On the pathology and bacteriology of Landry's paralysis / by E. Farquhar Buzzard.

With the author's compliments

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On the Pathology and Bacteriology of Landry's Paralysis

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E. FARQUHAR BUZZARD, M.D., M.R.C.P.

Assistant Physician to the Royal Free Hospital, and to the Belgrave Hospital for Children, and Pathologist to the National Hospital for the Paralysed and Epileptic

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Assistant Physician to the Royal Free Hospital and to the Belgrave Hospital for Children, and Pathologist to the National Hospital for the Paralysed and Epileptic.

The following paper was read at a meeting of the Neurological Society on April 2, 1903, and comprises :—

(1) A brief, critical review of our present knowledge of the pathology and bacteriology of Landry's paralysis.

(2) The record of an investigation of a fatal case of the disease, including :—(*a*) the isolation from the blood of a micrococcus which does not conform with any previously-described organism; (*b*) its discovery in the dura mater of the patient; and (*c*) the result of its inoculation into rabbits.

To the above has been added, in the form of an appendix, a more detailed description of the micro-organism and of the experimental part of the investigation.

I do not propose, to-night, to do more than touch upon the discussion which has arisen as to what is really meant by the term "Landry's Paralysis"; what cases should and what cases should not be included under that term; and what are the particular clinical symptoms and pathological findings which justify its use.

The confusion of ideas on these points may, in my opinion, be ascribed to three principal reasons; in the first place, the name was brought into use at a time when histological methods were not as advanced as they are at the present day, and more especially before the introduction of the Marchi and Nissl methods of staining nervous structures;

in the second place, it has only slowly become recognised that a disease, which was first of all regarded as invariably fatal, may sometimes take a more favourable course; and in the third place, even some of the recent numerous writers on the subject have failed to point out that both the clinical and pathological manifestations of what is generally admitted to be an infective or toxic process must necessarily vary in accordance with the length of its duration, and the virulence of the poison at work. Enough stress has not been laid upon the relative duration of symptoms when comparing the symptomatology and morbid anatomy of one case with another.

Death ensues in this disease when the muscles of respiration cease to meet the requirements of life, and depends, therefore, upon the incidence of the morbid process, upon certain parts of the nervous system, and, again, upon the intensity of its influence on those parts. Thus the fatal issue may be brought about by a rapid and intense affection of the spinal and bulbar centres within a few hours or days of the onset of symptoms, or, on the other hand, it may be considerably postponed or averted when the poison is less active in its effects.

It is not unreasonable to assume that if it were possible to examine microscopically the same case of Landry's paralysis at intervals of a few days, the results might be found to approximate very closely to many of those which have been described in the large number of cases now collected in medical literature. At an early period in the course of a case of moderate severity, we could imagine that a condition of marked motor palsy, with absent reflexes, no electrical changes and slight paræsthesiæ, would reveal, *post mortem*, no abnormalities which could be demonstrated even by osmic acid or Nissl methods of staining in any part of the nervous system. A little later, more advanced motor and sensory disturbances accompanied by slight electrical and trophic changes might find their counterpart in early degeneration of both motor and sensory neurones, and in commencing chromatolytic changes in certain ganglion cells. Again, a few days and we should expect both the clinical

and histological evidences of the disease to be more marked, the additional phenomena of sphincter trouble and early muscular atrophy on the one hand being counterbalanced by the presence of advanced cell changes in the central nervous system, and an extension of the degenerative process to muscle fibres on the other.

Such a picture or series of pictures must necessarily be modified by what we know of the varying susceptibility to the action of particular poisons presented by different neurones, and also by the varying degree of virulence displayed by the same organism, supposing Landry's paralysis to be a specific disease, or by different organisms if it is capable of being produced by more than one member of the bacterial world. At the same time it must be admitted that the anatomical changes are sometimes inadequate to explain the cessation of functional activity, and we must look forward to more precise methods of examination to make clear this discrepancy.

A study of the now extensive literature on this subject assures one, at any rate, that the imaginary progression of events which I have just sketched is not without some basis of probability, and if we look for a moment at the cases which have occurred within the last few years, and which have been subjected to a careful and complete *post-mortem* examination by recent methods, we find examples of all the three conditions I have referred to.

The cases in which no pathological changes are to be found have become remarkably few, but Giraudeau (1) and Levi record an instance in a patient who displayed the clinical picture of the disease in an acute form, and who died ten days after the onset of symptoms.

Among the cases which exhibit definite *post-mortem* evidence of disease, a certain number have been only remarkable for the signs of degeneration in the peripheral nerves, and, on account of the absence or scarcity of cell changes in the cord, have been held to prove the peripheral origin of the disease. A majority of recent cases, however, have shown significant changes in the nerve-cells of the cord, and especially in those of the anterior horns, and this

condition has often been associated with early myelin degeneration both in the peripheral nerves and in the white matter of the central nervous system. The intensity of the process as it affects the cellular elements has been of all degrees, and has varied from a condition which could hardly be regarded as abnormal to one which has closely resembled an acute anterior poliomyelitis.

The anterior roots have shown Marchi degeneration more frequently than the posterior roots, but in the latter, and even in the posterior ganglion cells, changes have also been described.

The most constant of all changes has been the marked vascular engorgement both in the cord itself and in the leptomeninges, and this hyperæmia has been accompanied in some instances by minute capillary hæmorrhages, and in others by an exudation of small round cells into the walls of the vessels and into the perivascular spaces. This last condition of cell infiltration is more remarkable, however, for its absence than for its presence in the class of case to which I am now referring.

This list comprises the morbid findings of modern times in a majority of the cases of Landry's paralysis, but there is a smaller group of cases in which the pathological process is much more severe, and amounts to a diffuse but intense inflammation of the cord and its meninges. It is characterised by engorgement of the vessels in the meninges and cord, by well-marked round cell infiltration of the vessel walls and perivascular spaces, and by the presence of areas of softening, sometimes limited to the gray matter and often to the anterior horn region. This condition may be found after a very short duration of illness and, although it is frequently associated with the clinical course of Landry's paralysis, really belongs pathologically to the category of meningo-myelitis. In a few members of this group bacteria have been demonstrated in the substance of the cord.

In order to complete a very brief summary of what we know of the morbid anatomy of this disease it is only necessary to add that in a few isolated cases hyaline degeneration of the vessel walls, thickening of the intima resembling

endarteritis syphilitica, and one or two other conditions have been placed on record, but cannot be said to possess great significance in view of their rarity.

Apart from the neuro-muscular system, only two morbid conditions are met with sufficiently often to justify their mention—enlargement of the spleen and evidence of extensive pleurisy in the form of old or recent adhesions; the frequency of the latter is quite remarkable, even when its prevalence in all autopsies is taken into consideration.

Experimental evidence is afforded by the work of many investigators, that all the pathological changes described in my first group of cases can be produced by circulating microbic toxins, even in the absence of the microbes themselves from the tissues, and this fact justifies one in thinking that in a particular case in which more or less of these changes are found, the condition is in all probability due to some intoxication, and this in spite of the fact that bacteriological examination may have proved negative.

This conclusion has been arrived at by many modern writers on the subject, and notably by American observers who have contributed largely to our knowledge of the disease, but there is an inclination on the part of some to assume that the toxic action is limited either to the spinal cord or to the lower motor neurons, or even by others to the peripheral nerves. In my opinion such views are too narrow, and I would regard the intoxication as affecting all parts of the central and peripheral nervous system, but with an intensity which varies with the susceptibility of the different neurons to the poison, and with the energy and duration of its activity.

Assuming, then, that Landry's paralysis is a species of acute intoxication of the nervous system, the following questions arise :—

(1) Is it a specific disease due to one micro-organism?

(2) If there is a specific micro-organism, can the same symptom-complex be also produced by other organisms, such as the bacillus of influenza or of typhoid fever, by the gonococcus, &c., acting vicariously?

(3) Is the same condition capable of being brought about

by some poisons or poison, the result of disordered metabolism, as has been suggested by an abnormal state of the urine in a case related by Worcester (2)? In other words, is it ever the sign of an auto-intoxication?

The fact that these questions can be put and, in the present state of our knowledge, cannot be answered, is a practical admission that Landry's paralysis is at present to us only a symptom-complex and not a disease. We must look, therefore, to bacteriology to answer these questions and to put into some sort of scientific order a group of cases which are in clinical and pathological confusion.

During the last few years a considerable number of investigations have been made with a view to discovering a microbic origin for the disease, but the majority of these investigations have produced negative results, many of them have been incomplete and therefore unsatisfactory, and some of those in which bacteria have been found belong to my second pathological group and are, in fact, cases of meningomyelitis.

If we compare the cases in which some sort of bacterial examination has been made and has proved negative, with those in which positive results have been obtained, one or two interesting facts present themselves.

There are, as far as my researches have discovered, twenty-five members of the first class, *i.e.*, in which bacteria were looked for and not found either by cultivation or by staining tissues or by both methods. With very few exceptions, there was no *etiological* factor to be obtained in any member of this class, although influenza is mentioned several times as preceding the development of symptoms. "Influenza" used in this way is a well-abused term, generally referring to a febrile disturbance accompanied by pains in the back and limbs, and can hardly be looked upon as a scientific datum. The *pathology* of this class comprises the changes which I have described above as being capable of production by microbic toxins in the absence of microbes, and need not be detailed again.

The second class includes thirteen cases, some of which deserve more detailed notice.

In Centanni's (3) case, he found numerous bacilli in the peripheral nerves associated with interstitial neuritis, some meningitis and degeneration of the peripheral zone of the spinal cord; the author describes the case as a "neuro-mycosis."

In Eisenlohr's (4) case, the palsy came on in a patient suffering from pulmonary tuberculosis and two varieties of staphylococci were cultivated from the nerves, spleen and other organs. Areas of softening were found in the cord and the case appeared to be one of general infection by a common organism occurring in a patient whose resistance was lowered by another infective process.

Burghart's (5) case also died of pulmonary tubercle, and a streptococcus was cultivated from the blood.

Friedländer and Giese (6) describe a case of staphylococcic pyæmia in which the symptoms of acute ascending paralysis supervened. The organism was cultivated from an abscess.

In the patient described by Mouravieff and Montourine (7) there was no *post-mortem* examination, but the staphylococcus albus was found in the blood during life.

In a case of variola recorded by Oettinger and Marinesco (8) there supervened symptoms of ascending paralysis, and cocci were found in the sections of a softened cord.

In 1876 Baumgarten (9) found bacilli in the lungs, spleen, spinal cord and blood of a patient who had the clinical symptoms of Landry's paralysis.

Remlinger (10) in the case of a malarial patient who had an acute attack of ascending paralysis, found a few streptococci in sections from the spinal cord and succeeded in growing the same organism in pure culture from the same part. Inoculations into rabbits proved negative.

Marie and Marinesco (11) describe bacteria resembling anthrax bacilli and a diplo-bacterium in the cord of a case in which softening of the anterior horns was found *post mortem.*

Curshmann (12) discovered what he believed to be typhoid bacilli in the cord of a patient suffering from enteric fever who presented symptoms of a rapidly-spreading palsy.

Not one of these nine cases can be said to throw much light on the etiology of Landry's paralysis, and are interesting only because they seem to show :—

(1) That many of the common pathogenic organisms can, especially in patients debilitated by disease, give rise to symptoms of acute ascending paralysis and can produce changes in the cord and nerves resembling those which are found in cases of Landry's paralysis.

(2) That the organism of a specific disease such as enteric fever may sometimes invade the spinal cord, and produce clinically an ascending paralysis, and pathologically a diffuse or disseminated myelitis.

The following records are more interesting and more suggestive :—

(1) Courmont and Bonne (13) describe a case of Landry's paralysis in which microscopical changes were present in the form of chromatolysis of ganglion cells and fine diffuse Marchi degeneration of the myelin in the white columns. The blood of the patient during life proved sterile. From the cerebro-spinal fluid and from the cord was grown a diplococcic organism which was sometimes seen in chains, and which retained its colour by Gram's method. The authors considered that, although bearing certain resemblances to the meningococcus of Weichselbaum and to the pneumococcus, it probably belonged to the streptococcic group. Inoculations into rabbits a month after its isolation proved negative.

(2) Piccinino (14) found oval cocci in groups and small chains in the vessels, perivascular spaces and cells of the cord. The micrococcus was said to resemble the diplococcus of Weichselbaum, but no cultures were made. The pathological changes in this case were of the nature of anterior horn cell degeneration.

(3) Roger and Josué (15) have recorded a case of acute ascending paralysis, without any known etiological factor, in which they found Nissl changes in the lumbar enlargement. Sections stained for bacteria did not demonstrate the presence of any organism, but cultivations from the heart blood produced a growth of a diplococcus resembling the

pneumococcus. Injections of this coccus into a mouse did not prove fatal. A rabbit submitted to the same experiment died at the end of twenty-one days with symptoms of paraplegia, and the diplococcus was recovered from its blood.

(4) Another diplococcus similar in some respects both to the organism described by Weichselbaum, and to that described by Still was found by Dr. Risien Russell (16) in a case of ascending meningo-myelitis under Dr. Buzzard at the National Hospital.

(5) Although they have, perhaps, only an indirect bearing on the subject of this paper, it is worth while to record briefly the results of an investigation into an epidemic form of ascending paralysis among the inmates of a lunatic asylum, undertaken by Chantemesse and Raymond (17). The paralysis in these patients was preceded by vomiting and œdema, and was followed by rapid muscular atrophy. The morbid anatomy consisted of degenerative changes in the peripheral nerves and in the ganglion cells of the cord, with some vascular lesions. Cultures from the cerebro-spinal fluid and from various organs revealed the presence of a bacillus resembling in some particulars the proteus of Hauser. Inoculated into rabbits, it produced symptoms of ascending paralysis and a condition, *post mortem*, of meningo-myelitis. Inoculations of the toxins *without* living baccilli produced, also, a fatal ascending paralysis with œdema and congestion of the gray matter of the cord and degenerative changes in the ganglion cells. These cases bore a strong resemblance to beri beri of the East and cannot be considered as an example of an epidemic form of ordinary Landry's paralysis.

These last experimental results are analogous to those obtained by other observers such as Claude (18) with snake poisons, and Moltchanoff (19) with the gonococcus toxin. The latter found chromatolytic changes in the anterior horn cells, and later in the cells of the posterior root ganglia, besides diffuse degeneration in the white columns of the cord and in the peripheral nerves of the animals into which the toxins were injected.

The conclusions I deduct from this summary of our

present knowledge of the pathology and bacteriology of Landry's paralysis are briefly the following:—

(*a*) Even by modern histological methods a few cases present no demonstrable lesions.

(*b*) In the large majority of cases the lesions are such as can be produced in the central and peripheral nervous system by the action of microbic toxins apart from the microbes themselves. In these cases it is the rule to find that bacteriological investigations have given negative results.

(*c*) In a few cases the lesions are those of a disseminated or diffuse myelitis or meningo-myelitis of varying degrees of intensity, and in some of these pathogenic organisms have been demonstrated in the meninges, spinal cord, and cerebro-spinal fluid, and occasionally in the blood and other organs as well.

In other words it has been shown by investigations on man and the lower animals that the clinical manifestations of Landry's paralysis are the result of either a local infection, a general pyæmia, or lastly, and most frequently, of an acute intoxication.

It is in the hope that they may throw some light on the obscurity of these intoxications that I bring before you my observations on a case which I shall now record.

Before doing so I would express my gratitude to Sir William Gowers for his permission to make use of the notes of the patient who was under his care in the National Hospital, and for some valuable suggestions he made with regard to the investigation.

G. L., a man 33 years old, was admitted into hospital on December 20, 1902, and the clinical notes from which I quote were taken by the house physician, Dr. Stanley Barnes.

The patient had had syphilis fifteen years previously, and since 14 years of age had followed the occupation of a printer, which had recently necessitated his working in close proximity to a hot stove and standing on a hot floor.

Fourteen days before his admission he had noticed "pins and needles," numbness, and burning in his upper and lower

extremities. Stiffness and heaviness in his hands and feet supervened three days later and prevented him from continuing his work. The signs of paresis spread up the extremities from the peripheral to the proximal muscles, and he became unable to walk four days before he came under observation. For several days he had also suffered from shortness of breath and some difficulty in swallowing.

On examination the man was found to be thin and pale, cheerful, placid, and perfectly intelligent. His special senses and cranial nerves appeared to be healthy, but he had distinct paresis of his neck muscles. Respiration was embarrassed when he talked, and was purely costal in type, the diaphragm being absolutely paralysed. All trunk muscles were very weak. The legs and arms were markedly paralysed, and the proximal muscles seemed to have suffered more severely than the peripheral in all four extremities. There was no muscular atrophy, and no diminution to electrical excitability.

The subjective paræsthesiæ mentioned above were present, but objective sensation was perfect, except for a slight blunting to touch below the knees.

All deep and superficial reflexes were absent, and the sphincters acted normally.

The paralytic phenomena became more marked, especially in relation to respiration, and the patient died four days later. The temperature varied between 99° and 100°, and the pulse between 100 and 130. The duration of his symptoms extended over eighteen days.

At the autopsy, which was performed early in the afternoon of the day on which he died, I found rigor mortis present, and noticed a rather unusual lack of moisture in most of the tissues. The cranium, vertebral column, and soft meninges appeared healthy; the dura mater I will refer to later. The brain and spinal cord were noticeable for nothing except their marked vascularity, and both were firm in consistence and free from any suggestion of softening.

The central nervous system together with pieces of several peripheral nerves and spinal ganglia, and a few pieces of muscle were put aside to harden in 10 per cent. formalin.

The heart, liver and kidneys were healthy in appearance; the spleen was full-blooded and moderately large and firm. The right lung was adherent to the parietes over its entire surface, but beyond some hypostatic congestion showed no sign of disease. The left lung had some slight adhesions at the apex, but presented no evidence of old or recent tubercle.

At the beginning of the autopsy I inoculated various culture media with material from the cerebro-spinal fluid, spinal cord, blood and spleen with all due precautions, and also prepared film specimens from some of the same tissues. The culture tubes together with sterile pipettes containing an additional supply of heart's blood and cerebro-spinal fluid were handed over at once to Dr. Eastes, from whose report I shall quote later.

Histology.

Portions of the spinal cord, spinal ganglia, peripheral nerves and muscles were removed from the formalin after forty-eight hours, and examined by the following staining methods, sections being embedded and cut in gum, paraffin and celloidin :—Weigert-Pal, Marchi (using Busch's fluid), Nissl (using thionin and methylene blue), Van Giesson, and hæmatoxylin and eosin; for bacteria, methylene blue, carbol-thionin, carbol-fuchsin, and Gram's stain were also made use of.

The results of my examination must be summarised for the sake of brevity without much further reference to the technique employed.

The vessels of the pia-arachnoid and of the cord were all dilated and filled with blood; in some sections the red corpuscles had escaped from the capillaries and had formed minute scattered hæmorrhages. The vessel walls showed no evidence of disease. Every now and then a slight round cell exudation about a vessel was come across, but this condition was distinctly exceptional. A few vessels seemed to contain a greater quantity of leucocytes than is usual, but as a rule the normal proportion of red and white cells was maintained.

The pia mater and the connective tissue elements of the cord showed no change; here and there the sub-pial tissue had the appearance of being the seat of some proliferation.

No myelin change was detected by the Weigert-Pal method, but sections stained in Busch's fluid from all parts of the cord presented a large number of black dots scattered indiscriminately throughout the white columns. These dots, under high powers, appeared to represent droplets of altered myelin, some within the myelin sheaths and some lying between contiguous fibres. Parts of the peripheral zone of the cord were the seat of more intense black staining by this method. Most of the ganglion cells of the cord were deeply stained by the osmic acid.

The axis cylinders in the cord and roots were unusually well stained by logwood, and were possibly slightly swollen; this condition has been pointed out to me by Dr. Batten and Dr. Collier as frequently present in toxic processes.

The ganglion cells of the anterior and posterior horns, and of Clarke's column presented in the large majority of cases a normal condition as regards their nuclei and their chromatin granules, but a certain number, and in my opinion more than is the rule in healthy cords, showed various degrees of chromatolysis and excentration of nuclei. This opinion was arrived at from the examination of a large number of sections, and has reference to the lumbar enlargement in particular, where many of the cells appeared to be unduly swollen.

Except for vascular engorgement and the presence of rather an unusual number of so-called "mast-cells," the spinal root ganglia presented no remarkable features.

The peripheral nerves (sciatic, ulnar, and external popliteal) stained by Busch's fluid resembled the white matter of the cord in being the seat of numerous small scattered drops staining black with the osmic acid; by other methods the only noticeable condition was the number of mast-cells, many of which had burst and dispersed their basophilic granules in the connective tissue around them.

The muscles examined showed no abnormal features by the logwood methods, but treated by osmic acid presented

undoubted evidence of an early degeneration affecting a large number of the fibres. In transverse sections the gray-staining fibres, interspersed among the healthy ones, gave a most striking and unusual appearance to the preparations.

The obvious deduction to be made from this account of my microscopical examination is that the morbid changes were very slight in degree of intensity, rather widely distributed, toxic in character, and, finally, of such a kind that they might easily have escaped detection by the older methods of staining.

Bacteriological.

Before recording the bacteriological results of this inquiry I should like to express my thanks to Dr. Eastes for the time and skill he expended on the cultivation of the micrococcus which was found, and for the benefit of his valuable opinion in the study of its characteristics.

The tubes inoculated at the autopsy were incubated at 38° C.; the material in the pipettes was inoculated into broth and on to the surface of blood serum and agar, and incubated aërobically at the same temperature. Inoculations from the same source were made on to glucose-formate broth and incubated anaërobically.

All the tubes inoculated with blood from the spleen and with cerebro-spinal fluid remained sterile, though kept under observation for fourteen days.

The solid media and the glucose-formate broth inoculated with the heart blood remained sterile.

In the broth tube inoculated direct from the heart blood, and in another tube of broth inoculated with the blood received in the pipette, after a week's incubation under aërobic conditions a slight flocculent deposit was observed, which proved to consist of a micrococcus.

The growth in the two tubes was sub-cultivated on blood-agar, glycerine-agar, broth, glucose-peptone, blood serum, and milk.

By the end of another week growth had occurred in sub-culture in broth, and on one of the tubes of blood-agar. On

the surface of the latter there were two kinds of colonies, the only macroscopic difference between them being that of size. Each proved to consist of a micrococcus resembling that found in the original cultures, though the cocci in the smaller colony proved to be more uniform in size than those in the larger colony, which were distinctly pleomorphic. This micrococcus occurred usually in cultures as a diplococcus of about the same size as the gonococcus, though in its pleomorphic condition many of the cocci were much larger and others were smaller than the gonococcus. The organism stained moderately well with methylene blue, but did not retain Gram's stain.[1] It was remarked that the large cocci, which may perhaps be regarded as involution forms, stained somewhat irregularly, portions of the coccus taking up the methylene blue with avidity.

The smaller colonies contained cocci which, besides being more uniform in size, were less frequently diplococcic and more equally stained than those in the large colonies.

Each half of a diplococcus was hemispherical in shape, and the opposed surfaces were distinctly flattened. Occasionally two diplococci lying close together formed a tetragenous group.

The blood-agar tube was filled up with broth and re-incubated for six days, by which time a flocculent growth was apparent. This tube was handed over to Dr. Eyre, who was kind enough to do some inoculation experiments on rabbits for me. I shall refer to these experiments when I have detailed the results of my bacteriological examination of the human tissues.

Sections of the cord from different levels, sections of the spinal ganglia, and sections of the peripheral nerves were stained by Löffler's methylene blue, and by carbol-thionin, and carefully searched, but no definite bacteria could be found. Portions of the pia-arachnoid were stained in the same way, spread out and examined with the same result. Smears from the heart blood only showed the presence of one or two doubtful organisms. The spleen and kidney

[1] In sub-cultivated specimens the coccus *did* retain Gram's stain fairly well; see Appendix.

substance also proved negative as far as bacteria were concerned.

As a result of my experience with one of the inoculated rabbits, I determined to examine the soft vascular tissue which lies on the outer side of the spinal dura. This tissue in my case appeared to be more œdematous and much more engorged with blood than did the same tissue in patients who died from a different cause. It was found impossible to remove the thin vascular membrane on the surface without taking a portion of the fibrous structure underlying it at the same time, and only a few pieces out of a large number of attempts were thin enough to stain and examine under a high power. In all of these the vessels were seen to be choked with red corpuscles, and in parts the blood had escaped into the surrounding tissue. Many of the specimens proved negative as regards the presence of bacteria but in a few there were areas in which minute cocci were present in large numbers. The cocci were generally to be seen in close proximity to capillary vessels, sometimes lying free and almost in the walls of the vessels, sometimes lying within cells at a little distance, and sometimes appearing in conglomerate clusters in which it was difficult to distinguish the individual cocci. In consequence of the thickness of the preparations in which the cocci were suspended, the individual members of one group often lay in different planes, and the morphological characters of the organism were very difficult to make out except by careful focussing with high powers ; a diplococcic appearance, similar to that of the micrococcus cultured from the blood, was every now and then to be distinguished. There was less variability in size, and the usual diameter was a trifle smaller than that of the majority of the cocci in the smaller culture colonies. The examination of this dural tissue was otherwise only remarkable for the presence of a moderate leucocytal reaction, and for the presence of numerous mast-cells of unusual size. The majority of these appeared to be bursting with granules, and many had burst, with the result that the scattered granules were at times rather difficult to distinguish from the micro-organisms. The points of difference

were, however, definite enough, the granules being as a rule smaller, more spherical, always staining redder with methylene blue than the bacteria, and never to be found within the tissue cells.

Experimental.

I now come to the experimental inoculations; for the carrying out of these I was fortunate enough to secure the services of Dr. Eyre, Bacteriologist to Guy's Hospital, to whom I am deeply indebted for the trouble he took in the matter.

The material employed for injection into rabbits was obtained from the blood-agar culture of the coccus derived from the heart blood of the patient, and revivified by filling up the tube with nutrient broth, and incubating at 37° C. for nine days. The broth was uniformly turbid, and on microscopical examination showed the presence of cocci in pairs and short chains, but the majority in tetrads.

Rabbit "A" received ·5 cc. of the turbid broth intravenously on February 2, but remained unaffected until March 4, when it was killed and revealed nothing *post mortem*.

On the same day Rabbit "B" received ·5 cc. of the turbid broth in the subdural space through the frontal bone (anæsthetic A.C.E.); a few hours after inoculation, the breathing became stertorous, and the animal remained in a condition of stupor for two hours, when the respiration again became normal and the rabbit commenced to take food. The wound healed by first intention and the animal seemed to be unaffected until February 9, when some weakness of the hind limbs was noticed. On February 12, all four limbs were found to be paralysed, but the animal continued to feed well. On February 14, I examined the rabbit carefully, and noted as follows:—

Respiration is rapid, diaphragm acting; trunk muscles are probably weak. Left hind limb, moderate strength and knee-jerk obtained; right hind limb is very weak, flaccid, and the knee-jerk is absent. Both fore limbs are very weak, the right weaker than the left. The animal cannot stand,

and generally lies on its right side with the right limb under the left.

On February 23, the rabbit's condition remained the same, and it was killed. The heart blood was examined microscopically with negative results; cultures taken from the same source immediately also proved negative. Some of the heart blood was aspirated into a sterile pipette and incubated at 37° C. for seventy-two hours. The experimental inoculations performed with this reinforced blood proved negative as far as they have gone. Cultivations were made from the reinforced blood upon various media. Some of the blood-agar tubes and one of the broth showed scanty growth at the end of nine days; as this did not increase, the tubes were filled up with serum broth and again incubated. The growth which had resulted by March 20 was removed and carefully centrifugalised, and the deposit used for microscopical examination and for further inoculation, which has, up to the present time, given negative results. The organism in this deposit was very pleomorphic, and took Gram's stain better than previous specimens had done.

The only positive result was therefore obtained in Rabbit "B," in which a non-fatal general paralysis supervened a week after the inoculation, and was accompanied by no signs of interference with the natural functions or general health of the animal.

I removed the central nervous system and a portion of one sciatic nerve of the rabbit within two hours of its death, and placed them in 10 per cent. formalin solution. In doing so it was observed that the wound produced at the site of inoculation had healed perfectly without suppuration, and that the brain presented no evidence of injury beyond a minute red spot no larger than a pin's head and situated some distance in front of the motor region.

The *technique* followed in examining the histological appearances of the nervous structures and meninges was practically identical with that employed in the case of the human subject, and the results which were obtained will only be briefly summarised.

(1) Marked engorgement of the vessels of the meninges and of the cord.

(2) Punctate hæmorrhages here and there into the substance of the latter.

(3) A few patches of leucocytal infiltration in parts of the pia-arachnoid, but little or none around the smaller vessels within the nervous tissues.

(4) Diffuse Marchi degeneration in the white matter of the cord, and especially in the peripheral zone.

(5) A few degenerated fibres in the sciatic nerve.

(6) Complete absence of organisms from the cord and leptomeninges.

(7) Only a few sections were stained by Nissl's method, and I found no definite cell changes in those which I examined.

The dura mater of the rabbit is sufficiently thin and transparent to allow of its being stained and spread on a glass slide for examination.

With the methylene blue stain, and less clearly with Gram's method, a micrococcus was found in abundance in many parts of it, and was seen to take a similar position in regard to the vessels to that taken by the coccus in the same tissue in man. The microscopic appearance of the tissue differed from that seen in the human theca by reason of the entire absence of any mast-cells, but resembled it in the small amount of leucocytal reaction. The micrococcus was often diplococcic, sometimes tetragenous, and appeared to be similar in size and shape to the organism observed in the case of Landry's paralysis, but it was less frequently found within the tissue cells. I was able to satisfy myself that the cocci were situated nearer the external than the internal surface of the dura; that is to say, in the more vascular part of the membrane.

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Put shortly, the results of the investigation are as follows:—

(1) A micrococcus was isolated in pure culture from the blood of a patient who died of Landry's paralysis.

(2) An organism, indistinguishable from that which was cultivated, was found in large numbers in the external part of the spinal dura of the same patient.

(3) A subdural injection of the cultivated coccus into a rabbit produced after some days a rapidly-spreading palsy.

(4) The same organism was discovered in the dura mater of the rabbit and isolated in pure culture from its blood.

(5) The changes in the nervous system in both the patient and the rabbit were of the kind produced by toxins, and in neither case was the microbe to be demonstrated in the nervous structures themselves or in the pia-arachnoid.

The slow and scanty growth of the organism in the primary cultures from the blood of both the man and the rabbit, its absence from the blood smears which were examined and from the interior of vessels seen in sections, lead me to infer that this micrococcus is not to be found in abundance in the blood; in other words, the condition of neither the man nor the rabbit was a true blood-infection.

The sterility of the cerebro-spinal fluid in the case of the man, and the absence of the organism from the lepto-meninges in the man *and* the rabbit, points to the conclusion that the cerebro-spinal fluid is not the favoured medium for its growth.

The fact that, although introduced sub-durally into the rabbit, the organism was found only in the external layers of the spinal theca is in harmony with the view that it was carried from the former situation to the latter by the cerebro-spinal fluid and this suggestion is supported by the investigations of the late Dr. George Elder (20) and of Professor Leonard Hill (21). Dr. Elder injected small quantities of Prussian blue sub-durally and traced the granules into the perivascular and other lymph spaces of the theca where it was taken up by the endothelial cells. Dr. Hill concludes from his own observations that "the pathway of the filtration of the fluid from the cranial cavity may be through the Paccionian bodies, *through the dura*, or through the veins of the pia mater."

The question at once suggests itself:—Does the lodgment of the organism in the perivascular spaces and cells of the theca merely represent a terminal stage in the combat of the tissues with the organism, and did the actual growth of the coccus take place in the cerebro-spinal fluid at an

earlier date? The other alternative appears to be that the organism reached this tissue either through the blood or through the cerebro-spinal fluid and there found the conditions necessary for its growth and multiplication. I am inclined to favour the latter alternative for two reasons; in the first place no cocci were to be seen in the leptomeninges where one would have expected to find them, if they had flourished in the cerebro-spinal fluid; in the second place the appearance of the coccus in pairs and tetrads in the dura suggests active life in that tissue. On the other hand some of the preparations seem to show that the organisms in the theca had seen their best days by the way in which they had been taken up by the cells and sometimes collected into shapeless clusters. This evidence, if it is evidence, of a short life is certainly in harmony with what we know of the clinical course of the disease, the victims of Landry's paralysis usually dying within the first three weeks of the onset of symptoms or recovering altogether.

The answer to these questions must be left until further researches have been made, but I cannot help thinking that some light might be thrown on the matter if the dura mater were the subject of more careful investigation in the future, not only in cases of ascending paralysis, but also in other diseases of the nervous system which are undoubtedly, or probably, of microbic origin.

The mode of entry of the micrococcus into the system of the patient is a subject on which I feel quite unprepared to offer any suggestions.

The question of the identity or non-identity of the organism in my case with better-known organisms, and notably with those which are associated with the names of Weichselbaum, Still, and Risien Russell, is one which cannot be definitely decided at the present time; nevertheless, it must be stated that although it has certain morphological resemblances to the two former it differs materially from all three in its staining and cultural characteristics.

If, for purposes of identification or reference, the organism described in this paper deserves a name, its predilection for the spinal dura mater naturally suggests the term "micrococcus thecalis" as its proper designation.

In conclusion, I do not claim that my investigation proves that all, or even many cases of Landry's paralysis are due to this organism, but I venture to hope that it may, if confirmed by other observations, help to expose a hiding-place from which members of the bacterial community have been wont, unknown to us, to exert their pernicious influence on the delicate structures of the central and peripheral nervous system.

Description of Figures in Plate.

Fig. 1.—This represents the micrococcus as seen in films made from one of the larger colonies on blood agar. Note the extreme pleomorphic character of the growth.

Fig. 2.—The same from one of the smaller colonies. Magnified in both about 1,000.

Fig. 3.—This is a drawing of a small portion of the spinal theca in Rabbit "B." Magnified about 1,000. Stained by Löffler's methylene blue.

Fig. 4.—Three small portions taken from different parts of the theca in the patient, G. L. The same magnification and stain as in the other figures 1, 2, and 3. Two mast-cells are represented with some detached granules.

Note.—Microscopic specimens showing these conditions and also the pathological findings in the cord, peripheral nerves, and muscles were exhibited at the meeting of the Neurological Society, at which the paper was read.

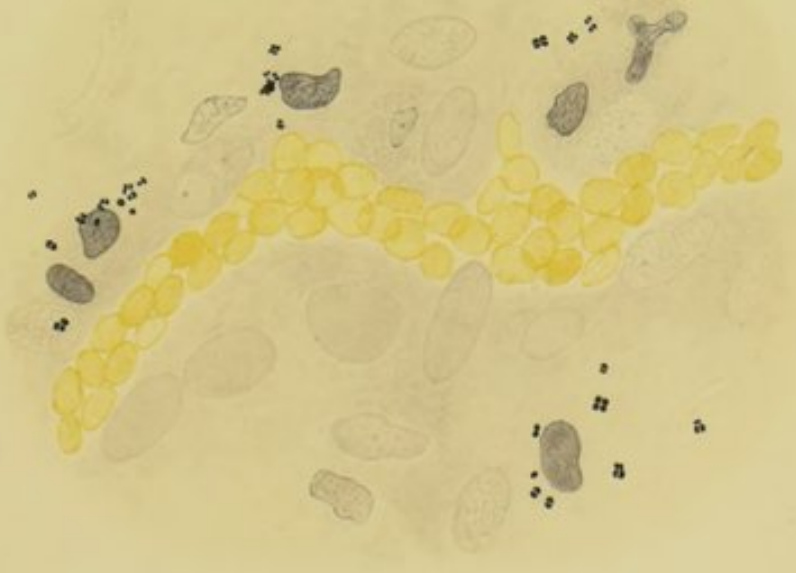
Appendix.

A.—(Chiefly from Dr. Eyre's report.)

The material employed for injection into rabbits was obtained from the blood-agar culture of the coccus derived from the heart blood of the patient, and revivified by filling up the tube with nutrient broth and incubating at 37° C. for nine days.

The broth was uniformly turbid, and on microscopical examination showed the presence of cocci, some in pairs and short chains, but the majority tetrads; all, however, stained but feebly with the ordinary aniline dyes, and only partially retained the stain when treated by Gram's method. Subsequent cultures showed marked irregularity in size of cocci, similar variations in arrangement, and, finally, that the coccus stained by Gram.[1] Sub-cultivations upon agar,

[1] The technique employed was: anilin gentian violet for three minutes, wash; Lugol's iodine until film ceases to become appreciably blacker, wash; absolute alcohol until no more colour is discharged, and alcohol runs off colourless.



3.

Bale & Danielsson, Ltd., Lith.

glycerine-agar, blood-agar, blood serum, and in nutrient broth, incubated at 37° C., remained sterile at the end of seven days.

Inoculation Experiments.

Rabbit "*A.*"—Weight, 1,800 grams, received on February 2, 0·5 cc. of the turbid broth intravenously (posterior auricular). The animal remained unaffected until March 4, when it was killed. *Post-mortem* examination, *nil.*

Rabbit "*B.*"—Weight, 3,320 grams, received on the same day 0·5 cc. of the turbid broth in the subdural space, introduced through a trephine wound in the frontal bone (anæsthetic A.C.E.). A few hours after inoculation the breathing became stertorous, and the animal remained in a condition of stupor some two hours, when the breathing again became normal, and the rabbit commenced to take food. The wound healed by first intention, and the animal appeared to be unaffected until February 9, when some weakness of the hind limbs was noticed. On February 11 the right hind leg was completely paralysed, and on the following day all four limbs were found to be paralysed. The animal, however, continued to feed well.

On February 23 the rabbit was killed.

Post mortem: (1) Central nervous system, examination by E. F. B., see p. 20; (2) heart blood examined microscopically, result negative; heart blood examined by cultivations, result negative.

About 3 cc. of the heart blood was aspirated into a sterile pipette, and the point sealed off in the flame. The pipette was placed in the incubator at 37° C. for seventy-two hours. At the end of this time :—

(*a*) Inoculation experiments were made with the reinforced blood.

Rabbit "*C.*"—Received 0·5 cc., reinforced blood intravenously. The animal was never visibly affected. On March 24, that is, four weeks after inoculation, the animal was killed. *Post-mortem* examination, *nil.*

Rabbit "*D.*"—Received 0·5 cc., reinforced blood under

the dura mater, through a trephine wound as in Rabbit "B." The animal was apparently unaffected, the wound healing rapidly and well. On March 19 about 5 mg. centrifugalised deposit from serum broth culture (*vide* Rabbit "E") emulsified with 0·5 cc. broth was introduced into the cranial cavity through the original scar. The animal still appeared to be unaffected. It was killed March 30. *Post-mortem* examination:—No changes in the central or peripheral nervous system. A considerable number of the same micrococci were found in the dura mater as in Rabbit "B."

(*b*) Cultivations were made upon various media and incubated at 37° C. Some of the blood-agar tubes and one of the broth showed scanty growth at the end of nine days, but as the growth had not visibly increased four days later the tubes were filled up with serum broth and again incubated. The scanty growth which had resulted by March 20 was removed from each tube and carefully centrifugalised, and the deposit used for microscopical examinations and for inoculation.

Rabbit "E."—This animal received about 5 mg. of the centrifugalised deposit emulsified in 0·5 cc. broth under the *dura mater*, as in Rabbits "B" and "D." The rabbit remained unaffected, and *post mortem* showed no changes and no cocci.

B.—The following is a brief summary of the characteristics of the organism as far as they have been ascertained:—

Cultural.—Growth took place at 37° C. only on blood agar and in broth, and only aërobically. The growth was never apparent until seven or more days after the inoculation of the tubes, and it took the form of large and small greyish-white colonies on blood agar. After a few days growth ceased and the organism died quickly.

Morphological.—In cultures the coccus was generally diplococcic, each diplococcus having the appearance of a split pea; frequently they were grouped as tetrads, or as sarcinæ. They exhibited very marked differences in size, some of the cocci being quite three times the size of others. In the smaller colonies the cocci were less often diplo-

coccic and more uniform in size than in the larger colonies. In the tissues of both the man and the rabbit the organism exhibited the same morphological characters, except that they were less pleomorphic. They were frequently intracellular. They were never encapsulated or lanceolate.

Staining.—In cultures the cocci took the aniline dyes indifferently well, and often unequally. Specimens taken from the primary cultures did not retain any colour by Gram's method, but those taken from sub-cultures, and from cultures derived from the blood of the rabbit, were partially or completely stained by that method. The cocci in the human and the rabbit's theca were stained well by methylene blue, and in the latter they were coloured by Gram. The human theca was not stained by Gram.

Experimental.—The primary cultures proved pathogenic to a rabbit when introduced subdurally, but not when inoculated intravenously. Secondary cultures from the rabbit appeared to have lost their virulence.

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