ON SOME PROBLEMS OF HISTOLOGICAL DIAGNOSIS AND INTERPRETATION OF CIRCULATORY DISTURBANCES IN THE BRAIN.*

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ORIGINALLY the conception of disturbances of the cerebral circulation was closely associated with that of gross arterial and venous disease, and it was in these conditions that the typical pictures of hæmorrhages, hæmorrhagic and anæmic infarctions (softenings), scars and cysts as their sequelæ were first studied. These sequelæ are in all essentials the same in the brain as in other organs with similar vascular arrangements, such as the kidney and the spleen, with the exception of some peculiarities due to special structure or special staining reactions. Recent ischæmic necrosis of the grey matter appears in Nissl-stained specimens as areas of pallor, and examination under high magnification often reveals a special type of ganglion-cell change called ischæmic by Spielmeyer (16), which so far has maintained its reputation as being highly specific. A further peculiarity is provided by the activity of the glia in all processes of breakdown and repair. In vascular disease especially, a type of mobile glial-mesodermal activity is met with (Spielmeyer (16)), that is to say, the glia acts jointly with the mesenchymal tissue in the production of scavenger-cells and of fibres.

Many efforts have been made to distinguish the sequelæ of vascular lesions from degenerative or toxic ones, in which the nocuous agency is supposed to act directly upon the parenchyma. This diagnostic histological distinction has become of paramount importance, since it has been established that "vascular lesions" of the type described above may occur without any primary visible damage to the blood-vessels themselves. This may sound paradoxical, but it is a fact that even gross changes, such as thrombosis or endarteritis, need not be the cause of tissue damage associated with them. A thrombosis may follow prolonged stasis, and an endarteritis may be part of the mesenchymal reaction, just as an inflammation may constitute a reaction to the breakdown of parenchyma. Recent research, in its earlier stage associated particularly with the names of Ricker and Spielmeyer, has made it clear that the same vascular lesions which are observed in gross arterial and

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venous disease may follow functional disturbance of the organically healthy vessel. Much attention has been paid to vasomotor disturbances, particularly the consequences of angiospasm, prestasis and stasis. It is impossible to go into detail, nor is this necessary, since Spielmeyer himself laid his evidence before you at an earlier annual meeting (19).

It may, however, be instructive to examine how far this new conception has modified our views on a familiar subject, the apoplectic attack. Previously the production of tissue changes was considered to be due to either rupture of vessels or miliary aneurysms with subsequent hæmorrhage, or to obliteration by thrombosis or endarteritis and subsequent infarction. Yet ruptures are rather rare, and careful experimental work on arteriosclerotic vessels near necrotic areas by Riser (14) has shown that the arteries still allow the easy passage of stained test fluids. This is in agreement with numerous pathological observations, showing that damage of the tissue occurs in places in which the arteries appear to be practically unimpaired. Still more marked is the disproportion between arterial disease and lesions produced in the so-called hypertension disease. There the same lesions occur in the main as in arteriosclerosis, and with a similar localization. Yet the primary changes of the vessel walls are much less advanced. They often do not develop before the final stage of the disease is reached, and there are post-mortem records in which typical hæmorrhages and disseminated softenings are reported without any rupture or obliterating change. Such discrepancies between organic damage of the vessel and destruction of the brain-tissue have enforced the acknowledgment of a functional factor. At first the functional principle was obviously over-rated, but more and more both the organic and functional principles are being allotted their due place. The problem is still controversial, but there is no doubt that important clinical and pathological features of the apoplectic attack cannot be understood without invoking functional disturbances of the circulation. An attempt to give a detailed report of the current views would lead too far afield from the present subject. Those interested in the problem will find all necessary information in the recent reviews by Schwartz (15), Neubürger (11) Hiller, (7), Alajouanine and Thurel (1), Nordmann (12) and others.

It is of more immediate interest to the psychiatrist that vascular lesions have been described in a surprising variety of conditions profoundly differing in ætiology, such as epilepsy, head injury, intoxication (carbon monoxide, chloroform, ether, carbon dioxide, morphine, potassium cyanide, toxæmia of pregnancy, eclamptic uræmia), infectious processes (whooping-cough, typhoid fever), and in many other conditions frequently associated with psychoses. It has been suggested that, whatever may be the original ætiological agency, the final action upon the brain-tissue is exerted via functional vasomotor disturbance of the circulation. Thus circulatory disturbances are thought to be a final pathway common to many more conditions than has been realized

before. This conception has also had important repercussions on the interpretation of clinical symptomatology. Krapf (8) in particular has dealt with the subject in his monograph on hypertension disease, and he will give you a further exposition of his views in the paper to be read later at this meeting (8*a*).

In the histological analysis of these widespread vascular lesions much use has been made of the fact that there are regions in the brain which are particularly vulnerable to disturbance of blood-supply. In them ischæmic changes manifest themselves earlier and with greater clarity than elsewhere. Such regions are the cornu ammonis, the Purkinjë cell-layer of the cerebellum and —under certain circumstances—the pallidal system (globus pallidus and zona rubra), dentate nucleus and inferior olivary body, to mention the most important ones. It has been the merit of Spielmeyer and his school to have examined these regions with regard to their diagnostic significance, and thus of having supplied, as it were, a system of indicators for vascular lesions which have proved to be valuable.

A sclerosis of the so-called Sommer sector of the cornu ammonis has for long been regarded as a sort of curiosity in epilepsy. It has been shown, however, that this sclerosis represents a late stage of typical ischæmic necrosis. If one happens to catch the earliest stage of the lesion, one can occasionally demonstrate an anæmia in the vulnerable sector contrasted with hyperæmia in the adjacent part (Spielmeyer (17)). The change in the cornu ammonis is now commonly regarded as a result of the epileptic convulsions. The knowledge of its ischæmic character is one of the main histological criteria of abnormalities in the circulation associated with the epileptic fit. Typical selective lesions of the cornu ammonis have been described in a great variety of vascular diseases, but also in many toxic, infectious and other processes—for instance, after poisoning with carbon monoxide, cyanide of potassium, carbon dioxide, ether, insulin overdosage, eclampsia and hypertension disease. The appearance of ischæmic change after poisoning with insulin (Bodechtel (2)), Stief and Tokay (20)) is particularly interesting in view of the increased attention which the treatment by insulin shock has obtained recently in schizophrenic psychoses.

Illustrations of the various lesions of the cornu ammonis and other sites of predilection have been given in previous papers by various authors, including the present writer. Only two cases will be described here at a somewhat greater length.

The first is that of a patient who had suffered from concussion from which he fully recovered. He died a long time afterwards from a short intercurrent disease. The histological examination of the brain revealed nothing except a number of small circumscribed foci of " dropping out " in the vulnerable sector of the cornu ammonis, suggesting that there were associated with the concussion vascular disturbances of a functional nature. Head

injuries are often looked upon as purely mechanical, and although this mechanical factor cannot be neglected, there is the functional effect on the circulation which is a potent factor in producing lesions far away from the locality of primary attack. This circulatory factor explains without difficulty why occasionally the lesions after head injuries (as also after some of the poisonings) do not set in immediately, but after a longer or shorter interval.

The second case is that of a mongol in whom no epileptic fits or other neurological signs had been reported. In his brain a typical sector sclerosis of the cornu ammonis was found. There was also a rather diffuse glial sclerosis within the white matter of the hemispheres and the cerebellum, with only slight demyelination. Without attempting a discussion of the pathogenesis of this case at any length,* it is quite possible that the defect in the cornu ammonis provides a clue to the diffuse and ill-defined changes in the white matter.

Like the cornu ammonis, the cerebellar cortex and particularly the Purkinjë cells, with their dendrites, are a vulnerable spot in vascular disturbance. There often develops a peculiar microglial proliferation, resulting in softening, called by Spielmeyer (16) glial " shrub work " (*Gliastrauchwerk*). It has been found in many infectious and toxic conditions (whooping-cough, typhoid fever, poisoning particularly by thiophene (5)), in epilepsy, etc., and seems to indicate the ischæmic nature of the condition.

Of the other vulnerable regions, only the globus pallidus may be mentioned. In the past, lesions of this region have been regarded as specific to carbon monoxide poisoning, but in course of time they have been found also after poisoning with potassium cyanide, ether and morphine, in respiratory failure following head injury, secondary anæmia and methæmoglobinæmia and in conditions of early childhood (état dysmyélinisé, *Kernikterus*).

There is little doubt that Spielmeyer's method of approach constitutes, as it were, a novel type of pathogenic analysis, as far as the pathology of the brain is concerned. A sclerosis of the cornu ammonis or of minute parts of cerebellar cortex has apparently not the slightest significance as a substrate of mental or physical disorder, but if it indicates an abnormal function underlying the psychosis, it fulfils many of the demands which in this difficult situation can reasonably be put to the histologist. In fact, the large group of psychoses associated with infections, toxic, traumatic conditions, heart and kidney diseases, etc., thus comes within the reach of histological investigation, though the actual findings are frequently negligible as a substrate. Until now, in no uncomplicated case of schizophrenic psychosis has a lesion in any of the vulnerable regions been recorded. Yet this may possibly only mean that our histological " seismographs " are not sensitive enough to indicate more delicate circulatory fluctuations. It has been stressed by Spielmeyer

* This has been done meanwhile by Meyer and Cook (to be published in a later issue of the Journal).

that a functional disturbance of the circulation needs a certain degree of intensity in order to become recognizable by histological means.

With all due acknowledgment to the advance made in the pathogenic analyses of circulatory disturbances, it is necessary that certain limitations and obscurities should be frankly faced. Only a few points may be mentioned with a view to showing where the danger of too dogmatic an application of the new conceptions lies. To begin with the selective lesions in vulnerable regions, we know indeed very little about the cause of their selective susceptibility (9). Though there is much in favour of a vascular origin, there are apparently differences in detail. Lesions of the cornu ammonis are mostly associated with convulsive conditions, whatever their origin. In thiophene poisoning the cerebellar cortex is preferably affected. Selective lesions of the globus pallidus occur particularly when there is a primary disturbance of the external and internal respiration (9). In cases of strangulation it is particularly the striate body that suffers most (Gamper and Stiefler (6)). Although such distinctions have at present a merely provisional significance, they definitely show that the assumption of a vascular pathogenesis in all these conditions is at best only a part of the truth.

It has been tacitly implied that from such " indicator " findings conclusions can be drawn as to the nature of findings in other regions of the brain. Yet one should be aware that this may be valid only to a certain extent. In epilepsy, for instance, in which a vasomotor factor is commonly accepted as being important in the pathogenesis of the convulsions, diffuse lesions are found, such as the so-called marginal sclerosis, of which a vascular origin is at least questionable. It may be that quite different factors (for instance, increased intracranial pressure, swelling of the brain, etc.) may play a part in its production.

The recognition of a " vascular " lesion is not difficult if the histological appearance of the tissue damage is typical, and if the localization is in conformity with the region of supply of arteries or veins. Great difficulties arise, however, in atypical cases. Experience has taught that the histological appearance of vascular sequelæ may vary greatly with the intensity of the process, the locality of the lesions and the age of onset. With regard to the latter point a good example is provided by the curious fact, first discovered by Bodechtel (3) and recently confirmed on a large scale by Meyer and Cook (10), that in vascular disease, for instance, in heart failure, the white matter is the more vulnerable in early life and the cortex in adult life. This point is naturally of considerable interest for the pathology of mental defect. Still more marked are the differences due to the intensity of the process. Such variations are best studied in pathological or experimental conditions the ætiology of which is known—for instance, in poisoning experiments with carbon monoxide, potassium cyanide, anæsthetics and others. It is of theoretical interest that the histological appearance and localization of the lesions even varies with

the species of animals used (9). If the primary disturbance of the circulation is mild, the resulting damage to the tissue, instead of showing the typical ischæmic necrosis, softening and glia-mesodermal repair, may be one of merely glial repair, the glia-cells taking over the task of the mesodermal scavenger-cells, often even without transformation into compound granular cells. Or the disturbed circulation stimulates the glia only to fibrous proliferation without any considerable breakdown of the parenchyma, nerve-cells and fibres. In the end stages one meets, then, with circumscribed or even diffuse glial sclerosis concealed behind inconspicuous myelin pictures. In my opinion such pictures of glial sclerosis, particularly of the white matter, are directly comparable to what the general pathologist describes as fibrosis of the organs, which he is accustomed to regard as the result of mild stasis of long standing (Boyd (4). The problem is, of course, how to distinguish such lesions, which at first glance appear to have all the criteria of " degenerative " lesions. It is interesting to see that many " degenerative " lesions turn out to be in reality of a vascular nature, as for instance the so-called glial proliferation in the molecular zone of the cerebellum, called " shrub work " by Spielmeyer, or that type of degeneration of ganglion-cells known as the severe type of Nissl. Since it has become known that functional vascular lesions may be diffuse and not show a clear spatial relation to a region of supply of a single blood-vessel, a direct diagnosis may become impossible. On the other hand, a perivascular scar is too often taken as evidence of the vascular nature of the condition, though it should be realized that it may be the result of direct toxic effect of an agency carried by the blood-stream. In general pathology it is understood that interference with the blood-supply is likely to result in tissue changes furthest away from the artery, hence the characteristic pictures in interstitial myocardial degeneration, in which the muscle-fibres round the arteries are spared, or in the liver, in which congestion results in degeneration of the central, perivenous parts of the lobule. If a perivascular lesion is found, the general pathologist thinks more of a direct toxic or inflammatory process producing it (Boyd (4)). Whether similar distinctions have to be made in the brain cannot be discussed here, but the fact itself should be used as a necessary check on too far-reaching diagnostic conclusions.*

There is a last point of uncertainty with regard to the conception of functional vascular disturbance. It is often thought that, as in organic vascular disease, the functional abnormality is situated in the local vessels on which the damaged tissue draws its blood-supply. Accordingly the idea has been widely held that local vasomotor disturbances, angiospasm, followed by prestasis and stasis, are the origin of such lesions. That local vasomotor disturbances occur has been shown by Ricker (13) in some organs (not the brain), and they are widely accepted on the strength of bioptic experiences in

* How far general considerations of this kind apply to the condition known as Pelizæus Merzbacher disease will be the subject of a later communication.

epilepsy. Angiospastic phenomena have also been seen in the retinæ of patients suffering from the malignant type of hypertension disease. Yet the ease with which clinicians and pathologists have acquiesced in the supposition of local vasomotor disturbances is in strange contrast to what we really know about the anatomy and physiology of the vasomotor system in the brain. In my opinion the importance of localized spasm and stasis in the brain has been greatly overrated. Far more often the brain lesions are produced by general disturbances of the circulation in which the brain is merely passively involved (Hiller (7)), and which for circumstances not yet known affect individual vessel systems often more markedly than others.

The final effect of a circulatory disturbance (organic or functional) upon the tissue is that of oxygen deprivation. Recent work has suggested, however, that any other type of anoxæmia—for instance, that produced by asphyxia, hæmoglobin destruction, inhibition of respiratory enzymes (as in carbon monoxide, potassium cyanide and narcotic posioning)—may have the same final effect. It is conceivable that the interference with enzymes activating oxygen consumption may even take place in the ganglion-cells themselves (so-called histotoxic type of anoxæmia). We have learned recently that the normal function of some vitamins, particularly B and C, consists of the activation of oxygen consumption, and that, conversely, deficiency may have an adverse action on the oxygen supply of the tissue. It is interesting that C. and O. Vogt (21) have mentioned the occurrence of the ischæmic ganglion-cell change in avitaminosis—a fact which need not discredit the specificity of this type of degeneration for ischæmia. It is, of course, difficult to separate the effects of these sources of anoxæmia from those produced by vasomotor disturbances, since even slight changes in the oxygen content of the blood have their repercussion on the blood-vessels. There is no more powerful dilator than increase of carbon dioxide content of the blood. Yet the absence of oxygen or the enzymic inhibition of oxygen consumption may also have a direct effect. Findings of diffuse degeneration of nerve-cells in epilepsy, which surprised Spielmeyer (18), or other diffuse affections—for instance, that of the white matter in carbon monoxide poisoning—may thus find a plausible explanation. The implications of these considerations are not without interest to our present discussion. For, if we find in many toxic, infectious, traumatic and other conditions sequelæ which are identical in appearance with those in gross arterial or venous disease, this does not mean that it is always the same event that has caused them. Those who have been perhaps frightened by what appeared to them to be an undue simplification may be comforted by the thought that this vascular pathology, absorbing as it were conditions of the most varying nature, contains in itself again a variety of different pathogenic possibilities, at the significance of which we can merely guess at present. The old traditional histological classifications into vascular, degenerative or toxic processes lose more and more their meaning in a measure as we approach the

real physico-chemical factors in the brain producing the lesions. This point will be taken up in its broader aspects on another occasion, but it has been necessary to mention it here because it throws light upon the enormous diagnostic difficulties, and upon the danger of a too dogmatic interpretation which might obscure what is, in my opinion, a remarkable advance.

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