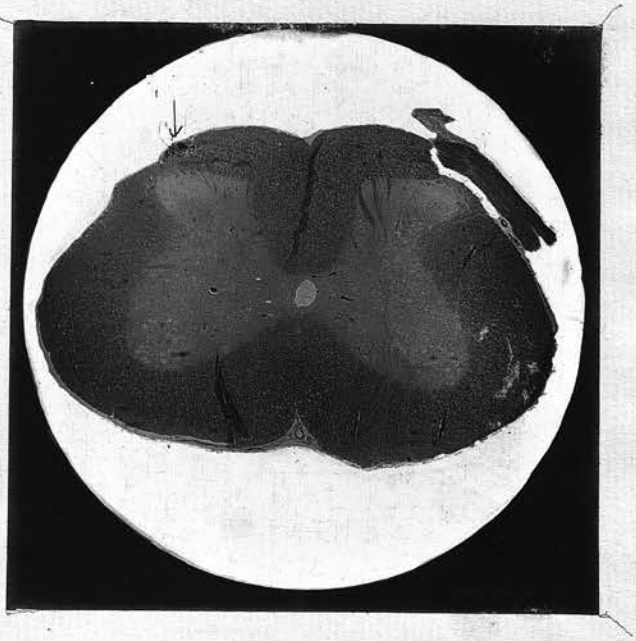
April 25th, 1899.

One of the specimens taken from a rabbit which died with marked diphtheritic paralysis has now been prepared by Marchi's method. As will be seen from the photograph subjoined distinct changes have occurred [redacted] in the posterior columns, especially in part of Lissauer's tract. This is interesting as, so far as I am aware, exactly analogous changes have not been described - at least under conditions which preclude the possibility of streptococcic infection. The alteration probably affects the nerve root in that region, but until further observations confirm this one it is recorded with all reserve, as the appearances may result from accidental causes.

H.R.

From Case of Diphtheria in a rabbit.

Preparation made by Marchi's method.



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The following list does not aim at offering a complete bibliography of the subjects referred to in the Thesis. Of the older papers only those important for the present purpose are recorded; more than this being rendered superfluous by the full bibliographies supplied by Bühler, Goldscheider and Flatau, James Ewing, S.E. Jelliffe, van Gehuchten, and Lenhossèk.

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