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on

FROIN'S SYNDROME

and its Relation to Allied Conditions

in the

CEREBRO-SPINAL FLUID

by

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On FROIN'S SYNDROME and its RELATION to ALLIED  
CONDITIONS in the CEREBRO-SPINAL FLUID.

The study of the cerebro-spinal fluid is a field of investigation which during the present century has yielded a rich harvest to the neurologist. It has enabled him to diagnose certain progressive diseases of the nervous system at a stage when the patient is hardly aware that he suffers from any disability, and to distinguish with certainty between diseases which may present identical pictures. Among the many changes which the cerebro-spinal fluid may undergo certainly the most striking to the clinical observer is a yellow colouration associated with the formation in the fluid soon after it is received into a test-tube of a coagulum, which may be so firm as to allow of the tube being turned upside down without a drop of fluid escaping. This combination of appearances was described first by Froin in 1903, and in French literature has since gone under the name of "Syndrome de coagulation massive et de xanthochromie" or "Syndrome de Froin". The rarity of appearance of this syndrome, the variety of the cases in which it has been found, and the occurrence of all gradations of change from normal fluids to those presenting the typical syndrome have combined to confuse our knowledge of its aetiology and significance. And as far as British work is

concerned, no attempt has been made to establish its pathogenesis or diagnostic value; in fact, beyond passing references, in text books and papers on the cerebro-spinal fluid, I have been unable to find any reference to the subject in British publications.

American schools have taken up the study of the cerebro-spinal fluid with greater keenness than has been shown by the British schools, and several papers have recently appeared there on the Syndrome of Froin which shew intimacy with the continental work on the subject.

During the past ten years I have seen several spinal fluids which have presented the typical appearances of the Syndrome of Froin, as well as a very considerable number in which changes of less degree but similar character were present. These fluids have been found in a great variety of forms of nervous disease, and in many of the cases I have been able to establish the diagnosis by following the case to operation or autopsy. This experience has been sufficient to enable me to test the value of current theories on the evolution of the syndrome, and to form some opinion as to its diagnostic value. Unfortunately I have not been able to do any experi-

mental work on the subject, partly owing to lack of time, but chiefly to the stringency of the Home Office regulations with regard to paraplegia, ~~which is~~ an almost necessary result of operations designed to reproduce the conditions giving rise to the syndrome.

The present time is ripe for a critical review of the subject, in that some recent American work, on the circulation of the cerebro-spinal fluid, has solved questions which have long been in dispute, and has thus made it more possible to understand the changes in the fluid which result from abnormalities in its circulation. At the same time it must be confessed that the causation of certain of these changes remains hidden in an obscurity which can only be cleared away by work in a more general field of chemical physiology.

## HISTORY of the SUBJECT.

In surveying the literature dealing with the syndrome of Froin it has been considered useless and tedious to detail every case in which the syndrome has been encountered either in a complete or a modified form. This has, in fact, recently been done by Lantuéjoul who has brought up to date the cases in which the syndrome was typically present, and by Raven who has collected a large series of cases of spinal compression in which the cerebro-spinal fluid showed similar changes. I have therefore considered it more helpful to a proper understanding of the subject to trace the growth of knowledge and theory with regard to it, recording only the first cases of any special affection in which the syndrome was encountered. It has seemed advisable to give some of these observations at length, especially when the nature of the disease was doubtful, or where the case presented some features of special interest as regards the condition of the cerebro-spinal fluid.

1) Early Observations.

The presence of fibrinogen in the cerebro-spinal fluid of cases of acute meningitis was observed by Fürbringer and Netter in the closing years of last century, but it was not until 1903 that it was found in more chronic affections of the nervous system. In this year Jean Lépine first drew attention to the formation of a coagulum "involving about half the fluid" in the tube, in a case diagnosed as lumbar rheumatism.

Froin (14) in the same year published three cases which he described as "Inflammations meningées avec réactions chromatique, fibrineuse et cytologique du liquide céphalo-rachidien". The first case was that of a woman of thirty-six years who had a paraplegia apparently of syphilitic origin. Four lumbar punctures were performed on her. The first gave a golden yellow fluid coagulating solid in the tube within a few minutes; the second, twelve days later, a slightly yellow fluid with less dense coagulum; the third, a fortnight after the second, gave a fluid which was only slightly yellow and formed a spider's web coagulum after two hours. The fourth puncture, performed two months after this, gave a fluid with a very faint yellow tinge and only a few flakes of fibrin. The

albumen and globulin contents of the fluids obtained at the first two punctures were greatly increased.

The second case was that of a girl of twenty-three who suffered from multiple foci of tubercular osteitis, and developed in July 1903 slight meningeal symptoms. Sixteen days later a lumbar puncture gave a clear, very yellow fluid with a compact clot. It was very albuminous and contained very many polymorphonuclear cells. Eight days later the symptoms had improved, and lumbar puncture gave a clear fluid yielding a spider's web coagulum and containing an excess of albumen and globulin. Many lymphocytes and polymorphonuclear cells were present in the deposit.

His third case was that of a man of forty, who rapidly developed a paraplegia which began in his legs and then affected his trunk and arms. The sphincters were affected. Lumbar puncture seven days after the onset of the disease gave a slightly yellow fluid, which, one hour after withdrawal, gave a copious coagulum which retracted easily. Albumen and globulin were moderately raised and numerous lymphocytes were present. A second puncture gave a fluid with similar characters.

In the same year, 1903, Babinski (2) described a case of spastic paraplegia which he diagnosed as due

to "Meningite haemorrhagique fibrineuse". It was probably of syphilitic origin, and was cured by mercury. It was that of a woman of thirty who in September 1902 had pain in the back and weakness of the legs, which rapidly increased. In October there was also weakness of the arms. When seen in the following February by Babinski she showed an Argyll-Robertson pupil on one side. Lumbar puncture performed by him gave a greenish yellow fluid which coagulated "en masse" soon after being withdrawn. It showed numerous lymphocytes. The fluid obtained on the following day by a second puncture was stirred with a glass rod immediately it was drawn and did not clot. A week later a third puncture was performed and paler fluid obtained which did not clot. A fortnight later still the fluid obtained by a fourth puncture was clear, gave no coagulum and contained fewer lymphocytes. Fifth and sixth lumbar punctures were also performed. He considered that the condition of the fluid was due to a special form of meningitis, which was improved by repeated punctures. He drew attention to the diminution in the quantity of fibrinogen in the fluid obtained by the second and successive punctures.

In the following year (1904) Cestan and Ravaut (5) reported similar changes in the fluid of a case of flaccid paraplegia. At the autopsy they found a meningo-myelitis affecting the sacral enlargement of the cord. The meningitis at this level had matted together the membranes and nerve roots producing a "véritable symphyse fibreuse des méninges et de la moelle". They considered that the changes in the fluid were due to haemorrhage complicating meningo-myelitis.

(2) Occurrence of the Syndrome in Landry's Paralysis and polyneuritis.

Several writers, however, found that the syndrome might occur in other conditions than meningo-myelitis. Julius Donath (10) in 1905 reported a case diagnosed as "Landry's paralysis" in which these changes in the cerebro-spinal fluid were found. It was that of a man of twenty-six who was a heavy drinker, and had had attacks of malaria since the summer of 1904. In December 1904 he began to suffer from formication and weakness in the hands and feet, and about ten days later had to take to bed. On examination at this time he showed absence of knee and ankle jerks, but his plantar reflexes were of the normal type. The pupils

reacted well and the optic discs and retinae appeared normal. A few days later his abdominal reflexes and arm jerks disappeared. His speech became nasal and aphonic, and he had facial weakness especially on the right side. He developed loss of sensibility to touch in his forearms and hands, and to thermal sensation in his legs. Painful stimuli were everywhere well appreciated. He improved rapidly and left hospital in the following March almost completely recovered.

The first lumbar puncture was performed at the end of December, during the height of the malady. The fluid came out at first rose-red, but later was colourless. This latter half on standing set solid in the tube like gelatine, "so dass die Eprouvette gänzlich umgekehrt werden konnte".

The second lumbar puncture a fortnight later gave a clear, slightly yellow fluid which flowed down the sides of the tube like gelatine. It contained albumoses.

A similar case in a young miller of nineteen diagnosed as alcoholic polyneuritis, was described by Claude in 1909(6). In 1908 he had suffered from pain in the back and numbness of the legs. In September 1909 he had headache, giddiness, pain in the neck, back and

70.  
legs; and also slight delirium. The lower limbs soon became completely paralysed, and then the upper limbs were affected to a less degree. On examination all the deep reflexes were found to be abolished, but there was no loss of skin sensibility or of sphincter control and the plantar responses were of the normal down-going type. There was loss of faradic excitability in the muscles of the legs and to some extent in the extensors of the wrists and the muscles of the thenar and hypothenar eminences. Two lumbar punctures performed at an interval of six days gave slightly yellow clear fluids which coagulated "massively" in the tube. They contained some red cells and a few leucocytes.

Renon and Monier-Vimard (33) in the same year described a case of Landry's paralysis with similar changes in the cerebro-spinal fluid. It was that of a man of thirty-six who in February 1909 developed tingling and weakness in the lower limbs, and a few days later in the arms. A week or two later he had a tingling feeling in the tongue; his speech became difficult; he had to hold back his head when drinking, and could only swallow small quantities of fluids.

On examination he had extreme flaccid weakness of the limbs, but no loss of cutaneous sensibility.

11.

The sense of position of his limbs was, however, grossly defective. Pressure and palpation of the muscles was painful. The deep reflexes were absent. There was weakness of the left side of the face; the speech was monotonous, and the labials and dentals poorly articulated. The heart was rather irregular, giving numerous weak beats which were not transmitted to the wrist. He improved rapidly so that he could walk with the help of sticks in May, and when seen in July had almost completely recovered, and showed signs of return of the deep reflexes.

The cerebro-spinal fluid obtained by lumbar puncture on the 25th March was clear and limpid but gave a coagulum after standing for twenty-four hours. It was highly albuminous, but contained no cells, and Théroüanne found the albumen to be composed only of serum albumen with no trace of globulin. Fluid obtained by lumbar puncture on 10th May appeared normal.

These three cases of polyneuritis, or Landry's paralysis, made it recognised that the syndrome of Froin could appear in these conditions. The significance of this seems to have been missed by the later writers on the subject, notably by Mestrezat(25), in whose theory of the etiology of the syndrome there

seems to be no place for polyneuritis.

(3) "Cavité close" conception of the aetiology of the syndrome.

Sicard and Descomps<sup>(36)</sup> in 1908 described a case in which similar changes were found in the cerebro-spinal fluid. They noted that a second puncture, performed within a few days of the first, gave a much less albuminous fluid which did not coagulate. A fortnight later the fluid had resumed the characters of that obtained at the first puncture. A fourth puncture two days later again gave a clear fluid without coagulum. At the autopsy they found a mass of fibrous and caseous tissue in the epidural space at the level of the eleventh and twelfth thoracic vertebrae, with thickening of the dura and of the soft membranes from the tenth thoracic to the second sacral vertebrae. The dura was adherent to the arachnoid in some places, but not everywhere. The condition appeared to be tubercular in origin but no tubercle bacilli could be found in sections.

Re-viewing the changes in the cerebro-spinal fluid, in relation to the condition found at autopsy, they considered the meningeal inflammation to be a necessary but not sufficient cause for the syndrome,

the other necessary factor being a process of adhesion whereby the plasma and corpuscular elements resulting from the inflammation were retained in a limited space. Vascular compression and local oedema they considered adjuvant causes of the syndrome. They explained the alterations in degree of the changes in the cerebro-spinal fluid at the several punctures, by supposing that fresh cerebro-spinal fluid from above filtered through the adhesions after the fluid below them had been drawn off. They laid stress on the value of the syndrome as an indication of meningitis rather than of tumour, but this was soon proved to be erroneous.

Rindfleisch<sup>(34)</sup> in 1904 reported three cases of diffuse sarcomatosis of the meninges in which changes in the cerebro-spinal fluid were found. In two of his cases the fluid was yellow, contained albumen in increased quantity (0.24% & 0.1%) and gave a deposit of tumour cells. In the third the fluid was highly albuminous, but colourless and showed very few cells. None of the fluids showed massive coagulation.

Blanchetière and Lejonne<sup>(3)</sup> in 1909 seem to have been the first to describe the full syndrome of Froin in a case of spinal tumour. Their case was one of

slowly developing paraplegia, with sensory loss below the level of the seventh thoracic segment in a man of sixty-six. The first lumbar puncture gave a lemon-yellow fluid coagulating "en masse", but containing very few lymphocytes. Later punctures extending over a period of sixteen months invariably gave exactly similar fluids, with no reduction of the tendency to coagulate. They give a table of some of the results of the examination of the cerebro-spinal fluids obtained at these various times which is of sufficient interest to justify its insertion here.

<u>Date of puncture.</u>	<u>27.10.07.</u>	<u>24.9.08.</u>	<u>30.9.08.</u>
Fibrin (parts per 1000)	1.70	1.61	1.63
Globulin "	8.08	( 27.25	27.66
Albumen "	17.42	(	
Chlorides "	---	7.39	7.55
Urea "	---		0.59

At the autopsy a tumour was found lying under the dura mater and compressing the cord at the level of the 7th, 8th and 9th thoracic segments. There seemed to be some adhesions between the dura mater and the dorsal surface of the cord, but the membranes stripped off the cord easily and there was no meningitis. The tumour, which was of the form and size of a large

olive, gave the histological appearances of a very vascular round-celled sarcoma.

In the same year Derrien, Mestrezat and Roger (9) published a case of spastic paraplegia with anaesthesia and sphincter trouble, diagnosed as being due to subacute meningo-myelitis in the lumbar region of the cord. The first lumbar puncture gave fluid which came out very slowly and stopped completely after 4 to 5 c.c. had escaped. It had a bright golden yellow colour and on standing set "en masse". The serum from this gave only a slight fibrin web, until fresh guinea-pig serum was added, when it set again. On centrifugalisation the fluid gave a deposit of red blood corpuscles and some lymphocytes. A second puncture a week later gave fluid at higher pressure, and less yellow, which did not clot until serum had been added. It contained 0.96% albumen. The fluid obtained by a third puncture eight days later was only slightly yellow and gave a thin fibrin clot. It was found to contain fibrin 0.03% and albumen 0.6%. A fourth puncture a week later gave almost colourless fluid containing 0.4% albumen and no fibrinogen. A fifth puncture, a fortnight later, again gave a fluid containing a trace of fibrinogen but no spontaneous coagulation. The

Fluids obtained by the sixth and seventh punctures were similar, but that from the eighth puncture between which and the seventh an interval of a month had been allowed to elapse, was more definitely yellow and coagulated spontaneously, giving a spider's web of fibrin. It contained 1.08% albumen. In these fluids the glucose content was often increased, two readings being as high as 0.08% and 0.09%. They considered that their case was due to a haemorrhagic meningitis similar to that diagnosed by Froin(14), Babinski(2) and Cestan and Ravaut (5) .

In commenting on Blanchetière and Lejonne's (3) case they held to the theory of "cavité close" formulated by Sicard and Descomps(36), and considered the changes in the fluid in that case due to transudation of the principles of the plasma from the sarcoma. As adjuvant factors, they postulated obstruction of the perivascular sheaths, and compression of the cord by the tumour. These several factors, taken together, would transform the terminal part of the sub-arachnoid space into an isolated pouch in which the transuded plasmatic elements would be retained.

This theory was insisted on by Mestrezat (25) in his monograph on the cerebro-spinal fluid published in 1912. He considered two factors necessary for the production of the syndrome (1) that the lumbar cul-de-

sac should be shut off from communication with the fluid around the upper part of the cord by meningitis, tumour, or disease of the bones of the spine, and (2) that there should be congestion of the spinal veins below the level of this block, or alteration of the vessel walls by inflammatory processes. He did not insist on the necessity of a process whereby the perivascular channels were sealed up, but noted that substances such as iodides, nitrates, and collargol when injected into the lumbar theca did not escape from it. He also drew attention to the fact that in all the cases which had been followed to autopsy the level of the block was low down in the thoracic region of the cord, or at the lumbar enlargement. As has been noted above, his theory, being based only on cases where the pathological process had actually been seen at operation or autopsy, did not take any account of the cases of polyneuritis or Landry's paralysis in which the syndrome had been found. Cases of these affections which have come to autopsy have given no evidence of any process which would divide the sub-arachnoid space surrounding the cord into upper and lower portions, or which would prevent free circulation of the cerebro-spinal fluid to the lowest parts of the lumbar cul-de-sac. But it is conceivable that oedema of the cord or

slight inflammation of the meninges might have this effect. If so the block must be only a temporary one as it has been seen that the fluid in these conditions rapidly loses its pathological characters.

(5) Changes in the Cerebro-spinal Fluid in Pott's Disease.

In 1910 Sicard, Foix and Salin (37) drew attention to the characters of the cerebro-spinal fluid in Pott's disease. They gave four cardinal signs in the fluid, which, if present together, they considered pathognomonic of the disease. These were (1) yellow colouration (2) excess of albumen without increase of cells (dissociation albumino-cytologique) (3) the presence of albumoses (4) the presence of haemolysin to rabbit's red cells; the fluid by itself might not be haemolytic but might require the addition of fresh guinea-pig serum. They laid chief emphasis on the presence of albumoses, which they considered to have the same significance as Bence-Jones albumose in the urine, and to indicate disease of the bones of the spine. They did not insist that this should be necessarily tubercular, but considered that albumoses might also occur in malignant disease of the spine. On the other hand they pointed out that albumoses were only found in the fluids which showed the greatest changes, and then only at the first puncture. Mestre-

19.

zat in his monograph considered that they were due to autolysis of the albumen stagnating in an isolated cul-de-sac, a theory which would explain why they were found only in the fluid drawn off by the first puncture. It should be noted that Mestrezat's technique for the detection of albumoses was rather more delicate and perhaps less free from error than that adopted by Sicard and his fellow-workers. Mestrezat performed the biuret reaction, after the albumens had been removed by the addition of saturated lead acetate and filtration, and it is possible that this filtrate might have contained a trace of albumen sufficient to give the biuret reaction. Sicard boiled the cerebrospinal fluid after salting it with sodium sulphate, filtered off the precipitate and saturated the filtrate with ammonium sulphate crystals. If albumoses were present, they gave a haze which disappeared on heating and reappeared on cooling. But as saturation with ammonium sulphate does not show one part in ten thousand of albumen, a trace of albumoses could not be detected by this method.

In the same year Cooper<sup>(7)</sup> published in America the report of a case of localised segmental lesion of the cord from which he obtained clear fluid "of a yellowish brown colour" which gave "a well-marked cobweb

coagulum". An operation was performed at which an angio-sarcoma was found pressing on the cord and he noted "a strongly marked oedema of the membranes below the site of the tumour. The transudate character of the fluid was thus explained". This appears to be the first case published in the English language in which such a condition was found, and the writer does not seem to have had any knowledge of similar cases published by French observers.

(6) Nonne's "Compression Syndrome".

<sup>(29)</sup> Nonne in 1910 detailed six cases of tumour compressing the spinal cord in which his "Phase I reaction" (Nonne-Apelt reaction) was strongly positive in the cerebro-spinal fluid without any lymphocyte increase. He did not give any details as to albumen percentages, or the presence or absence of fibrinogen, but considered that excess of globulin, with no excess of lymphocytes, was diagnostic of spinal compression. The authority of his name gave this new syndrome an importance in German literature to which it was by no means entitled, and it is unfortunate that the term "Syndrome of Nonne" or "compression syndrome" should have been applied to fluids of this character, which had previously been found to occur also in other conditions such as polyneuritis.

In 1912 Raven (31) in Nonne's clinic collected forty-seven cases in which this "compression syndrome" had been found. He paid little attention to the presence or absence of fibrinogen, but noted that a coagulum formed in some cases. He agreed with the theory of Derrien, Mestrezat and Roger (9), that the local compression of the cord isolated the fluid distal to it from that on its proximal side and considered the increase of albumen due to transudation from the blood vessels in the pia-arachnoid which were congested as a result of the blockage, ("Stauungshyperamie"). The yellow colour was considered as probably due to multiple small haemorrhages but the stagnation of the fluid in the lower part of the sub-arachnoid space might contribute to it. He observed also that the yellow colour in the compression syndrome was often much more intense than that resulting from cerebral haemorrhage.

(7)

Punctures above and below the level of the lesion.

In two of his own cases Raven observed that he got by lumbar puncture a fluid of a deep yellow colour giving a heavy coagulum with the Nonne-Apelt reaction, whereas the fluid obtained by puncture above the site of compression of the cord showed no abnormality either

in colour or in globulin content.

In 1913 Marinesco and Radovici(23) published four cases observed in Bucharest in which Froin's syndrome was found. In the first, which was diagnosed as syphilitic meningo-myelitis, three successive punctures made in the lumbar region gave yellow fluid which coagulated spontaneously. A fourth made between the eleventh and twelfth thoracic spines gave fluid of similar character, but a puncture between the second and third thoracic spines gave clear fluid which did not coagulate. They explained the yellow colour as due to a "local bile formation", from blood corpuscles entering the sub-arachnoid space in minute haemorrhages, and considered that the albumen was also derived from such haemorrhages.

In the same year Marie, Foix and Robert(22), found a similar disparity in the fluids removed from above and below the lesion in two cases of tubercular disease of the spine. In a third case, diagnosed as intramedullary tumour, no such difference was found.

Marie, Foix and Bouttier(21) returned to the subject of "double puncture" in the following year, and in one case found that the fluid removed from above the lesion was five times as rich in albumen as that

obtained by lumbar puncture. They considered that this result verified the theory of the "cavité close" put forward by Sicard and Descomps and by Derrien, Mestrezat and Roger.

During the discussion of their case Cl., Vincent stated that he had found yellow, highly albuminous fluids in several cases of tumour of the ponto-cerebellar angle. If in such a case a second puncture were performed within the next few days the fluid obtained would be normal or almost so, but if a third puncture was performed, after an interval of some weeks, the fluid would again be found to be highly albuminous. He considered that these facts proved that the fluid altered its character after it was secreted.

It must be remembered that tumours of the ponto-cerebellar angle are sometimes associated with tumours of spinal nerve roots, and it may have been to some such cases that Vincent referred. At the same time it is not impossible that these changes might be present in the fluid of cases of solitary eighth nerve tumour, though I have not personally encountered this.

(8)  
Froin's syndrome in epidemic cerebro-spinal meningitis.

In 1915 Duncan Forbes and Adam (13) reported an unusual type of cerebro-spinal fluid in some fatal cases of epidemic cerebro-spinal meningitis. They said that "sometimes in chronic cases which are evidently becoming worse . . . . . one finds the usual cloudy fluid replaced by a yellow, at times clear fluid in which organisms may apparently be absent. This yellow fluid becomes like a jelly on standing even for a short time . . . . . In no case, in which such fluid has been found have we had a recovery".

Recent American literature has contained several references to the syndrome of Froin. Mix (27), in 1915, gave a clinical lecture on a case of spinal tumour in which the syndrome was found; in this he reviewed, fairly completely, the French work on the subject.

Hanes (16) in the following year reported five cases of the syndrome. Two of these are of special interest. In the first case, which was that of a child of nine months, with spastic paraplegia, the fluid obtained by lumbar puncture was the colour of picric acid and coagulated massively. It contained great proteid excess and 16 cells per c.mm. Hydrocephalus developed later and fluid of a normal character was drawn from a ventricle. At the autopsy he found a ring of tuber-

cular thickening of the meninges round the medulla.

In the second case laminectomy disclosed a cyst of the pia-arachnoid at the level of the 7th thoracic vertebra, below which the arachnoidal veins were seen to be greatly distended and tortuous. In this case a normal fluid was obtained by lumbar puncture six weeks after the operation.

(9) Experimental production of the syndrome.

In 1913 Salin and Reilly<sup>(35)</sup> in the course of some experiments on the passage of antibodies from the blood into the cerebro-spinal fluid, reproduced the syndrome of Froin experimentally. They injected a few drops of an emulsion of tubercle bacilli into the epidural space of dogs, and produced a tubercular inflammation round the dura mater. At various intervals they tested the blood and cerebro-spinal fluid for anti-bodies to the tubercle bacillus, by means of the Bordet-Gengou reaction. In the first experiment they found that the fluid drawn from the cisterna magna became albuminous without developing a corresponding increase in cells. It was found to contain anti-bodies. In their second experiment they obtained fluid both from the cisterna magna and by lumbar puncture, a month after the injection of tubercle

bacilli. The fluid from the cisterna magna showed a slight increase in albumen, while that from the lumbar theca was very highly albuminous. A similar result was got from a third experiment.

More recently an attempt was made by Ayer (1) experimentally to produce the conditions of pressure on the cord in which the syndrome of Froin may be encountered. He injected 1.5 c.c. of melted paraffin (melting point 55°C) into the epidural space of cats, and removed fluid from the cisterna magna and lumbar region of the theca at varying intervals thereafter. Yellow fluid, coagulating spontaneously, was obtained by lumbar puncture within twenty-four hours of the operation in two of these experiments. But after the lapse of several days or weeks the cerebro-spinal fluid obtained from both situations was normal. The result of his injections was to cover the outside of the theca for a considerable distance with a layer of paraffin which was never more than 3 m.m. thick, and to produce a local myelitis of the cord at the site of injection. The latter effect was probably due to the high temperature of the "injection mass" and was associated with the presence of polymorphonuclear leucocytes in the subarachnoid space.

In a recent paper (1920) Raven (32) collected one hundred and forty-five cases of compression of the spinal cord by tumour or by disease of the vertebrae or meninges. From an analysis of these he came to the following conclusions :-

(1) The presence of increase of globulin content without any change in colour is uncommon in intra-medullary tumours and is more common in extra- than in intra-dural tumours.

(2) Although xanthochromia is not limited to cases in which the site of the tumour is low in the spinal canal, it is more commonly found with tumours of this region than those compressing the cervical region of the cord. Cases of increase of the globulin content without other change in the fluid decrease in frequency as the site of the tumour is lower in the spinal canal.

(3) Xanthochromia is no indication as to whether the tumour is intra- or extra-medullary.

(4) Rapidly increasing severe compression is more likely to cause xanthochromia than more slowly progressive forms of compression. In this connection he quotes a case of dislocation of the cervical spine in which a yellow fluid, in which no red blood corpuscles

could be seen, was obtained by lumbar puncture 24 hours after the accident.

(5) Spontaneous coagulation is found equally in extra- and intra-medullary tumours.

(6) The nature of the compression is without bearing on the intensity of the changes in the fluid.

(7) The character of the tumour is without influence on the development of the "compression syndrome".

In 1920 Lantuéjoul and Souques (20) described a case of syphilitic meningo-myelitis presenting the typical syndrome of Froin, in which very high percentages of albumen and of fibrin were found. The albumen was estimated in two puncture fluids at 4.285% and 4.205%; the fibrin at 0.275% and 0.155%. At the same time as the last lumbar puncture, another puncture was made between the 9th and 10th thoracic spines. This gave cerebro-spinal fluid under slightly increased pressure which contained only 0.045% albumen, the albumen contents of the fluids from the dorsal and lumbar punctures thus being in the proportion of 1 to 93.

In this year also Lantuéjoul (19) in the course of a review of the syndrome of Froin found only thirty-eight pure cases in the literature, excluding all but those in which the fluid coagulated spontaneously and massively. He noted that not only had lumbar punctures on successive days given, in certain cases, fluids of different composition, but in two cases the colour and nature of the fluid had altered considerably as it flowed out of the needle; the yellow, highly albuminous fluid which came first being followed by paler or colourless fluid showing little departure from the normal. It appeared as if, during the puncture, the lower, abnormal fluid had been progressively diluted by normal fluid from above.

### Personal Observations.

During the past two years I have examined three cerebro-spinal fluids which gave the typical appearances of Froin's syndrome, as well as numerous others which resembled these in yellow colour and notable increase of albumen, but which either did not coagulate at all or not sufficiently "en masse" to justify their presentation as true cases of the syndrome. They are recorded here in order to illustrate the type of disease in which the syndrome occurs and to throw what light they may on the aetiology of the changes found in it. For the clinical notes of these cases I am indebted to the clinical staff of the hospitals in which they occurred.

#### I. TYPICAL CASES of FROIN'S SYNDROME.

##### Case 1. Paget's Disease of the Spine.

V.C., male, age 63, was admitted to the National Hospital for the Paralysed under Dr. Kinnier Wilson in March 1920 with the diagnosis of paraplegia. He had complained of weakness of the legs for one year and nine months. In the summer of 1918 he had "grogginess" of the legs which would give way so that he fell down, but there was neither pain nor numbness.

In November 1918 his legs felt heavy and stiff in walking. By the end of December he had complete paraplegia with no voluntary power in the lower limbs, but reflex spasms in them and a feeling as of a band in the upper part of the abdomen. The doctor discovered that he could not feel at all in the legs. He never had any pain in the spine, limbs or body.

On admission it was noticed that his spine was held very rigid, and there was a prominence of the 9th thoracic spine, but no tenderness or kyphosis. There was complete paralysis of the lower limbs and lower part of the abdomen and the lower intercostals, with anaesthesia fading away in the region of the 6th and 7th thoracic segments. Ankle clonus was present but the knee jerks were diminished owing to spasticity. Plantar stimulation gave upward movement of toes on both sides.

On 17th March lumbar puncture was done and a very small quantity of yellow fluid was obtained. This coagulated solid in the tube so that on inversion of the tube it did not escape. The amount of fluid was too small (less than 1 c.c.) for any examination except that for cells of which only red blood corpuscles could be seen. The Wassermann reaction on the blood performed at the same time was negative.

On 11th May 1920 an operation was performed at the level of the 1st to the 4th thoracic vertebrae. No tumour was found but there was a diffuse thickening of the laminal arches. No pulsation was visible in the dura mater covering the cord until after the laminectomy had been increased upwards.

The patient died shortly after the operation. An autopsy limited to the spine was performed about twelve hours after death. At the level of the laminectomy the vertebral laminae looked rather thicker and cut more easily than normal. Below this level the thickening and increased softness of the laminae became progressively more evident, so that in the lower thoracic and upper lumbar regions the bone could be picked away with dissecting forceps. The thickening of the bone caused narrowing of the spinal canal, so that the dura mater was everywhere in contact with the bone, to which also it was abnormally adherent all over. The cord was removed and appeared normal. It was then seen that a small nodule projected backwards from the lower part of the body of the 8th thoracic vertebra. A smaller nodule of similar character was seen on the body of the 6th thoracic vertebra. At the lower end of the 10th thoracic vertebra the spine had a sharp concavity as though the body of the 11th

thoracic vertebra had been displaced forwards. This body was shorter than those of the other vertebrae. Below this level the contour of the spine was rather irregular. No sign of thickening of the tibiae or femora could be made out and no thickening or bossing of the skull, but a dissection of these parts was not allowed.

Microscopically the laminae showed great rarefaction of the bony trabeculae with numerous large osteoclastic cells in contact with them. The tissue spaces were abnormally wide, and were filled with myxomatous cells with oval or elongated nuclei and long fine branching processes. There was also a sprinkling of small rounded lymphocyte-like cells through the interstitial tissue, and in some places collections of blood-forming marrow cells. The appearances seemed to be those of osteitis deformans.

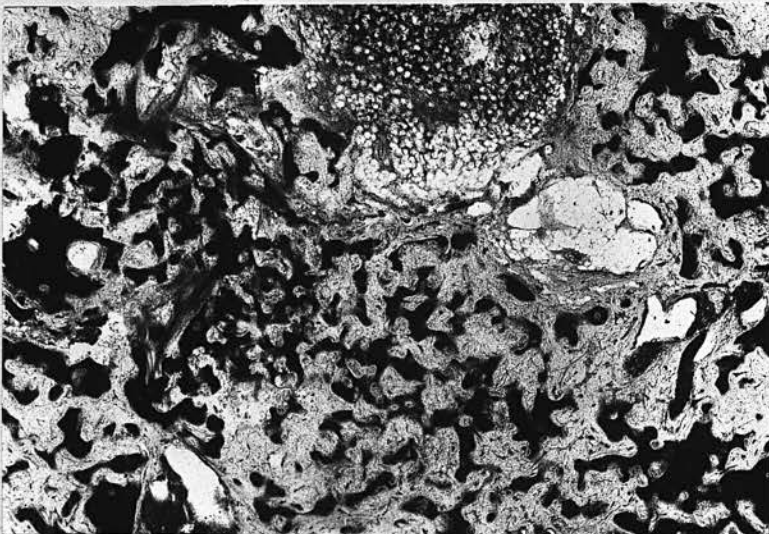


Fig.1. Section of laminae removed at autopsy, showing thinning of bony trabeculae and in one place an area of red bone marrow.

Case 2. Carcinoma of the Spine.

Annie F., age 45, was admitted to the National Hospital for the Paralysed on 6th September 1919 under Dr. Holmes, complaining of loss of use of legs of one year's duration. This came on with severe pain in the bottom of the back which, however, had passed off. The left leg was affected in May 1918, the right in the following September; by November 1918 she had complete loss of power of movement in both legs.

On examination she showed a nodular tumour of left breast with a gland in the axilla. She was completely paraplegic in flexion with involuntary flexor spasms, and very slight power of movement. Sensation to cotton wool was lost completely between the 4th lumbar and the 2nd sacral segments with increased loss for two segments above this, but there was no loss in the 3rd and 4th sacral segments. Sensation to pain and temperature were dulled over the same area, and there was loss of sense of movement of the ankles. The left epigastric reflex was obtained but no other abdominal reflexes. The knee jerks were diminished, the ankle jerks brisk with a tendency to ankle clonus. Stimulation of the sole of the foot gave an upward

movement of the great toe on both sides.

On the 9th September lumbar puncture was performed and a yellow fluid obtained which coagulated spontaneously into a fairly dense jelly. It contained albumen :- 1.2%. Only a very few lymphocytes were seen in films. The Wassermann reaction was negative in blood and cerebro-spinal fluid.

On September 20th laminectomy was performed by Mr. Sargent who found diffuse malignant disease of the lumbar vertebrae which proved on histological examination to be a scirrhus carcinoma.

Case 3. Intra-dural Myxoma. Operation, recovery.

Alfred W., aged 42, was admitted to the National Hospital for the Paralysed on the 22. 10. 20 under Dr. Hinds Howell complaining of pain in the left side and paralysis of both legs. The pain had come on in the summer of 1918 but he had not felt his legs weak until July 1920. The first symptoms noticed in the legs was numbness, especially in the left leg, and soon after this the left foot dropped, and he suffered from shooting pain running up his left leg and sometimes down the right. He also had slight difficulty in starting micturition.

On examination he was found to have a spastic paraplegia, with considerable weakness of the lower limbs especially in dorsi-flexion at the ankle joint, but he could walk in his boots with the help of two sticks. There was some wasting of the lower limbs and fibrillary contractions were seen in the hamstrings and the insides of the calf of the left leg. There was no inco-ordination of movement. Skin sensibility to cotton wool touches was slightly impaired on the right lower limb. Pin-prick was not appreciated over the whole extent of the limbs below a horizontal line about half way up the thighs, and in a band on the left side of the body running round below the lower margin of the ribs to a point midway between umbilicus and pubis. Between this line and the anaesthesia on

the legs, pin-prick was felt "like an electric shock". There was no loss of sensibility to pin-prick over the saddle area. The knee jerks were brisk, especially on the right side. The ankle jerks present on the right but feeble on the left side. The upper abdominal reflexes were present, the lower absent. The plantar response was of the Babinski type on both sides.

On the 26. 10. 20 a lumbar puncture was performed and golden yellow fluid escaped which coagulated solid in the tube in a few minutes. No cells were found in it. It contained 0.75% albumen. No opacity was produced on 28% or 33% saturation with ammonium sulphate, but half saturation gave a very heavy precipitate. The Wassermann reaction was found to be negative in the blood and cerebro-spinal fluid.

On the 9. 11. 20 a laminectomy was performed by Mr. Sargent on the lower thoracic and upper lumbar regions of the spine. A large, soft, oval, gelatinous tumour, in shape and size like a pigeon's egg, was found on the left side of the cord opposite the cut arches of the 11th thoracic vertebra. It lay under the arachnoid membrane, to which, however, it was very loosely attached, and indented the cord considerably on its left posterior surface. Before the theca was

opened it was noted that it pulsated normally above the tumour but not at all below it. The tumour was removed. It measured 2.5c.m. in length and 2c.m. in transverse diameter, and weighed 5 grammes. On section it was found to be composed of myxomatous tissue, with very few branching cells, the processes of which reached for long distances and contained in their meshes clear, serous fluid; a few groups of endothelial cells were also seen in the tumour (v. Figs 2 & 3).

The patient made a rapid recovery, and on the 19. 2. 21 could walk almost normally, and the only motor weakness noted was weakness of dorsiflexion of the left ankle.



Fig 2.

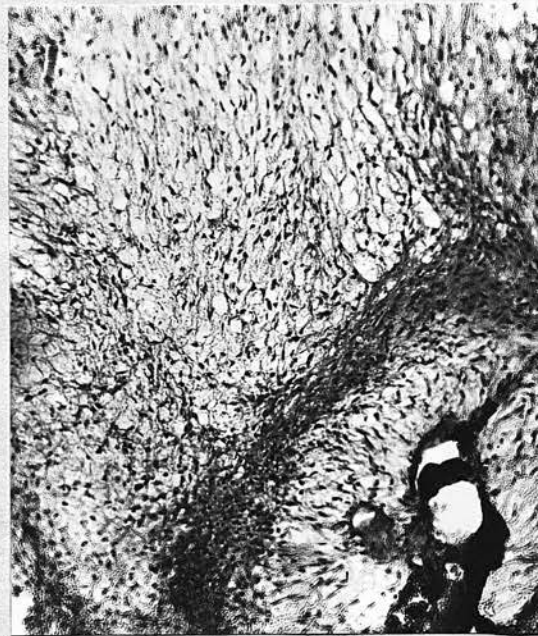


Fig. 3.

Naked eye and low power microscopic views of tumour removed from Case 3.

II. INFLAMMATORY DISEASES of the MENINGES with HIGHLY ALBUMINOUS YELLOW FLUIDS.

Case 4. Acute Myelitis of Unknown Origin.

Gertrude S., aged 23, was admitted to the National Hospital for the Paralysed in November 1920 under Dr. Taylor for paralysis of the lower limbs which had come on suddenly four months previously. The history of the onset was that on July 15th 1920 she woke with pain over the left eye, and the same evening had pain in the legs and back with headache, and was feverish. During the night she lost the sight of her left eye, and within a few hours of the right eye also. On the next day she could not distinguish light from darkness, and had complete loss of power of both legs and loss of sensation up to the face. She also had retention of urine and faeces. On the 18th July, two days after this, she had a profuse red rash. After a fortnight of total blindness her sight improved gradually so that on admission to hospital she could see well. On admission she was found to have a complete paraplegia of both lower limbs which were swollen, oedematous and quite flaccid, with incontinence of urine and faeces. All forms of sensibility were completely lost below the waist as were also both deep and superficial reflexes.

Lumbar puncture on the 29. 11. 20 gave a clear lemon-yellow fluid with no coagulum. It contained 0.6% albumen, and with 28% saturation with ammonium sulphate gave a slight opalescence indicating fibrinogen. No cells were found in it. The Wassermann reaction was negative in both blood and cerebrospinal fluid.

The diagnosis appeared to be acute meningo-myelitis of the lower thoracic region which had completely abolished conductivity in the cord.

Case 5. Staphylococcal Meningitis, limited by adhesions in pia-arachnoid to region above 10th thoracic segment.

Pte B.C.O., aged 30, was admitted to Tooting Military Hospital on 12. 2. 19, with history of four days headache with pains round chest and the lower part of the back. He had vomited frequently since the onset; he was very constipated and had had retention of urine at first.

On admission he was found to have weakness of the neck muscles and head retraction. All movements of the arms were possible but weak. Only slight extension movements of the lower limbs were possible; there was no power of flexing the legs. Both plantar reflexes were of the up-going type.

Lumbar puncture was performed on 16. 2. 19. Clear dark yellow fluid with a greenish tinge was removed. It showed seven small lymphocytes per c.mm. and contained 3% albumen, 0.65% chlorides, and sugar in diminished quantity.

On the 17. 2. 19 he had a fit at 8 a.m. with at first an opisthotonic position. There was tremor of both arms with clutching movements of the right arm and hand. Shortly after the fit an attempt was made to puncture the cisterna magna by inserting a lumbar puncture needle between the atlas and the foramen

magnum. When this was done thin yellow pus came out in large quantities under increased pressure. This was full of polymorphonuclear cells with numerous, intracellular staphylococci which on culture proved to be staphylococcus pyogenes aureus. After the pus settled the fluid above it was clear and colourless. It contained 0.1% albumen and 0.63% chlorides. Glucose was absent.

The patient died at 3.20 p.m. on the same day, and an autopsy was performed on the following day.

The brain was covered on its inferior surface with purulent exudate which filled the basal cisterns but did not run up over the outer aspect of the cerebrum. Punctate haemorrhages were seen over the inferior surfaces of the frontal lobes.

The cord, from its upper end to the 10th thoracic segment inclusive was covered both anteriorly and posteriorly with pus. Below the 10th thoracic segment this stopped suddenly and the surface of the cord appeared perfectly normal.

At the apices of both lungs there were small chronic cavities with hard calcaneous surroundings and puckering of the overlying pleural surface. Spreading out from these was a peri-bronchial spread

of recent miliary tubercles. The other organs presented no abnormality beyond congestion of liver, spleen and kidneys. There was slight atheroma of the aorta.

Case 6. Cerebro-spinal Syphilis.

F.G., male, aged 35, was admitted to the National Hospital under Dr. Hinds Howell on the 12. 5. 19. in 1917 when in the army on board a transport to India he started putting on much weight, and arrived in India about three stone heavier than he left England. On arrival he became unable to speak and was sent to hospital and treated with thyroid gland extract. As he was unfit for service he was sent back to England and discharged.

On examination he was a very stout man and extremely slow in his mental processes. He presented no definite physical signs of disease of the nervous system, but the plantar reflexes gave a somewhat suspicious response.

A lumbar puncture was performed on the 19. 5. 19 and the fluid was examined by Dr. Nabarro who found it to be a clear yellow fluid forming a heavy coagulum on standing. It contained 5 to 10 cells per c.mm. and

1.9% albumen. The Wassermann reaction was strongly positive in the fluid, and less strongly in the blood.

A second lumbar puncture was made on the 30.6.19 when I found the fluid to be clear and yellowish without a coagulum. It contained 100 to 150 cells per c.mm. mainly of the lymphocyte type with a few polymorphonuclear cells. The albumen totalled 0.75%. The Wassermann reaction was again strongly positive in the fluid.

## III.

Case 7. Pressure on spinal cord due to thoracic aneurysm producing a yellow, highly albuminous fluid.

H.N., male, aged 53, was admitted to the National Hospital for the Paralysed on the 26th August 1920 under Dr. Turner with a history of pain in the back and hips for five months and of loss of use of the legs for two months.

On examination he was found to suffer from spastic paraplegia, with sensory loss over the thighs, and loss of joint sense in the feet. Anaesthesia was nowhere complete, but there was loss of sensibility to heat and cold in the area supplied by the 5th lumbar and the sacral segments. His abdominal reflexes were absent; the plantar responses were definitely of the Babinski type on the right side, less definitely on the left with ankle clonus.

While in hospital he developed on the 27th September a pleural effusion on the left side, with elevation of temperature to 102° F.

Lumbar puncture on the 30th August gave a yellowish clear fluid with no coagulum. It contained 15 cells per c.mm., most of them being large cells with a rounded nucleus, which were rather larger than the ordinary large mononuclear cell found in the cerebrospinal fluid. These cells were occasionally seen in

groups and were diagnosed as probably tumour cells. Albumen totalled between 0.5% and 1%, but owing to the small quantity of fluid obtained a more accurate reading was impossible. The Wassermann reaction was negative in blood and cerebro-spinal fluid.

A second lumbar puncture on the 19th October gave a clear colourless fluid containing no cells, with only 0.035% albumen and a weakly positive Nonne-Apelt reaction.

X ray examination revealed a pulsating tumour on the left side of the thoracic spine, and an aneurysm of the descending thoracic aorta was diagnosed. This seemed to have eroded the vertebrae and produced pressure on the cord.

IV. THREE CASES of POTT'S DISEASE PARAPLEGIA giving YELLOW; HIGHLY ALBUMINOUS FLUIDS.

Case 8. Pott's disease, paraplegia and tubercular meningitis.

Sam M., aged 21, was admitted to the National Hospital under Dr. James Collier in May 1919 with Pott's disease and paraplegia. Pain had commenced in the lower thoracic region of the spine in June 1918 but he was examined and passed "fit for service in France". In November 1918 his back became curved and in December his legs gave way under him. He had been treated with extensions on his legs for four months in Nottingham General Hospital.

On examination he showed a kyphosis, almost angular in type, with the greatest prominence at the 8th thoracic spine. There was weakness of the lower part of the rectus abdominis and complete paralysis of both lower limbs with involuntary flexor spasms. The deep reflexes were much increased in the lower limbs. The plantar reflexes were of the Babinski type. He had normal control of his sphincters. Sensibility to pinprick and cotton wool was blunted up to the lower costal margin.

On the 12. 7. 19 an operation for the relief of pressure on the cord was performed by Mr. Sargent who resected the laminae of the 6th to the 10th thoracic vertebrae and evacuated some cheesy pus from the body

of the 9th thoracic vertebra. It was noticed that the peri-theccal fatty tissue was matted and infiltrated, but the dura mater looked normal.

After the operation he gradually regained slight power in his lower limbs. In October he developed a slight pleural effusion on the left side.

Towards the end of February he showed signs suggesting meningitis and on the 20. 2. 20 a lumbar puncture was performed which gave a yellow fluid. It did not coagulate and showed only one cell per c.mm. It contained albumen (rather over 0.5%) chlorides 0.75% and glucose about 0.04%. Albumoses were also present. The Lange curve was 0.0.1.1.2.2.2.3.3.3.

The patient died on the 24. 2. 20 and an autopsy was performed at which old-standing tuberculosis of the left lung and tubercular pleurisy covering both lungs was found, but no evidence of recent spread in the chest. The spleen, however, showed many miliary tubercles under its capsule and elsewhere in its structure. The spine at the level of the laminectomy showed a right-angled bend over which the cord was stretched. A considerable quantity of pus escaped from the remains of the body of the 9th thoracic vertebra. The dura mater at this level was covered over with tubercular granulations and pus which had infil-

trated it, and at this level the dura mater was adherent to the cord. Above this level the cord and the base of the brain were covered with a thick gelatinous tubercular exudate. Below it the surface of the cord was clearly seen and the membranes looked perfectly healthy.

Case 9. Pott's Disease and Paraplegia.

Cr., male, aged 49, was admitted to the National Hospital for the Paralysed on the 10. 2. 20 under Dr. Risien Russell complaining of pain in the neck and weakness of the legs. The pain in the neck had begun in May 1919 and he noticed a lump in the back. He continued at work until Christmas when he had to stop owing to pain spreading down from the shoulder and weakness of the knees. About three weeks before admission his feet felt cold and he gradually lost power in them until he could not move them at all. About three days before admission he lost control of the bladder and rectum.

On examination he showed a sharp angular curvature in the lower thoracic region, the 10th thoracic spine being the most prominent. Except for slight movement at the right hip and knee the lower limbs were completely paralysed, and there was loss of

sensibility to all forms of stimuli from the 10th thoracic segment downwards increasing on passing towards the periphery.

On the 16. 2. 20 lumbar puncture gave a clear yellow fluid which did not coagulate until after the addition of a drop of fresh blood. No lymphocytes were found in it, but it contained 1.5% albumen. The Wassermann reaction was negative in blood and cerebrospinal fluid.

On the 22. 2. 20 an operation for the relief of pressure on the cord was performed by Mr. Armour who found a tubercular cavity in the body of the 10th thoracic vertebra. The dura below the level of the curvature did not pulsate until after the removal of the laminae above, when pulsation returned.

#### Case 10. Pott's Disease and Paraplegia.

Eben H., aged 17, was admitted to the National Hospital under Dr. Buzzard in April 1920 with Pott's disease and paraplegia. He had suffered from spinal curvature since the age of seven and from paralysis of the legs since January 1919. This had come on gradually so that he could walk until August 1919. The paralysis had improved slightly since November 1919.

On examination he showed a spinal curvature in

the dorsal region in which scoliosis predominated over kyphosis, and the costal margins were approximated to the iliac crests. He had paraplegia in extension with dropped feet. There was almost complete paralysis of the right leg, and considerable loss of power in the left. Sensibility to cotton wool and pin-prick was much diminished from the knees up to the umbilicus. There was some loss of sphincter control. The deep reflexes of the lower limbs were greatly exaggerated. The plantar reflexes were of the Babinski type.

Lumbar puncture performed on the 13. 4. 20 gave a clear lemon-yellow fluid which did not coagulate. It contained one lymphocyte per c.mm. and 0.8% of albumen. The Wassermann reaction was negative.

These three cases are recorded as they showed very great increase of albumen in the cerebro-spinal fluid. I have examined the fluids of several other cases of paraplegia due to Pott's disease, in which changes of a similar nature, though of less degree, were found.



V. NINE CASES of SPINAL TUMOUR with YELLOW, highly ALBUMINOUS FLUIDS.

Case 11. (?) Recurrence of spinal tumour.

B., female, aged 37, was admitted to the National Hospital for the Paralysed under Dr. Tooth. She had commenced to develop paraplegia in June 1906 and had previously been admitted to the National Hospital completely paraplegic in 1913. In January 1914 a laminectomy had been performed and a tumour found which completely blocked the spinal canal between the cut laminae of the 4th and 6th thoracic vertebrae. The tumour lay in the mid-line on the posterior surface of the cord and was removed except for its attachment to the ribbon of cord lying in front of it.

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On the 2. 11. 19 a lumbar puncture was performed and yellow cerebro-spinal fluid containing some blood admixture was removed. It formed a heavy coagulum on standing and was found to contain 2.3% albumen and 0.76% chlorides. No cells were found in it.

On the 24. 11. 19 a second lumbar puncture again gave a yellow fluid which this time did not clot. It was found to contain a large number of mononuclear cells and 3.6% albumen. The Wassermann reaction was negative in the blood and cerebro-spinal fluid. The lymphocytes in the fluid obtained by the second puncture were explained by the haemorrhage into the sub-arachnoid space caused by the first puncture.

Case 12. Neurofibromatosis of cauda equina.

Fred A., aged 50, was admitted to the National Hospital under Dr. Kinnier Wilson on 23rd October 1920 with the diagnosis of lesion of the cauda equina. The history of his disability started in 1915 when his left leg became stiff and painful, and his heel tended to rise from the ground. In 1916 he had some pain in the left knee, and noticed wasting of the left leg. About this time he had some hesitancy in micturition. His symptoms increased slowly and at Easter time 1918 he had pain in both thighs and during the summer of 1920 he developed numbness and weakness of the left leg which rapidly increased and affected also the right leg.

On examination the spine was slightly kyphotic in the lumbar region and there was some tenderness in the same area. Sensibility was impaired over the area of skin supplied by the 2nd to 5th lumbar segments, with partial loss in the distribution of the 1st sacral, but none on that of the lower sacral segments. There was wasting of the glutei especially on the left side and of all the muscles below this level especially those of the thighs. Some fibrillation was seen in the glutei.

The abdominal reflexes were diminished below the umbilicus. Neither plantar reflex nor knee jerk could

be elicited. The right ankle jerk was brisk, but the left feeble.

On the 26. 10. 20 lumbar puncture was performed and 5 c.c. of amber coloured fluid escaped. The flow then ceased abruptly. This fluid was ~~of~~ a deep golden yellow without a coagulum. It contained 9 lymphocytes per c.mm. and about 1.5% albumen. On fractional saturation with ammonium sulphate it gave a slight opalescence with 28% saturation which increased to a fairly heavy cloud at 40% saturation. The Wassermann reaction in blood and cerebro-spinal fluid was negative.

I am indebted to Dr. Oxley for a report on the examination of cerebro-spinal fluid obtained by him by puncturing between the 12th thoracic and 1st lumbar spines on the 11th October. This was a bright golden yellow fluid with a large firm clot, which contained in its meshes a few cells. The total albumen apart from the clot was 0.95%. There was thus very little difference between the fluids obtained by two punctures at a fortnight's interval.

On the 9th November a laminectomy was performed by Mr. Sargent in the lumbar region. The membranes were found distended by growth and formed a sausage-shaped mass twice the normal diameter of the theca.

The growth was a soft gelatinous and haemorrhagic mass attached all round the cord and surrounding the nerve roots at the conus medullaris and for about three inches above it. This was dissected off the nerve roots as far as possible.

Unfortunately the patient developed a very severe cystitis to which he succumbed on the 20th November 1920. A post mortem examination was made, limited to the lower part of the cord and the kidneys. The area from which the tumours had been removed was represented by a cyst formed by the membranes and containing blood. On the right side of the lumbar enlargement at a higher level there was a soft fleshy piece of tumour about one inch long and  $\frac{1}{4}$  inch wide lying among the nerve roots to which it was loosely attached.

The tumours gave the typical microscopic appearances of neurofibromata.

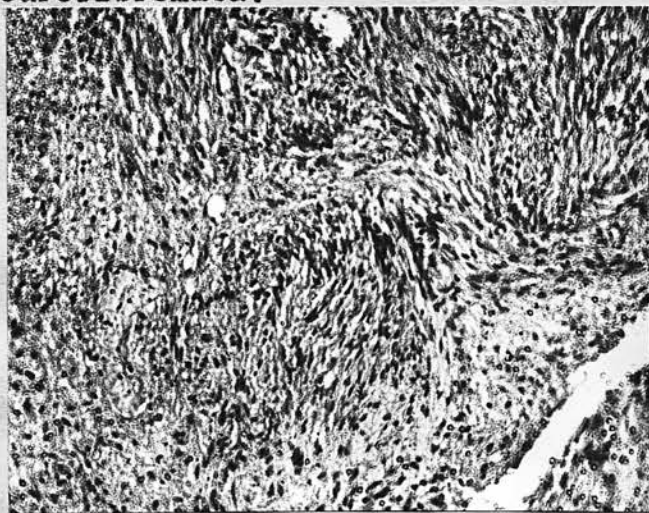


Fig. 4. Low power view of neurofibroma of Case 12 removed by operation.

Case 13. Endothelioma pressing on the mid-thoracic region of the cord.

Dorothy F., aged 19, was admitted in February 1920 to the National Hospital for the Paralysed under Dr. Tooth, suffering from inability to walk. Her symptoms commenced in August 1918 when her legs became cold and numb. On examination she showed complete paraplegia with loss of sphincter control, and of sensibility to all forms of stimuli below the 11th thoracic segment. On the right side the loss of sensibility to pin-prick reached up to the 7th thoracic segment and faded away between this and the 5th segment.

On the 24. 2. 20 lumbar puncture gave a very slightly yellow fluid containing about 4 small lymphocytes to the c.mm. and 1.5% albumen. It did not clot. No albumoses were found in it. The Wassermann reaction was negative in blood and cerebro-spinal fluid.

A laminectomy was performed by Mr. Sargent on the 15. 5. 20 and an intra-theccal tumour of about the size of a walnut was found opposite several of the lower thoracic vertebra. It was vascular, soft and fleshy, and had to be removed in several pieces.

Histologically it gave the appearances of a fibrous endothelioma containing many round areas of fibrous tissue in some of which calcification was commencing.

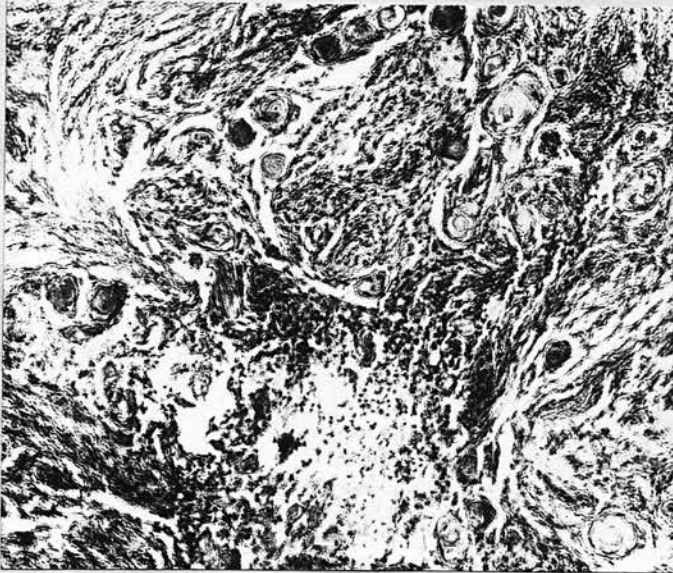


Fig.5.

Low power view of endothelioma of Case 13 showing whorls and knots of fibrous tissue.

Case 14. Intramedullary tumour of the spinal cord.

Mrs. S., age 48, was admitted to the National Hospital for the Paralysed under Dr. Buzzard complaining of paralysis of the legs of one year's duration. Her first symptom was intercostal neuralgia low down on the left side; soon after this she had pain in lower part of spine, and later pain in the left side of the lower abdomen. In May 1918 she developed very severe pain in the epigastric region

with adductor spasm of the legs, followed soon after by a feeling of tightness round the right ankle, and then numbness first in the right leg and then in the left and spreading up the body as far as the waist. Her walking became impaired and since Christmas 1918 she had not been able to walk at all. Since then she had had involuntary jerkings of the legs and sphincter trouble. In February 1919 laminectomy was performed at the South London Hospital by Miss Davis Colley who found thickening of the meninges in the mid-thoracic region.

On admission the scar of a laminectomy wound was seen extending from the 4th to the 8th thoracic spines. She had complete loss of voluntary movements of the lower limbs which were spastic and wasted, and complete loss of all forms of sensibility up to one inch below the umbilicus. The abdominal reflexes were absent, the knee and ankle jerks present, and there was a tendency to ankle clonus on both sides. The plantar responses were upward movements of the great toes. On the 20. 6. 19 laminectomy was performed enlarging the previous operation downwards. The cord opposite the body of the 8th thoracic vertebra was swollen and pale, and below that level the membranes were matted. No

tumour was found outside the cord. A shallow incision through the postero-median fissure gave exit to a single drop of glairy fluid.

A lumbar puncture on the 20. 11. 19 gave a yellow fluid with a heavy coagulum. Albumen was about 1% and two large mononuclear cells were found per c.mm.

Case 15. ? Granuloma of Spine.

A., male, age 36, admitted 18. 5. 20 to the National Hospital under Dr. Buzzard, diagnosed as spinal tumour.

Since November 1919 he had weakness in his legs which dragged when he tried to get about and soon after Christmas he felt as though he were walking on a cushion. Since then walking had become impossible. On examination he showed complete spastic paraplegia with no voluntary power below the waist, and complete loss of all forms of cutaneous sensibility below the 1st lumbar segment with diminution between this and the 10th thoracic segment. But vibration sense and sense of position in space, though impaired, were not completely lost in the lower limbs. He had normal control of his sphincters. The knee jerks and ankle jerks were increased, abdominal reflexes absent, and

plantars of Babinski type on both sides.

A lumbar puncture on 25. 5. 20 gave a clear cerebro-spinal fluid of a pale lemon-yellow colour which contained four cells per c.mm. and about 1% of albumen. No coagulum formed until after a drop of blood was added and then only a very thin web. Albumoses and peptones were absent. The Wassermann reaction was negative in cerebro-spinal fluid and blood.

On 9. 6. 20 laminectomy was performed by Mr. Sargent who found an extra-theccal tumour adherent to the dura and infiltrating and eroding bone in the region of the 8th and 9th thoracic vertebrae. Numerous fragments of this growth were removed weighing altogether about eight grammes. Microscopically the tumour appeared to be composed of vascular inflammatory tissue and fibrous tissue, the more cellular parts showing various forms of cells among which small lymphocytes were most numerous, but polymorpho-nuclear and plasma cells were not rare, and a few larger endothelial cells were seen.

Case 16. Intramedullary sarcoma in upper dorsal region.

William W., aged 40, was admitted to the National Hospital in October 1920 under Dr. Rissien Russell with the diagnosis of spinal tumour.

In 1917 he had had pains in the right hypochondrium which were diagnosed as due to gall-stones. In 1918 he began to have weakness and stiffness of his legs and a tendency to retention of urine. Since August 1920 he had become very weak on his legs.

On examination he showed spasticity of both legs, with comparatively little loss of power. There was diminution of sensibility up to the 6th thoracic spine with an area of hyperaesthesia reaching from this level to the 2nd costal cartilage. Vibration was defectively felt below the xiphisternum. The knee and ankle jerks were exaggerated, and the plantar responses of the Babinski type.

Lumbar puncture on the 25th October gave a clear yellowish fluid without any coagulum. It contained 6 cells per c.mm. and 0.75% albumen. Ammonium sulphate in 28% saturation gave no opalescence, but at 33% and still more at 40% saturation there was definite opalescence, The Wassermann reaction was negative in blood and cerebro-spinal fluid.

On the 18th December 1920 a laminectomy operation in the upper thoracic region was performed and an intra-medullary growth found, a small portion of which was removed for examination. It proved histologically to be a sarcoma of the perivascular type, being composed of a mass of small rounded cells grouped round blood vessels, the walls of which were very thick and in places hyaline. At a certain distance from these vessels the tumour cells tended to degenerate, so that the blood vessels appeared to be surrounded by a collar of cells with a degenerated area outside this.

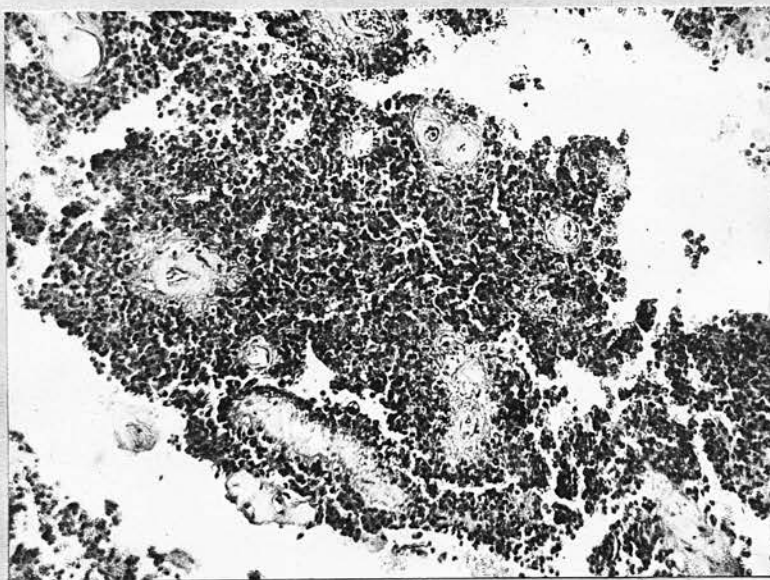


Fig. 6.

Low power microscopic view of tumour of Case 16 showing collars of small round cells around thick-walled blood vessels.

Case 17. Intra-medullary tumour.

Geo. B., aged 28, was admitted to the National Hospital under Dr. Hinds Howell on the 11. 7. 19 with the diagnosis of lesion of the cauda equina. This history dated back to March 1917 when the right leg became weak and he had pain in the lumbar region and in the right leg. In August 1917 he had an attack of pyrexia associated with frequent involuntary jerks in the lower limbs. After this he could scarcely walk at all. On examination he was found to be almost completely paraplegic with sensory loss to all forms of cutaneous sensibility up to the upper lumbar segments fading away gradually and disappearing at the 12th thoracic segment. The sense of position was absent in the great toe but present in the knees.

On the 15. 7. 19 a lumbar puncture gave a yellowish clear fluid which did not clot even after the addition of a drop of blood. It contained four cells per c.mm. and 0.3% albumen. Glucose was present in about normal amount and the chlorides were estimated at 0.71%.

On the 28. 7. 19 a laminectomy was performed by Mr. Sargent, at the level of the 7th thoracic to the first lumbar spines. No tumour was found, but the dura mater was adherent to the pia mater and the latter

to the nerve roots. The cord looked irregular and bulged through the dural opening. A shallow incision into the postero-median fissure showed gliomatous matter and a little fluid escaped.

Case 18. Intradural haemangioma.

Thos. P., aged 51, was admitted to the National Hospital for the Paralysed under Dr. Risien Russell in March 1920 with symptoms of paralysis of the left arm and leg. The history of his affection commenced in August 1919 with pain in the left shoulder. In November 1919 the left arm began to lose its power and by Christmas the left leg was awkward and stiff.

On examination there was flaccid paralysis with slight general wasting, greatest in the shoulder and upper arm. There was spastic weakness of the left leg and inco-ordination of both lower limbs. The gait was that of left hemiplegia. Sensibility to cotton wool was everywhere intact. To pin-prick it was diminished in the epaulet area of the left shoulder and over the right side from the fourth cervical segment downwards. Sense of position was defective in the fingers of the left hand and the left great toe. Stereognostic sense was defective in both hands.

The deep reflexes were present but weak in the left arm, absent in the right. In the lower limbs they were brisker on the left side than on the right. The plantar response on the right side was the normal downward movement of the toes, while on the left side the Babinski phenomenon was present.

A lumbar puncture on the 9. 3. 20 gave a very slightly yellow fluid without coagulum or cells. It contained 0.15% albumen and gave a strongly positive Nonne-Apelt reaction. The Wassermann reaction was negative in blood and cerebro-spinal fluid.

On the 17. 4. 20 a laminectomy was performed on the cervical region of the cord. On exposing the dura mater it was seen to be very tense and non-pulsatile below the 4th cervical vertebra. On opening it an oval sessile tumour measuring 15 by 5 m.m. was found lying against the left side of the cord, and slightly in front of it. It lay under the ligamentum denticulatum and the posterior nerve roots of the 3rd and 4th cervical segments. It was removed and the patient made a good recovery.

Microscopically the tumour is composed of papillary outgrowths and irregular strands in which numerous large vessels run. Between these strands are clear spaces in which here and there collections of serum

containing a few leucocytes and red blood corpuscles are seen. The tumour is composed partly of fully formed connective tissue and partly of collections of fibroblasts and endothelial cells, and in some places there are collections of brownish granules, apparently composed of haematoiden pigment, some of which are contained in large endothelial cells while others appear to lie free in the tissue. The walls of the blood vessels which are fairly thick are composed mainly of fibrous tissue and contain no muscle fibres. The tumour appears to be a haemangioma.

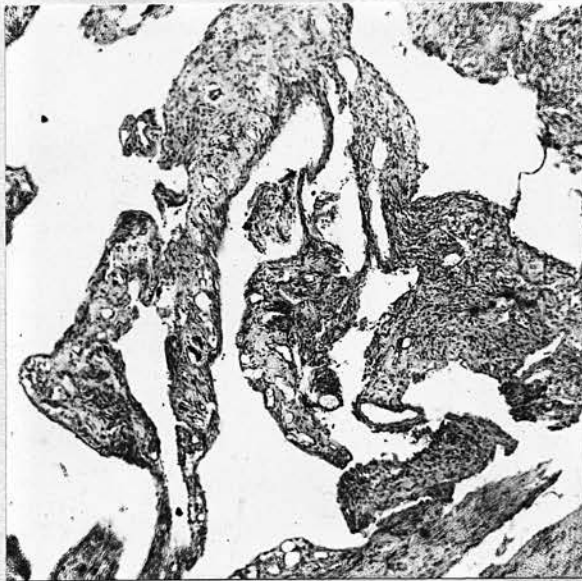


Fig.7.

Low power microscopic view of tumour removed from Case 18, showing strands of tumour tissue enclosing numerous large blood vessels.

Case 19. Tumour of the conus terminalis (perivascular sarcoma)

Mary E. G., aged 40 years, was admitted to the National Hospital for the Paralysed on the 22. 10. 20 under the care of Dr. Farquhar Buzzard. She had had for the previous two years weakness and wasting of the right leg, pain in the right thigh and defective sphincter control. On examination the right leg below the knee was found to be  $1\frac{1}{2}$  inches thinner than the left and the wasted muscles had lost their faradic excitability. There was loss of sensibility to pin-prick over the area supplied by the 3rd, 4th and 5th sacral segments on both legs and there was diminution of the sensibility to cotton wool over the same area with confusion of hot and cold contacts.

The knee jerks were present. The ankle jerks both absent. Lumbar puncture performed on the 26. 10. 20 gave a clear slightly yellow fluid which did not coagulate. It contained three mononuclear cells per c.mm. and 0.08% albumen and gave a trace of opalescence on 28% saturation with ammonium sulphate. The Wassermann reaction in the (unheated) fluid was positive, but in the serum negative.

A second lumbar puncture a fortnight later gave a clear colourless fluid with no clot. It contained no

cells and only 0.04% albumen. Percentage saturation with ammonium sulphate gave no opalescence below 40% but a definite haze between 40% and 50% saturation. The Wassermann reaction was negative in both blood and cerebro-spinal fluid.

On the 26. 11. 20 a laminectomy was performed by Mr. Sargent, and a tumour was found lying posteriorly over the lumbar enlargement. Its upper end was free but its lower end appeared to be attached to the lower end of the conus terminalis. It was removed as completely as possible.

After removal it was found to measure  $1\frac{1}{2}$  inches in length by about  $\frac{1}{2}$  inch in transverse diameter ( $\frac{3}{4}$  inch at its widest part) and weighed 10 grammes. It was pinkish white in colour, nodular on the surface and covered over by a smooth capsule in which veins and arteries ran. Microscopically it was found to be composed of small rounded or oval cells, with round nuclei, which surrounded thick-walled blood vessels, many of which were thrombosed. A small part of the lower end of the cord had been removed along with the tumour and this showed infiltration by tumour cells and much glial proliferation. Figs. 8. and 9.



Fig.8.

Naked eye appearances of tumour removed by operation from Case 19.

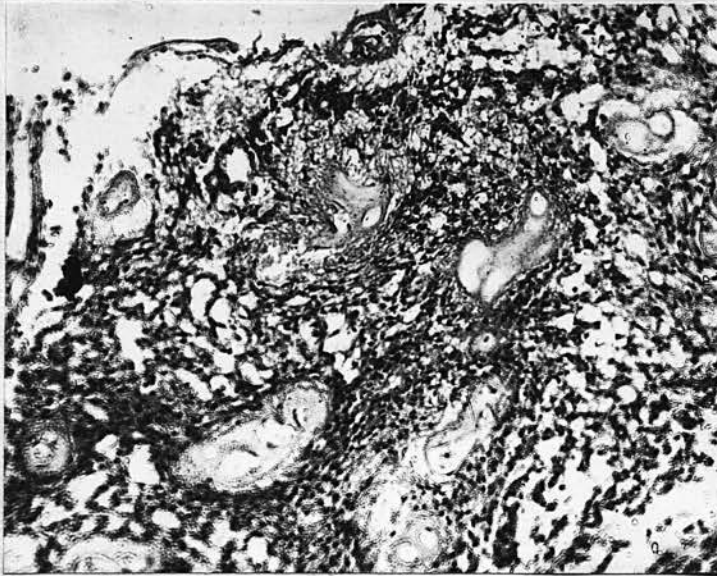


Fig. 9.

Low power microscopic view of tumour showing thick-walled blood vessels containing several channels running among tumour tissue composed of small round cells.

TWO CASES of MULTIPLE NEURITIS with YELLOWISH, highly ALBUMINOUS FLUID.

Case 20. R. A., male, aged 22, was admitted to the National Hospital on the 14. 9. 20 under Dr. Collier. Paralysis of the legs, arms and trunk commenced on the 2nd September 1920, followed on the next day by some loss of visual accomodation. This came on a few days after a sore throat and nasal catarrh. On September 5th he had some difficulty in swallowing, and two days later his voice was indistinct owing to difficulty in opening his mouth. The weakness of the legs and arms progressed so that on the 12th September he was completely paralysed in his legs except for some movement of his toes. His arms also became very weak and he had a numb feeling over the hands.

On admission he was found to be almost completely paralysed in the limbs and trunk, and there was also some weakness of the diaphragm and of the muscles supplied by the 5th and 7th cranial nerves, especially on the left side, and the pharyngeal reflex was diminished. There was some loss of sensibility to pin-prick over the arms, and over the legs there was some hyperaesthesia to pin-prick. Sense of position in the legs was defective but the co-ordination of the arms was good.

77.

All the deep reflexes were absent and plantar stimulation gave a downward movement of the great toe.

Lumbar puncture, performed on the 17th September gave a slightly yellow fluid which yielded on standing a fairly thick web of coagulum. Two lymphocytes per c.mm. were found in the fluid exuded from the clot. The total albumen content was found to be 0.25% by the Aufrecht tube and the Nonne-Apelt reaction was positive but not very strongly. 0.72% chlorides were found. The fluid gave a strongly positive Wassermann reaction in the unheated condition.

A second lumbar puncture performed on the 28th September again gave a slightly yellow fluid with a thick web of coagulum. Examination showed it to contain about 1 cell per c.mm., and albumen 0.35% (Aufrecht). This time, after heating, the fluid and blood both gave a negative Wassermann reaction. Lumbar puncture was performed after the patient had improved considerably on the 30th November, and a clear colourless fluid was obtained. No cells were found in this fluid. The albumen was 0.07% as measured by Mestrezat's method, and the Nonne-Apelt reaction was positive. The Wassermann reaction was again negative. The curve given by Lange's colloidal gold reaction was 0.0.1.2.3.3.1.1.1.0.

Case 21.

E.B., male, aged 25, was admitted to the National Hospital on the 18. 2. 21 under Dr. Tooth. Paralysis of the arms and legs commenced to come on about seven months before admission. It began to come on with twitching of the muscles at the back of the left shoulder and pain of a dragging and shooting nature down the arm. The right arm followed soon after and then the legs were similarly affected. Aching pains in the paralysed limbs have been a feature of the affection.

On admission he was found to present slight weakness of the right side of the face. The tongue was tremulous and wasted at the sides. The arms were almost completely powerless, the only movements possible being slight movements of the fingers and of the arms at the shoulder girdle. In the lower limbs the only movements possible were slight movements of the toes and of the thighs at the hips. No change in cutaneous sensibility could be made out.

All the muscles of the body were wasted and flabby. All the deep reflexes were absent, and plantar stimulation gave a slight downward movement of the toes. The sphincters had all along been unaffected. Lumbar puncture performed on the 21st February 1921

73  
gave a slightly yellow fluid containing 0.24% albumen (Aufrecht), with a positive Nonne-Apelt reaction. No cells were found in it. Lange's reaction gave a curve as follows :- 1.1.2.2.3.3.4.3.2.1.

74.

VII. FOUR CASES of CEREBRAL TUMOUR which showed  
YELLOWISH DISCOLOURATION of the CEREBRO-SPINAL  
FLUID.

Case 22.

J.H., male, aged 53, was admitted to the National Hospital for the Paralysed on the 19. 9.19 under Dr. Taylor with a diagnosis of tumor cerebri.

Lumbar puncture on the 23. 9. 19 gave a yellowish fluid containing 10 large and small mononuclear cells per c.mm., 0.06% albumen, 0.74% chlorides and about the normal quantity of glucose. The Wassermann reaction in the fluid was negative but in the patient's blood was strongly positive.

The patient died on the 14. 10. 19. after a decompression operation, and a post mortem examination revealed the presence of a large tumour in the region of the basal ganglia on the left side, pressing upwards and almost obliterating the left lateral ventricle, the anterior and posterior horns of which were only joined by a narrow channel above the tumour. The tumour was greyish and granular on section, haemorrhagic and softened in its anterior part. It did not infiltrate the brain substance but grew out into it in an irregularly radial manner. At the level of a section just below the corpus callosum the tumour measured 6.5 c.m. antero-posteriorly and 4.5 c.m. trans-

versely. Microscopically it gave the appearances of a gumma, with considerable necrosis in many places.

Case 23.

W.W., male, aged 55, was admitted to the National Hospital under Dr. James Collier on the 15. 9. 20 complaining of headache, symptoms of sensory aphasia and hemianopia. He had also papilloedema on both sides.

A lumbar puncture performed on the 21. 9. 20 gave a yellowish clear fluid without any coagulum. It contained 21 cells per c.mm. which were of the large and small mononuclear types. The total albumen content was 0.045%, and the Nonne-Apelt reaction weakly positive. The Wassermann reaction was negative in both blood and cerebro-spinal fluid. A decompression operation was performed on the 7. 10. 20 and the patient died on the 16. 10. 20.

At the post mortem examination a large tumour was found in the left cerebral hemisphere, projecting under the surface at the posterior end of the fissure of Sylvius, including the posterior part of the supra-marginal and the whole of the angular gyri. On section in the horizontal plane below the corpus callosum a wedge-shaped area of reddish, softened tumour

growth was found to extend from the cortex into the posterior horn of the lateral ventricle, cutting across the optic radiations.

Case 24.

G., male, age 44, was admitted to the National Hospital on the 21. 11. 19 under Dr. Holmes complaining of indigestion, pains in the head and sickness. He had some unsteadiness in his gait tending to fall to the right, and inco-ordination of the right arm. He had recently lost much flesh. On admission he was found to have a lump in the epigastrium just to the left of the middle line, and a large hard gland was felt above the left clavicle. There was slight papilloedema, weakness of the right external rectus muscle and nystagmus, coarse on looking to the left, slight on looking to the right. There was weakness and inco-ordination of the right hand. On standing and walking he tended strongly to fall to the right. On the 24. 11. 19 a lumbar puncture was performed giving a pale yellow cerebro-spinal fluid with a fine coagulum. It contained no cells, albumen 0.06% (Mestrezat). Nonne-Apelt reaction faintly positive. Wassermann reaction negative.

He died on 2. 12. 19. At the autopsy an extensive scirrhus carcinoma of the stomach was found with chains of enlarged glands in and behind the small omentum, but without involvement of the liver. A rounded tumour was also found in the right side of the tentorium cerebelli projecting through this so as to invade both the upper part of the cerebellum and the lower part of the temporo-sphenoidal lobe on the right side. That in the cerebellum measured in horizontal section 3.5 by 3 c.mms., and was pinkish and granular on the cut surface. The tumour in the temporo-sphenoidal lobe measured 4 c.m. in diameter.

Case 25.

Mrs. S., age 67, was admitted to the National Hospital for the Paralysed under the care of Dr. Grainger Stewart on the 31. 12. 20, with symptoms of cerebral tumour, headache, diplopia, and hallucinations of vision. There was no optic neuritis nor localising signs, beyond slight ptosis of the right eye, diplopia on looking to either side and slight weakness in convergence of the eyes. On the 18. 1. 21 lumbar puncture gave slightly yellowish-green fluid with no coagulum. It contained 12 cells per c.mm. mainly of the small mononuclear type with about 30% large mononuclear.

The total albumen was 0.18% Aufrecht; Nonne-Apelt strongly positive but no cloud was given by one third saturation with ammonium sulphate. Lange curve (0.0.0.0.0.1.2.3.2.1.) approximated to the meningeal type. The Wassermann reaction was negative in blood and cerebro-spinal fluid.

The patient died on the 28. 1. 21 and at the autopsy a glioma was found involving the right optic thalamus, right corpus mamillare and the anterior part of the fornix on the right side.

The AETIOLOGY of the CHANGES in the CEREBRO-SPINAL FLUID in the SYNDROME of FROIN.

A survey of these cases makes it clear that the essential feature of the Syndrome of Froin is a notable increase in the percentage of albumen in the cerebro-spinal fluid, and the presence of types of albumen normally absent, notably fibrinogen. Along with this there is usually some yellow colouration of the fluid of greater or less intensity, but it must be recognised that this is not a necessary concomitant of the syndrome, although fluids which coagulate sufficiently for the tube to be turned upside down without any escape of fluid constantly show some yellow colour. It is necessary to consider whence this great proteid increase is derived.

1. Obviously in tumours of the arachnoid and in cases of meningitis and myelitis the albumen may be transuded directly from the tumour or the focus of inflammation into the sub-arachnoid space. But tumours vary in vascularity and, as Raven<sup>(32)</sup> has shown, it is not by any means the case that vascular tumours are constantly associated with a greater proteid percentage in the lumbar fluid than less vascular tumours. And again the percentage of albumen usually found in the acutest forms of meningitis rarely rises above 0.3%, and very

seldom above 0.5%, whereas the percentages found in the syndrome of Froin are frequently above 1% and sometimes in the region of 3% or even 4%.

A survey of several cases of vascular tumour which obviously transuded serum into the cerebral ventricle or basal cisterns lends additional light to this problem (v. Cases 22 - 25). In all of them the fluid was abnormally albuminous and in one case contained fibrinogen, giving rise to a fine fibrin coagulum; in most it had a yellow colour, but although a large surface of tumour growth was in relation to the cerebro-spinal fluid, and seemed to be able to transude serum directly into it, the percentage of albumen was never above 0.2%.

There must therefore be some factor other than transudation concerned with the abnormal increase of albumen found in the cases of tumour of the cord or its coverings, disease of the bony walls of the spinal canal, meningitis and myelitis which have been quoted. And it will have been seen that in almost every case there was a partial or complete closure of the sub-arachnoid space round the cord at some level above that at which the fluid was drawn off. In the case of staphylococcal meningitis in my series (case 5) it was

possible to compare the fluids drawn from above and below this level, and although the fluid from the cisterna magna was purulent and frankly inflammatory in every respect it contained only one ~~tenth~~<sup>thirtieth</sup> of the percentage of albumen found in the lumbar fluid. Raven<sup>(31)</sup> Marinesco and Radovici<sup>(23)</sup>, Marie, Foix, ~~Bouttier~~<sup>(21)</sup> and Robert<sup>(22)</sup>, and Lantuéjoul<sup>(19)</sup> have quoted many cases where fluid was drawn off the sub-arachnoid space round the cord at various levels; the lower punctures gave fluids which showed the syndrome of Froin in a more or less typical form, whereas the higher punctures gave fluids which differed little from the normal. There seems therefore to be no room for doubt that the syndrome depends primarily on the damming off of the fluid in the lumbar cul-de-sac from communication with the ventricular fluid. This hypothesis was advanced first by Sicard and Descomps<sup>(36)</sup> who considered that two factors entered into the aetiology of the syndrome :- first the shutting off of the lumbar fluid from communication with the fluid derived from the ventricles, and, secondly, increased transudation from the meninges owing to congestion of the veins in the lumbar sub-arachnoid space. Other writers (Dejerine

(Derrien, Mestrezat and Roger<sup>(9)</sup>) have suggested that a third factor is at work, namely some process which seals up the perivascular channels and prevents the escape of sub-arachnoid fluid into them, for it has been noted that although in cases presenting the syndrome lumbar puncture usually gives a fluid under very low pressure, occasionally it is found that the fluid spurts out under considerably increased pressure even when the patient is lying with his head and spine horizontal.

#### Physiological Considerations.

In order to form any estimate as to the importance of these several factors it is necessary shortly to review our knowledge of the physiology of the circulation of the cerebro-spinal fluid.

Formation of the fluid. The theory long held on morphological grounds that the cerebro-spinal fluid is the product of the choroid plexuses has been recently proved in a decisive manner by the work of Dandy<sup>(8)</sup>. In a series of experiments on dogs he was able to produce hydrocephalus by artificially blocking the iter of Sylvius, when the resulting hydrocephalus affected only the lateral and third ventricles; he was also able to produce hydrocephalus of either or both lateral ventricles by blocking the foramina of Munro.

03

This being established he removed the choroid plexus from one lateral ventricle, at the same time plugging both foramina of Munro. The effect was to produce hydrocephalus as before in the ventricle in which the choroid plexus was left intact, but on the other side, where the plexus had been removed, the ventricle was collapsed and contained no fluid at all. It may therefore be taken as a fact, proved as definitely as any in medical science, that the cerebro-spinal fluid is produced by the choroid plexuses of the lateral, third and fourth ventricles and nowhere else. This does not, of course, exclude the possibility of substances other than cerebro-spinal fluid being added to it during its circulation. It is not necessary to enter here into the vexed question as to the exact nature of the formation of the cerebro-spinal fluid by the choroid plexuses, whether it is formed as a secretion (Dixon and Halliburton, Mott (28)), or as a product of selective dialysis (Mestrezat (25)).

Circulation of the Fluid. The pioneer work of Majendie, who considered that the fluid flowed up into the ventricles through the opening in the roof of the 4th ventricle known by his name, was proved to be wrong by clinical observers who showed that tumours compressing or involving the iter of Sylvius were constantly associated with hydrocephalus. It thus became

clear that the fluid was formed, at least in great part, above the iter of Sylvius and passed out through the foramina of Majendie and of Luschka into the sub-arachnoid space. Leonard Hill (17) found also that it passed out of the cranial cavity chiefly by the blood stream, and to a less extent by the lymphatic channels of the neck. Injecting a solution of methylene blue into the cisterna magna he found the urine coloured in less than twenty minutes, whereas the lymphatics of the neck were only seen to be coloured about one hour after the injection. The original work of Key and Retzius<sup>(18)</sup> on the arachnoidal villi in relation to the absorption of the fluid was largely discounted by the French workers on the subject (Sicard and Cestan, Milian, Mestrezat, Cathelin<sup>(4)</sup>) who considered that the fluid was absorbed into the blood chiefly by way of the perivascular lymphatic spaces in the cord, and sub-arachnoid space.

The question of resorption of the fluid has recently been taken up by Cushing's school of workers and Weed and Dandy (8) have added considerably to our knowledge. Weed (39) was able to show that the spinal resorption of the fluid was negligible in comparison with the intracranial resorption. He injected a read-

ily diffusible coloured fluid into the cisterna magna, and judged the rapidity with which it returned to the blood stream by estimating with the colorimeter the amount secreted in the urine at various periods after the injection. He then tied the dura mater tightly in the cervical region of the cord and, repeating the injection under otherwise similar conditions, found that the quantities of pigment recovered from the urine did not differ appreciably from those in the control experiment. Dandy formed a similar conclusion from a totally different series of experiments. Having found that the fluid did not escape through the floor of the third ventricle after blockage of the iter of Sylvius, he attempted to find out which was the chief area of resorption. He therefore surrounded the cerebral peduncles loosely with a wick of gauze dipped in iodine solution, in order that adhesions forming round the mid-brain should prevent fluid passing forwards from the posterior to the middle and anterior cranial fossae. This he was successful in accomplishing, and as a result the animals developed hydrocephalus, although more slowly than after the iter of Sylvius had been plugged. He therefore concluded that the resorption of cerebro-spinal fluid takes place chiefly from the middle and anterior cranial fossae, and that what

resorption takes place in the posterior cranial fossa and the spinal canal is insufficient to balance the amount secreted by the choroid plexuses even when the intra-cranial pressure is considerably raised. The work of Weed, confirming that of Key and Retzius on the arachnoidal villi, proved these structures to be the channels whereby the larger part of the cerebro-spinal fluid was returned to the circulation. He injected a solution of iron-ammonium sulphate and potassium ferro-cyanide either into the sub-arachnoid space in the lumbar region or into the cisterna magna, and after fixation in formalin and hydrochloric acid was able to trace granules of Prussian blue into the arachnoidal villi in relation to most of the large cerebral venous sinuses.

It is true that using a similar injection fluid under higher pressure he was also able to trace the injection to the perivascular lymphatics (Virchow-Robin space) of the brain and spinal cord, and even in some cases into the nervous tissue.

Both he and Mott (28) considered that the cerebro-spinal fluid passed up the perivascular channels to bathe the nerve cells of the brain and spinal cord, but these conclusions are not generally accepted. In

Weed's experiments as above described the injections were made under abnormally high pressures. Mott in his experiments had previously tied the carotid artery thereby producing anaemia of the brain, and his results cannot therefore be considered as conclusive for what takes place under normal conditions.

I have been able to inject the Virchow-Robin space in the lumbar region of the cord in a rabbit by injecting indian ink at moderately increased pressure into the lumbar sub-arachnoid space. But although the injection penetrated into the ventricles and the perilymph spaces of the internal ear, it did not enter the Virchow-Robin space anywhere except close to the site of injection.



Fig.10.

Section of rabbit's cord in lumbar region showing infiltration of the Virchow-Robin space with granules of indian ink which had been injected into the sub-arachnoid space at about the same level.

The Virchow-Robin space normally appears completely empty in histological preparations, unless filled with cells from within the nervous tissue, as in diffuse encephalitis or polio-myelitis or in degenerative disease or destructive lesion of the brain or cord, in which cases the cells can be traced in histological preparations to the meninges in the region where the vessel enters or leaves the brain or cord; during life similar cells can be found in the cerebro-spinal fluid. Acute syphilitic or coccal meningitis does not produce infiltration of the Virchow-Robin space except in the parts nearest to the sub-arachnoid space. It does not therefore seem likely that there is normally a constant flow of cerebro-spinal fluid up this space from the larger to the smaller branches of the vessels. Nor can cerebro-spinal fluid be absorbed by this route except by a process of diffusion in which some at least of the absorbed cerebro-spinal fluid is replaced by the tissue fluid which passes into the Virchow-Robin spaces from the nervous tissue.

The other possible channel for escape of the fluid is the peri-neural lymphatics. Undoubtedly some escape of cerebro-spinal fluid can take place by this route, but here again there is undoubtedly a current of lymph in the opposite direction, that is up the nerve toward the sub-arachnoid space and the cord. The work of Orr and Rows(31), who produced toxic infection of the cord by placing celloidin capsules containing living organisms in connection with the peripheral nerves, is supported by that of Meyer and Ransome(26), and recently of Teale and Embleton(38), who have shown that tetanus toxin reaches the spinal cord along the lymphatic channels in the perineurium. Here again, therefore, any absorption of cerebro-spinal fluid that occurred would merely be in exchange for the addition of a smaller or greater amount of tissue fluid to the contents of the sub-arachnoid space.

The spinal sub-arachnoid space may therefore be assumed to be a cul-de-sac from which only an extremely small bulk of fluid is drained. This does not necessarily mean that very little cerebro-spinal fluid is absorbed therefrom, although on the premises even this might be granted. But it appears that what little cerebro-spinal fluid is absorbed is replaced at least in large part by tissue fluids from the blood stream reaching it either by way of the Virchow-Robin space, or the peri-neural lymphatics. It must not, however, be considered that the fluid normally stagnates in the spinal cul-de-sac. Two pumping mechanisms are at work to prevent this. The cerebral arterial pulsation constantly changes the size of the brain, and as the skull and cranial dura mater form a firm, non-expandible vessel it follows that this pulsation must be conveyed to the fluid in the more expansive spinal theca. There is also the venous pulsation due to the varying phases of respiration, which though probably slight under normal conditions, can become very considerable when forced respiratory efforts are made. This acts both on the cerebral veins and on the large plexus of veins which lies between the spinal canal and the dura mater surrounding the cord. It is possible

that a considerable congestion of the latter plexus might almost completely empty the sub-arachnoid space surrounding the cord. It might be objected that as the rise in both cerebral and spinal venous pressures would necessarily occur at the same moment, it would merely cause an increase in the pressure of the contents of the spinal canal without any movement of the fluid contained therein. But as the cerebral veins are in much freer relation to the large vessels entering the heart than are the spinal veins, it may be assumed that the pressure in the intra-cranial veins is lowered a moment before that in the spinal veins, and that during this interval a wave of cerebro-spinal fluid passes toward the cranial cavity.

There is no evidence of any circulation of the cerebro-spinal fluid within the spinal theca in the sense of a current down one surface of the cord and up the other, or down the central canal and up the sub-arachnoid space (or vice versa) as has been assumed by some writers. The renewal of the fluid in the lumbar cul-de-sac must therefore be considered to take place by a process of mixing with the fresh fluid in the cisterna magna, free mixing being greatly assisted by the arterial and venous pulsations which are transmitted to the spinal fluid.

The amount of cerebro-spinal fluid which is normally formed and resorbed into the circulation must be considerable. In cases of fracture of the base of the brain, in cerebro-spinal rhinorrhoea, and after operations on the head or spine the leakage of cerebro-spinal fluid may amount to one or two litres each day. And although it is probable that these quantities are abnormally large it has been calculated by Mestrezat<sup>(25)</sup> that under normal conditions the cerebro-spinal fluid is replaced six or seven times a day. The quantity of fluid normally present being from 70 c.c. to 120 c.c., it is probable that in health from 400 to 800 c.c. of cerebro-spinal fluid each day are secreted, circulate and return to the general circulation. If therefore the communication between the various parts of the sub-arachnoid space is free, the normal slight addition to the cerebro-spinal fluid of lymph derived from the brain, cord and peripheral nerves is insufficient greatly to alter the chemical constitution of the whole. When, on the other hand, free communication between the ventricular and the lumbar fluids is hindered by any process which narrows the channel between the cord and dura mater, or which produces a matting of the meninges round a part of the

cord, the mixing of ventricular and lumbar fluids will be reduced, or will cease completely. The fluid in the lumbar cul-de-sac will then only be able to interchange with the lymph in the Virchow-Robin space and in the peri-neural lymphatic channels, and it will therefore come to approximate more and more closely in composition to lymph.

On the physiological evidence just reviewed no other factor need enter into the aetiology of the syndrome than the narrowing or complete obliteration of the channel by which the cerebro-spinal fluid in the cisterna magna mingles with that in the lumbar cul-de-sac. And when this factor alone is at play the albumen content of the lumbar fluid should rise with the completeness of the block. In this connection a phenomenon described by Lantuéjoul (19) and others is of interest. He states that in certain cases when the first puncture has given a yellow fluid coagulating spontaneously into a fairly dense jelly, a second puncture performed on the next day has given a clear colourless fluid differing little if at all from the normal; but after waiting for some weeks a third puncture has given a fluid similar or approximating to the first. The explanation of this seems to be that the obstruction in the sub-arachnoid space, although under normal conditions complete, is of such a nature that a

removal of the fluid below it will allow fresh fluid to pass it and reach the lumbar cul-de-sac. The obstruction in such cases may act as a ball valve, allowing the passage of fluid from above downwards but not from below upwards. This would explain certain cases which present Froin's syndrome, usually in an incomplete form, and in which the fluid obtained at lumbar puncture spurts out under increased pressure. But it is clear that no valve effect is needed to produce the phenomenon described by Lantuejoul when the obstruction in the sub-arachnoid space is incomplete. For the block may well be sufficient to prevent any but the slightest mixing of the fluids above and below it when the pressure on either side is approximately the same, but insufficient to prevent the passage of fluid past it when the pressure on one side is considerably reduced.

The aetiology of the syndrome in cases of acute myelitis and meningitis and of syphilitic meningo-myelitis presents little difficulty. In such cases a cul-de-sac is formed by inflammatory thickening of the arachnoid to the pia mater investing the cord. This process alone may obstruct the flow in the pial veins, and lead to capillary congestion below it; but in addition the inflammation of itself causes congestion of

the vessels of the cord. Nor is the inflamed area of pia arachnoid bounded by the lower limit of the adhesions in this membrane, but it extends considerably below it, and is bathed by fluid communicating with that in the lumbar cul-de-sac, which thus receives and collects the proteids formed by the inflammatory process.

It is unfortunate that fibrin ferment is so often lacking in the cerebro-spinal fluids which present the syndrome of Froin, and that in consequence the fluid does not clot spontaneously. It is in fact doubtful if fibrin ferment occurs naturally in any of the cases where the syndrome is produced by the pressure of a tumour, and this is probably the reason why the earliest cases, e.g. those described by Froin and Babinski, were of an inflammatory origin. In these fibrin ferment is constantly present, at any rate while inflammation is active. It is lucky for the history of the subject that in the operation of lumbar puncture the fluid is not always drawn off without blood contamination, for when this occurs, fibrin ferment is provided and clotting takes place. This occurred in case 3. Mestrezat has suggested that in order to demonstrate the presence of fibrinogen a drop of fresh blood or serum should be added to the fluid. The addition of

whole blood has its disadvantages, as when only a small quantity of fluid is available it may be necessary to contaminate the whole of it with blood in order to test for fibrinogen, and it is not always certain that the fibrin web thus obtained does not come altogether from the added blood. It is better to add a drop of fresh human or animal serum, but this is not so easily obtained.

{ I have several times seen highly albuminous yellow fluids coagulate during the Wassermann test after the addition of complement. This completely nullifies the result of the test, and ought to be guarded against. This may be done by coagulating the fluid previously with a drop of human blood (from a non-syphilitic) or by heating the cerebro-spinal fluid for half an hour to 56°C. It is stated by Starling that fibrinogen is precipitated by heating to 56°C - 60°C, but I have never found clotting occur in the Wassermann test after the fluid had been heated at the lower temperature. }

(2) The earlier French writers on the subject have insisted that for the production of the syndrome in addition to stagnation of fluid in the lumbar cul-de-sac, there should be venous congestion below the level of the block. Surgeons with great experience

in the operation of laminectomy have told me that in cases of spinal compression the veins on the dorsal surface of the cord below the compression are always congested owing to the current in these veins being chiefly upwards.

It is true that although the main effluent of the spinal veins is into the vertebral veins at the lower border of the foramen magnum, there are also emissary veins leaving the dural sheath along with all the nerve roots. These veins, however, especially in the lumbar region of the cord, are relatively much smaller than the accompanying arteries; and while it is possible that long-continued congestion, such as might occur below the level of a spinal tumour, might increase their lumen, the firmness of the dural sheath would form a considerable barrier to any such process. It would therefore seem to be a necessary corollary to any form of spinal compression that there should be an increase of blood pressure in the intra-theccal veins and capillaries below it.

It is probable that, apart from the effect of bacterial and other toxins on the walls of capillaries, the obstacle which these present to the escape of fibrinogen varies inversely to the pressure within them. It would follow, therefore, that the venous congestion

resulting from the pressure of a tumour would lead to the escape of a relatively higher proportion of fibrinogen than would otherwise occur. It is stated that there are no capillary vessels in the arachnoid and therefore the transudation of lymph into the spinal sub-arachnoid space must come from within the cord.

(3) Froin's syndrome in polyneuritis and Landry's paralysis.

While the theory of "cavit  close" is justified by the findings at autopsy or operation in a number of cases, it does not seem to explain the pathogenesis of the syndrome of Froin in the cases of polyneuritis and Landry's paralysis recorded in the literature. No such case, so far as I am aware, has come to autopsy while showing the syndrome in a typical manner, and it is therefore impossible to dogmatise on the subject. But the rapidity with which the cerebro-spinal fluid regains its normal characters as the patient is restored to health, militates against any theory which postulates inflammatory adhesions in the meninges. Nor are such adhesions found at autopsy in cases of acute polyneuritis. On the other hand it is possible that there may be in such cases considerable swelling

of the lumbar enlargement of the cord, and that this may form a slight barrier to the mixing of the fluid in the lumbar cul-de-sac with that at a higher level in the sub-arachnoid space.

Another factor influencing the amount of albumen in the fluid obtained at lumbar puncture in such cases is found in the inflammation of the nerves. It has been seen that there is a lymph current up the sheaths of the nerves towards the sub-arachnoid space and the cord. And although the quantity of lymph which travels along this path is probably very small in conditions of health, it may be very considerable when the nerves are acutely inflamed. And when the large size of the sciatic nerves is remembered, it is easy to understand how lymph travelling up them and reaching the sub-arachnoid space among the roots of the cauda equina would influence the character of the fluid drawn off from this situation.

It is, however, only a small proportion of cases of polyneuritis which shows more than a slight excess of albumen in the cerebro-spinal fluid. Mestrezat (25) considers that this increase is only shown by those cases in which the ventral horns of the cord participate in the inflammation. Eskuchen (12) thinks that the changes in the fluid in polyneuritis are due to in-

788.

volvement of the meninges. But as in the cases which I have examined no definite increase in cells has accompanied the increase in albumen, I find it difficult to accept this supposition.

It is also probable that vascular congestion is not a necessary accompaniment of the pathological picture of peripheral neuritis. It is stated by Durante (11) that neuritis of a purely toxic origin is not usually associated with vascular changes, though sometimes the nerves are oedematous and swollen. Again, Landry's paralysis does not always produce changes in the cerebro-spinal fluid, and Eskuchen (12) states that the cases which he has followed to autopsy have not shown any such changes. In the present state of our knowledge, therefore, it seems impossible satisfactorily to explain why the syndrome of Froin should be present in some cases of polyneuritis and absent in others.

(4) The composition of the fluids presenting the syndrome of Froin is thus accounted for in a general way by stagnation and vascular congestion. But there are some other points in connection with the syndrome into which it may be worth while briefly to enquire.

Situation of the block..

It has been shown by Raven<sup>(32)</sup> that the syndrome us-

usually occurs with greatest intensity when the block is low down in the thoracic or lumbar region. This may be explained on several grounds. In the first place the segmental vascular supply (i.e. excluding that derived from the vertebral artery) is much greater in the lumbar than in the thoracic region. Therefore a block, which obstructed the longitudinal vascular supply in the upper thoracic region, would produce more vascular congestion in the lumbar than in the thoracic regions of the cord. That is to say that, whatever the level of the block, the greatest lymph transudation would take place from the lumbar region of the cord.

Secondly the amount of cerebro-spinal fluid to which this lymph is added varies with the level of the block, being much larger when the block is high up than when it is in the lumbar region.

Thirdly the pulsations transmitted to the fluid in the spinal theca from the vessels of the brain diminish in force from above downwards, and are probably very weak when they reach the lumbar cul-de-sac.

#### Nature of the lesion producing the block.

This has been shown to influence the changes in the fluid only to a limited extent and only in rela-

tion to certain of its constituents. As regards the cellular picture, while acute inflammatory processes may lead to comparatively little increase of cells in the loculated fluid, meningitis of syphilitic origin usually shows its presence by a definite lymphocytosis.

It has been seen that usually as the albumen in the fluid rises, the glucose also rises in percentage although to a much less degree. But when the block is caused by acute meningitis, glucose may be diminished or absent.

The proportion of the various albumen fractions is a question to which little attention has been paid, probably owing to the difficulty of the chemical analysis involved. It has been seen that in tumours in relation to the ventricles or basal cisterns (cases 22 to 25) the total amount of albumen may rise considerably without more than a minimal rise in the quantity of globulin.

It is not difficult to make a rough estimate of the proportions of the various globulin fractions present in a fluid by fractional salting out with ammonium sulphate after the method of Kafka. According to him 28% saturation causes precipitation of fibrinogen, 33% saturation, of euglobulin, and 40% saturation, of pseudoglobulin. The method is not

delicate enough to show one part in 10,000 of a particular type of globulin, but will probably give a positive result with 2 or 3 parts in 10,000. I have recently applied this method to the examination of highly albuminous fluids, but unfortunately my attention was only drawn to it after the examination of most of the fluids included in this series had been completed. The number of cerebro-spinal fluids examined by this method has therefore been too small for me to draw any conclusions from it, but it is probable that, used over a larger series, the method might prove to have some diagnostic value.

The exact quantity of fibrin present in fluids presenting the syndrome of Froin has been estimated by several observers. Blanchetière and Lejonne<sup>(3)</sup> found 0.17% and 0.16% of fibrin in their case with 2.55% and 2.75% albumen. Lantuéjoul and Souques<sup>(20)</sup> found 0.275% fibrin with 4.285% albumen and 0.155 fibrin with 4.2% albumen. Derrien, Mestrezat and Roger<sup>(9)</sup> found 0.03% fibrin with 0.6% albumen, and no fibrinogen with 0.4% albumen. In several of my cases I have found albumen in the region of 0.2% or 0.3% without a trace of fibrinogen being discoverable. On the other hand I have never examined a meningitic fluid in which the albumen had reached these levels

and which did not give a copious fibrin coagulum. It would therefore appear that the proportion of fibrinogen to albumen in cerebro-spinal fluids presenting the syndrome of Froin is small by comparison with that found in acute inflammatory conditions.

The proportion of globulin to albumen, on the other hand, is much higher than in meningitis. Mestrezat found in one case globulin 0.13% to albumen 0.49%; in another globulin 0.22% to albumen 0.65%, in both cases a proportion of about 1 to 3. Blanchetiere and Lejonne found globulin 0.808% to albumen 1.742%, a proportion nearer 1 to 2. In meningitis the proportion of globulin to albumen is much lower, 1 to 8 (Mestrezat) or 1 to 12 (Eskuchen). In fact the proportion of globulin to albumen found in the syndrome of Froin is only equalled, and probably is not passed, by that found in progressive general paralysis, in which disease Eskuchen computes it at 3 to 7.

#### Albumoses.

Sicard (34) drew attention to the presence of albumoses in certain spinal fluids which presented the characteristics of the syndrome of Froin, especially in cases of Pott's disease of the vertebrae. He attributed it to the disease in the spinal bones, and considered that it had the same significance as the

Bence-Jones proteid in the urine of cases of sarcoma of the spine. Mestrezat, on the other hand, considered that the albumoses and peptones arose from the disintegration of the stagnating albumens. It is to be noted that both writers agree that albumoses are never found except at the first puncture, and then only in exceptional cases, in which the syndrome is present in its most complete form. Only one of my own cases showed the presence of albumoses by the biuret reaction after the albumen had been removed by boiling and filtering. This was a case of tubercular meningitis following on Pott's disease, and the albumoses may therefore have been produced either as a result of the disease in the bone, as in Sicard's hypothesis, or as a product of digestion of the pre-existing albumen in the fluid by toxins derived from the adjacent area of meningitis.

This is one of the many questions presented by the syndrome of Froin which still require elucidation. This can only come after new work on general tissue metabolism and the interchange of tissue fluids has cleared away the haze in which these subjects are wrapped; and when this is done many of the anomalies presented by the cerebro-spinal fluid will cease to exist.

SUMMARY of CONCLUSIONS.

1. The syndrome of Froin consists essentially in the approximation of the character of the fluid obtained by lumbar puncture to that of blood plasma. This approximation is never so complete as to render it identical.

2. This change takes place characteristically when the fluid in the lumbar cul-de-sac is completely cut off from communication with the fluid in the ventricles and cisterna magna. This may be produced by tumours or other disease in the bones of the spine, by tumours of the meninges or cord, or by inflammatory adhesions in the pia-arachnoid membranes.

3. The degree of change in the fluid depends more on the completeness of this block, than on the nature of the blocking process. But certain chemical constituents in the fluid may vary in relation to the nature of the obstruction.

4. The production of the syndrome is aided by venous congestion below the level of a compression, or by inflammation in the meninges and cord below an area of meningeal adhesion.

5. It is not necessary to postulate any obstruction of the perineural or perivascular lymphatics. The lymph which reaches the sub-arachnoid space along them aids in the production of the syndrome. Acute peripheral neuritis may in fact itself produce an analogous condition in the cerebro-spinal fluid.

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