size, may, on the other hand, offer no obstacle to the passage of the catheter, and it may not even be felt as an obstruction.

CYSTOSCOPIC APPEARANCES.

Looking over my case sheets I find that, in addition to the alterations in the rate of secretion and in the rhythm of the jets to which I have already referred, and the presence of blood or pus in the efflux, I have notes of certain changes at the ureteric orifice on the affected side as seen by the cystoscope; the following description is based on these notes. There may be no apparent departure from the normal, the orifice remaining slit-like and free from surrounding vascularity or oedema. Thus there were no obvious changes in three cases, in each of which a calculus was subsequently removed from the ureter, just proximal to its entrance into the bladder wall. In 20 out of the 50 cases, however, definite changes were specially described. These consisted of the following:

Some departure from the slit-like shape of the orifice, which had become sinuous, oval, circular, or irregular in shape. In some cases the orifice was more patulous than normal. In a few, the only noticeable change was increased vascularity, without swelling, round the orifice. In the large majority, however, there was a good deal of redness and oedema at and around the orifice. The opening of the ureter in some cases was completely obscured and perched on the top of a little mound or hillock of oedematous mucous membrane, and was only discovered by probing about with the tip of the catheter. The chief sign was, therefore, alteration of the shape of the orifice,

associated with oedema at the spot and for some distance around. The orifice, if not obscured, often appeared like a dimple in the centre of a raised area of mucous membrane. In a few cases oedematous tags resembling minute papillomata were seen surrounding the opening. Occasionally flecks of lymph were seen on the lips or shreds of purulent material projecting from the orifice.

A very characteristic sign was the presence of small haemorrhagic points and splashes around the orifice, extending in some cases along the interureteric bar as well as laterally. In four cases the calculus was actually seen in the depths of the orifice or about to drop into the bladder. In five cases, examined after an attack of pain, the calculus was seen lying at the base of the bladder.

I have thus had the opportunity of observing what may be termed the birth of the calculus. The ureteric orifice has more than a fancied resemblance to the vulva, and it is fascinating to watch the calculus, like a foetal head, advancing and receding as in the act of parturition. Like my friends the obstetricians I have "put on forceps" to assist nature, and in a few cases I have even performed a miniature cephalotripsy. When the dystocia has been insurmountable I have, like them, resorted to a form of Caesarean section; and finally, again like them, I have been amply rewarded for my trouble by the effusive thanks accorded to me when I have presented to the author of its being the fruit of his loins.

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ENCEPHALO-MYELITIS IN VIRUS DISEASES AND EXANTHEMATA.*

BY

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THE HISTOLOGY OF POST-VACCINAL ENCEPHALITIS.

I UNDERSTAND that the primary subject of the discussion is the nature of encephalo-myelitis following vaccination. It is no longer necessary to argue that an encephalo-myelitis is sometimes a complication of vaccination. The exact cause of the encephalo-myelitis need alone be discussed.

Is the encephalitis caused by the virus of vaccination lymph, or by some other infection introduced at vaccination, or does the vaccinal virus excite some latent infection? If the encephalo-myelitis is the result of an infection introduced at vaccination or excited by the vaccination, are the resulting histological changes due to the action of the introduced or excited infection alone or to the combined action or the interaction of such an infective agent and the vaccinal virus?

In finding an answer to these questions a great many methods are of service; one of these is comparative histology. To that method my remarks will be confined.

The histological changes in post-vaccinal encephalitis have been remarkably uniform in all cases which I have seen or of which I have read a description. The case of Paul (1928) may be an exception; I have not had access to the description of this actual case, but only to that of the example of severe poliomyelitis in which, he says, the changes were astonishingly similar. The description of seven brains and cords given by Turnbull and McIntosh (1926) amplified that of two brains by Bastiaanse (1925), and has in turn been confirmed, amplified, and in one point corrected by the descriptions of three brains and cords by Perdrau (1928), of one brain and cord and one segment of brain by Schürmann (1928), and of three brains by Lucksch (1927) in his later paper. I have subjected the formaldehyde-paraffin material from the first four of our seven cases to other stains, particularly Victoria blue and Mallory's phosphotungstic haematoxylin; with the

latter not only can the fibroglia and myelin be stained, but the bodies of the proliferated glial cells are sharply defined. A further case was obtained by Dr. Woods during my holiday in September, 1927: a male of three months, who became ill on the tenth day after vaccination and died on the twenty-fifth day. In this example, which for convenience may be referred to as our Case viii, the condition was subacute as in our Case iv.

To the naked eye congestion and oedema are visible in most examples; haemorrhage into the leptomeninges and subdural space of the brain, one or two punctiform haemorrhages into the spinal cord, and blurring of the demarcation between the grey matter and white matter of the cord have been observed in some examples (Turnbull and McIntosh).

Microscopically focal histological changes extend from the cortex of the brain to the lumbo-sacral cord. The incidence was maximal in the lumbo-sacral cord and the pons, and was least in the upper cervical cord of our first seven cases. Case viii differs in that the affection of the spinal cord is greatest in thoracic segments; there it is of great severity. Perdrau found the most severe lesions in the pons and upper medulla, and the maximal lesions in the spinal cord in the lower thoracic segments and the lumbo-sacral enlargement. Schürmann found the maximum in the pons and medulla. Lucksch (brain and brain-stem) in the pons and substantia nigra; we found the inflammation in the mid-brain to be greatest in the substantia nigra. Schürmann found a fairly severe affection of the optic tract and nerves.

We found the white matter in the cerebrum to be more affected than the grey, but in the central nervous system, considered as a whole, we estimated that the grey matter was more affected than the white. Perdrau found the white to be most affected in the cerebrum and cerebellum, but the grey in the brain-stem and spinal cord. In the brain and brain-stem Bastiaanse considered the white matter to be most affected, Lucksch the grey and white to be about equally involved.

The histological changes can be divided into acute and subacute types. The acute type is usually found in patients who die from fourteen to seventeen days after vaccination, and the subacute in those who survive longer.

In the acute type there is a slight, intermittent infiltration of the leptomeninges, chiefly about veins, with small and large lymphocytes, plasmacytoid and true plasma cells, large mononuclear leucocytes, and endothelial cells. The

* Read in opening a discussion in the Section of Pathology and Bacteriology of the Annual Meeting of the British Medical Association, Cardiff, 1928.

vessels are engorged, and frequently contain thrombi; occasionally there are haemorrhages. Within the central nervous system engorgement is again found; thrombi are occasionally met; haemorrhages are rare, and are small and perivascular. The essential change consists of perivascular and marginal zones of demyelination. After describing these zones of demyelination we unfortunately named them zones of "softening" — a term generally regarded as indicating complete colliquative necrosis in addition to rapid demyelination. We also described the occurrence of areas of infiltration without demyelination in the grey matter and very rarely in the white. I have stained my series again, and find, as Perdrau did, that there is some demyelination in all the zones without exception; for instance, round the vessel in Fig. 2 of our paper. The only extra-adventitial infiltration without demyelination is found in places such as the pons, where there is a diffuse proliferation of glial cells between numerous adjacent areas of demyelination.

The perivascular zones of demyelination (Figs. 1 to 4) form wide sleeves which surround vessels, almost always veins, for long distances and extend along their branches. The marginal zones are found most frequently along the edges of the ventral fissure of the spinal cord, but also in the remainder of the periphery of the cord (Fig. 4). Schürmann found them also beneath the pia of the brain,

are very deeply stained; they then give a positive reaction for fibrin with Weigert-Gram. This thickening I believe to be due to a fibrinous imbibition, and not to proliferation; I have seen the same change unaccompanied by any other beneath the pia in a cerebral sulcus. Usually the limiting membrane is unaltered or rarefied. Further from the vessel the fibrils form a wide-meshed net, and frequently appear to be diminished in number. The changes in the marginal zones are similar, except that I have not seen fibrinoid thickening of the limiting membrane.

Perdrau has found an incipient demyelination free from glial cells round many vessels. But in the conspicuous perivascular and marginal zones the wide-meshed net of glial fibrils usually contains, in the acute cases, a great number of proliferated glial cells. A few fibrous astrocytes are present, but not more than normally. The bulk of the cells have a relatively abundant cytoplasm, and are polygonal, round, or oval. The nuclei vary greatly in shape and depth of stain; various forms of degeneration to complete disappearance are seen. The cytoplasm is usually vacuolated, and may be foam-like. By Hortege's method Perdrau has found these cells to be microglia, and by Hérxheimer's method he proved the presence of fat within them. The cells contain myelin as well as fat. In addition to these glial cells there are neutrophil leucocytes where the inflammation is exception-

FIG. 1.—Perivascular demyelination in spinal cord. Second thoracic segment. Case iii of Turnbull and McIntosh. Female, 22 years. Weigert's iron-haematoxylin and van Gieson. (From the *British Journal of Experimental Pathology*.)

FIG. 2.—Perivascular demyelination in white and adjacent grey matter. Lateral aspect of ventral horn with white matter of fourth lumbar segment of spinal cord. Case iii, female, 22 years. Weigert's iron-haematoxylin and van Gieson; 2/3 in. obj., oc Zeiss 4. (From the *British Journal of Experimental Pathology*.)

the brain-stem, and the optic nerves and tracts. Further, he found a similar zone beneath the ependyma of the lateral ventricles.

The zones of demyelination appear under low magnifications sharply defined, especially the perivascular zones. Within them demyelination is usually complete, except at the margin. Only a fraction of the axis cylinders survive (Perdrau, Schürmann). The glial fibrils immediately round the vessel—the vascular limiting membrane—are sometimes thickened, form an abnormally close feltwork, and

FIG. 3.—Perivascular demyelination in white matter. Posterior white column, thoracic cord. Case i, male, 15 years. Weigert's iron-haematoxylin and van Gieson; 1/6 in. obj., oc Zeiss K6. (From the *British Journal of Experimental Pathology*.)

ally intense; lymphocytes and plasmacytoid cells are rarely present. Proliferated glial cells extend to a variable distance beyond the zones of demyelination and cause a diffuse infiltration in the most severely affected regions.

The adventitial sheaths of vessels occasionally contain coagulated albumin, even when there is no other change in the adventitia or surrounding tissue. Infiltration of the adventitia (Fig. 3) is an inconspicuous feature, and is frequently absent from vessels surrounded by zones of demyelination. The infiltrating cells are large and small

lymphocytes, plasmacytoid cells, plasma cells, large mononuclear leucocytes, and cells with a fibrocytic type of nucleus. The number of plasma cells here and in the meninges is in some cases sparse.

In addition to perivascular and marginal demyelination Perdrau in Marchi preparations found degeneration of isolated fibres scattered throughout the central nervous system, especially upon the ventral surface of the corpus callosum. He also found degeneration of isolated fibres in the posterior roots. In our subacute Case viii there are conspicuous areas of demyelination in the anterior roots in the ninth thoracic segment. The root ganglia may be slightly infiltrated (Perdrau) or unaltered (Turnbull and McIntosh, Schürmann). The bodies of the neurons are astonishingly well preserved (Fig. 2). There is often clumping of neuro-chromatin or tigrolysis, but loss of angularity and complete necrosis are very rare. Bastiaanse alone has described neuronophagia, in the locus niger.

In the subacute type the changes have usually continued for a longer period, consequently the adventitial sheaths are distended with a mosaic of large fat-granule cells. In Case viii these cells have completely replaced the small round cells in almost all sheaths, and they extend into the

FIG. 4.—Perivascular and marginal zones of demyelination; large area of confluent demyelination in left lateral column and grey matter. Ninth thoracic segment. Case viii (subacute), male, 3 months. Weigert-Pal.

leptomeninges, where they are very abundant opposite the most affected areas (Fig. 5). The perivascular zones of demyelination may be scanty and narrow, or may coalesce to form large areas, as in Perdrau's Case ii and our Case viii, in which there is almost complete demyelination of the lateral column and grey matter on the left side of thoracic segments (Fig. 4). The changes in the glia, particularly the fibroglia, in this later stage are obviously important in estimating the relation of the condition to disseminated sclerosis. I regret that an investigation of the glial changes in our Cases iv and viii is not yet (June) finished.

According to these histological changes post-vaccinal encephalitis is, as we reported in 1924, clearly distinct from poliomyelitis and encephalitis lethargica, and belongs, as Perdrau and Schürmann emphasized, to the group of conditions which are characterized by demyelination: certain examples of the disseminated myelitis of Westphal (1874), disseminated encephalo-myelitis of later writers, disseminated sclerosis, and encephalitis periaxialis diffusa of Schilder (1912).

There can be no doubt that a condition resembling post-vaccinal encephalitis has occurred independently of recent vaccination and observed exanthemata. Küssner and Brosin (1886) described accurately identical changes in the cord of a man who had suffered for a year from chronic gonorrhoea. The changes described in the cord in the first case of Francotte (1890) appear to be similar, whilst Krabbe (1913) described the changes in the brain. Very

similar but more chronic changes were described by Dreshfeld (1894). Wohlwill (1928) said that he had observed changes identical with those of post-vaccinal encephalitis in a patient who was not suffering from any known infectious disease. In the last two years in Germany a large number of cases have been observed, for instance by Redlich (1927), which resemble post-vaccinal encephalitis clinically. Similar cases have been observed in London by Hunter and Brain (1928). The histological changes found by Redlich in a patient who died after an illness of four and a half months appear to have resembled those of the acute form of disseminated sclerosis more closely than those of post-vaccinal encephalitis. I have commenced the examination of one of the London cases—a boy of 3 years who died after an illness of three days; I can only say that as yet (June) congestion, oedema, and a few small perivascular haemorrhages have alone been found.

Similar histological changes have been found in affections of the central nervous system complicating exanthemata. Wohlwill (1928) has described two cases complicating measles; the only difference from post-vaccinal encephalitis was the absence in the first case of adventitial and meningeal infiltrations. In other cases the encephalitis complicating measles appears to have differed in being essentially haemorrhagic (Winnicott and Gibbs, 1926; Musser and Hauser, 1928). The changes in the case of

FIG. 5.—Large fat-granule cells in pia and vascular sheaths; small fat-granule cells in pale perivascular and marginal zones of demyelination, and in large confluent area of demyelination in left lateral column. Sixth thoracic segment. Case viii (subacute), male, 3 months. Busch-Marchi.

Barlow (1886, 1887) were of yet another kind, if the description can be trusted. There can be little doubt that a similar encephalitis may complicate small-pox in view of the changes described in the cord by Westphal (1874) in two cases and by Eichorst (1913) in one. I have not found an adequate description of encephalo-myelitis in mumps and chicken-pox.

Finally, in paralysis complicating antirabic treatment the conditions found by Fielder (1914-15), Jochmann (1913), and Babes and Mironesco (1908) appear to be those of post-vaccinal encephalitis, although the descriptions lack precision.

Changes resembling those of post-vaccinal encephalitis have, therefore, been found complicating measles as well as, perhaps, small-pox, have probably complicated Pasteur's antirabic treatment, and have been found in cases in which there was no evidence of recent vaccination or of an exanthem.

As regards the nomenclature of this group of cases, most of the earlier examples quoted were called acute disseminated myelitis, the cord alone having been examined. It would appear correct, therefore, to call the condition "acute disseminated encephalo-myelitis." This term, however, has been applied to cases which can be distinguished from the post-vaccinal group histologically (Wohlwill, 1928), and are regarded by many as the acute form of disseminated sclerosis (Anton and Wohlwill, 1912). To avoid confusion, therefore, it would be advisable to use the

term "disseminated encephalo-myelitis of the post-vaccinal type." The question of the relation between acute disseminated encephalo-myelitis of the post-vaccinal type, acute and chronic disseminated sclerosis, and encephalitis periaxialis diffusa is one which others here are more competent to discuss. In the above remarks I have placed in one group the cases of post-vaccinal encephalitis with those which appear to have shown essentially the same histological picture, and have separated this group from acute disseminated sclerosis. Wohlwill (1928) has pointed out the cardinal point of differentiation: the whole length of a vessel is surrounded by demyelination in the former and only a segment in the latter. But the pathogenic processes are essentially similar; consequently the different pictures may simply represent modified reactions to a single agent, and the histological differentiation be artificial. I find it impossible to consider acute and chronic disseminated sclerosis to be other than varieties of one condition; transitions between the two and mixtures of the two have been the rule rather than the exception in my experience.

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ENCEPHALO-MYELITIS IN VIRUS INFECTIONS AND EXANTHEMATA.

AN EXPERIMENTAL AND PATHOLOGICAL STUDY.*

BY

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THAT an encephalitis or an encephalo-myelitis is at times liable to appear during certain acute infections has been known for some considerable time. Our knowledge, however, of the exact nature of this complication in some cases is very scanty. Encephalo-myelitis, whether primary or secondary, may be divided into two main groups—(a) purulent, and (b) non-purulent. The purulent form is the result of the localization of some pyogenic bacterium in the brain substance, while the non-purulent is usually the result of a virus infection, and it is this form which is under discussion to-day. Encephalo-myelitis is found in such virus infections as poliomyelitis, encephalitis lethargica, small-pox, vaccination, chicken-pox, measles, mumps, typhus, etc., and with these I propose to deal in the above order.

POLIOMYELITIS.

Symptoms suggestive of cerebral irritation are not uncommonly met with in cases of acute anterior-poliomyelitis, while in a few instances a definite encephalitis occurs, and to this form the name cerebral poliomyelitis has been applied. True cerebral poliomyelitis, however, is relatively rare, thus Wickmann, in the great Swedish epidemic of

1905, did not see any definite cerebral cases, and none were recorded by Peabody, Draper, and Dochez in the great New York epidemic of 1909. The first cases were described by Strumpell in 1884, and to them he gave the name poli-encephalitis, but in the light of our present knowledge it seems very probable that many of his twenty-four cases were not cases of true poli-encephalitis. It is certainly true that in the majority of the fatal cases of poliomyelitis small focal areas of encephalitis can usually be demonstrated in the cortex to the brain, while in the experimental disease in monkeys, although the major lesion is always in the cord, focal areas of inflammation can be found in the brain.

My own investigations have convinced me that an extensive cerebral involvement in acute anterior poliomyelitis is unusual and, as a rule, the lesions in the brain are slight and mainly consist of a few scattered areas of perivascular cellular infiltration of vessel sheaths.

Experimental Disease.

An experimental infection can readily be produced in monkeys by the inoculation of infective material from cases of poliomyelitis. The animal develops, after an incubation period of about a week, a very definite flaccid paralysis, and histological lesions in the cord identical with those in human cases are found. The maximal lesion is always found in the cord, no matter how the infection is made. In most cases isolated lesions are also to be found in the brain, and particularly in the grey matter at the base. Rabbits can also be infected, but with some difficulty.

ENCEPHALITIS LETHARGICA.

In encephalitis lethargica the main pathological lesion is an encephalitis of varying intensity, but, as a rule, most marked in the basal ganglia of the brain, while the cord is generally unaffected. The most characteristic histological lesion is a well-marked perivascular sheath infiltration, forming at times quite a distinct cuff round the vessel. The infiltration consists chiefly of lymphocytes with a number of plasma cells. Polynuclear leucocytes are conspicuously absent. In addition, there is a certain amount of infiltration of the perivascular parenchyma and glial proliferation. The nerve cells are usually not affected.

Experimental Disease.

As is generally admitted, encephalitis lethargica appears to have been unknown till the outbreak recorded by von Economo in 1916 in Vienna. I had the opportunity of examining some of the earliest cases which occurred in this country, and early came to the conclusion that we had to deal with an entirely new lesion and disease. In collaboration with Professor Turnbull, I was successful in inoculating material from an acute outbreak into monkeys and rabbits, and reproducing symptoms and lesions which showed great similarity to the natural infection in man.

Some writers have confirmed our findings while others have failed to do so, and base their arguments mainly on two grounds: (1) failure to produce any lesion at all, and (2) that lesions found in the experimental rabbit are due to the spontaneous encephalitis of rabbit, and not to the inoculum. But the great similarity of the lesion in man to that of the experimental disease in rabbits may be seen in photomicrographs, while histologically the spontaneous encephalitis of rabbits is quite another type, and no one familiar with the two lesions could use the second argument.

SMALL-POX.

Clinical accounts of small-pox contain frequent references to the appearance of symptoms which suggest involvement of the nervous system. For instance, there may be convulsions and delirium during the first fever or during the eruptive stage, while later there may appear definite parietic manifestations. A full account of the literature dealing with nervous complications of variola has been given in an earlier paper by Professor Turnbull and myself, so it is unnecessary to give it in detail here.

Fortunately, owing to the kindness of Dr. Garrow, medical officer for Chesterfield, I was able to examine the brain of a child who developed cerebral symptoms after

* Read in a discussion in the Section of Pathology and Bacteriology of the Annual Meeting of the British Medical Association, Cardiff, 1928.