CEREBRAL ISCHÆMIA AND MENTAL DISORDER.*

By F. A. PICKWORTH, M.B., B.S., B.Sc., A.I.C.(Exam.),
Director, Joint Board of Research for Mental Disease, City and University of Birmingham.

IT has been calculated that over one-third of the total number of cases receiving sickness benefit have some form of nervous disorder (1), and 1 of 22 persons has to be placed in a mental hospital at one time or another (Carrel, 2). Social prejudice, however, still bars adequate support of psychiatric research, and much scientific work is hampered through lack of financial help.

Focal cerebral anoxæmia in relation to the ætiology of mental disorder has occupied my attention for many years, forming in 1929 the subject of my contribution to the Mott Memorial Volume (3). My efforts were then limited to the collection of evidence of neuronic changes caused by oxygen deficiency, but the correlation with the clinical manifestations of psychiatry presented difficulties. The prevailing opinion of my teachers and colleagues, as to the ætiological causes of mental disorder, was that of biogenetically deteriorated or toxin-impaired cerebral neurones: visualized as having swollen or sclerosed cell outlines and processes, containing fatty globules or pigment, nevertheless making sporadic but futile attempts to carry out function, with the inevitable result of a disordered mind. The fundamental obstacle to this theory is the occurrence, in some cases, of natural remissions and of dramatic restorations of sanity during acute infections (e.g. pneumonia), or just before death; also excitation of structurally disordered or toxin-impaired neurones to be in consonance with the theory, should produce even more bizarre mental effects than before, whereas actually tranquil mental order and restoration of disintegrated personality are clinically observed. A few months later Loevenhart (4) demonstrated restorations of sanity by his methods of cerebral stimulation, giving further proof that not only the neurones but the neuronic patterns may be intact and capable of functioning after years of inactivity and disorder. Other methods of cerebral stimulation are now known, the most important of which, in connection with the present paper, is that of Hallay (5), who used "massage of the brain", which consisted of alternate compression of the jugular veins. The biogenetic theories of deteriorated and toxin-impaired neurones which we have cherished so long thus become

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untenable, and the colossal literature on the subject remains to indicate the time and energy expended in that direction.

The two main characteristics of mental disorder are mental dysfunction and a limitation of mental development with age, forming the two clinical groups of psychiatry and mental defect, but nevertheless by no means confined to these groups. In general, mental disorder presents wide differences from well-known acute or chronic bacterial and virus diseases, so that any simple infectious agent as a cause of the clinical condition is quite unlikely. In a few cases (such as syphilis, sepsis, lethargic encephalitis and rabies) where mental disorder has an intimate association with a specific infection, it is obvious that another factor of dominating importance must be present. For example, the spirochæte of syphilis may be present in the brain within a few weeks of primary infection—long before symptoms of general paralysis are due—and therefore it is not by itself the cause of the mental condition.

Much has been published on the action of toxins upon the cerebral neurones, but, as already shown, the neuronic patterns in mental disorder may be intact; also, after restoration of sanity by cerebral stimulation, a rapid relapse to the identical disordered mental state occurs, making even a theory of reversible toxic action inadmissible. A similar non-toxic phenomenon is seen in senile but otherwise mentally normal acquaintances: when undisturbed, speech and movement are slow, the eyes are lustreless and there is lack of expression; but mention a favourite topic and gradually the facial furrows disappear, the eyes sparkle, the features show emotion and there is an associated mental acuity; on changing to another topic of little interest the whole is reversed, like a cine-film put through the projector backwards. In the first few days following admission to a mental hospital the patient's mental state may be temporarily so improved that certification is sometimes difficult, and the well-known temporary improvement following any new treatment in mental disorder cases has given a bias not only to the multitudinous forms of treatment attempted in mental hospitals, but also to patients and their relatives in the use of much-vaunted patent medicines and palliative home treatments which are quite devoid of any real therapeutic value.

With possibly a few exceptions, mental disorder cannot be considered as due to any germ-plasm defect. Tuberculosis and general paralysis were until recently considered hereditary, and the work of Paterson (6), Penrose (7), Findlay (8) and Watson-Williams (9) has shaken the evidence upon which some of the former hereditary theories were based.

Importance of Circulatory Changes.

The inseparable association of nervous mechanisms with motor behaviour has obscured the fact that mental and emotional states are something apart from conditioned reflex action. A reflex is instantaneous in origin and effect,

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in contrast to the prolonged duration of mental and emotional phenomena ; this in itself is proof of the necessity for another physiological mechanism pertaining to such states distinct from the central nervous system, a proper understanding of which is essential to the study of the physiology of the mind and of the pathology of mental disorder itself.

Mott (10), Hill (11), Spielmeyer (12) and others recognized the hopefulness of study of the vascular supply of the brain in relation to the mind, but they found the extreme vulnerability of the ganglion cells of the brain to oxygen lack a stumbling-block to further progress in this direction. As I have shown, injury of the ganglion cells themselves is an unlikely cause of chronic mental dysfunction, and moreover, according to Fremont-Smith (13), each ganglion cell has a separate blood-supply to itself. It is known that posterior root ganglia (where cells are numerous) have a relatively poor blood-supply, whilst laminæ III and IV of the cortex (richest in synapses) have the richest blood-supply ; lamina I, rich in synapses, has a good blood-supply, not only from its contained capillaries, but from contact with the highly vascular pia, where the colour difference between arterial supply and venous return is normally very remarkable ; the enormous amount of oxygen normally consumed by the brain therefore must be utilized at the synapses. Decrement occurs at, and only at, the synapses, and it is now known that a slight ischæmia increases this natural decrement of the synapse to extinction of nerve impulse. My work with the capillary stain has shown ischæmia of the synaptic layers of the cortex, and enables me to put forward a new theory of the physiology of mental effort, emotion and instinct, conveniently pictured as a definite mosaic pattern of capillary activity amongst the millions of synapses, facilitating some, inhibiting others, and thus predetermining the motor behaviour which instantly follows sensory impulses passing through the area. Such capillary patterns may be initiated or " set " by the sum total of the activities of the central nervous system, but persist owing to sympathetic nerve action upon the small arteries and arterioles, and/or the action of metabolites and hormones upon the capillaries. Potential mental and emotional states thus exist without necessarily any concomitant activity of the central nervous system, and have an anatomical representation in the patterns of capillary activity. These capillary patterns, though complex, are infinitely less complex than the neuronic arborizations and synapses whose function they control. Any sensory nervous impulse through a chain of synapses must have a fixed type of motor response, which is determined by the capillary pattern existing at the time. The work of Sherrington (14) and Pavlov (15) is thus simplified ; conditioned reflexes do not depend upon the *permanent* establishment of a fixed path through alternative synapses, but are part of the essentially *labile* state of delicately balanced alternative synaptic paths, regulated by the conditioned mosaic pattern of vascular activity. The combined possibilities of such patterns determine the personality of the individual, and pathological changes in the

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capillary patterns are believed to be a fundamental cause of perverted mental activity, abnormal behaviour, and disintegration of personality, seen at their worst in mental hospital patients.

This theory opened up a new histological approach to the study of mental disorder and new methods became necessary ; the relative vascularity of local brain areas for obvious reasons could not be satisfactorily demonstrated by injection methods, and all staining methods known were unreliable for the purpose. By 1934 my capillary blood-stain method was perfected and published in the *Journal of Anatomy* (16).

As early as the year 1700 disease of the cerebral vessels was noted by Brunner. Ellis in 1909 correlated spontaneous cerebral hæmorrhages with atherosclerosis ; Orr and Rows in 1917, showed that staphylococcal toxin placed against the carotid artery of animals resulted in hyaline thrombi etc., in the cerebral capillaries ; and in 1928 I was able to show streptococci in the brain-vessels of an acutely excited case of dementia præcox. Jaensch studied capillary patterns, finding deformation in the brains of cretins, and Delbruch in 1927 showed that the finger capillaries of mentally defective children were mal-developed. Vogt's theory of pathoclisis based upon abiogenetic degeneration of the third layer of the cortex was disproved by Neuberger, who was able to get the same results of third-layer ischæmia in fat and air embolisms ; whilst Sträussler and Koskinas found laminated and third-layer atrophy both in atherosclerosis and general paralysis. My researches show clearly that lesions in the distribution of pial arteries can be correlated with such laminated atrophy. Keschner studied the mental disorder due to cerebral tumours and concluded that symptoms were due to vascular accidents ; and in 1928 von Braunmühl showed that excitement was followed by spastic hyperæmia of the cerebral vessels with capillary paralysis leading to congestion, local anæmia or hyperæmia, stasis and hæmorrhages. In 1930 Spielmeyer published an account of functional anæmia and degenerations of the cortex in mental diseases, and demonstrated that spasm of the small arteries was the cause of necrobiosis in cells of the cornu ammonis ; Royle in 1932 successfully applied cervical sympathectomy to the cure of early mental disorder. In 1935 Frazer showed that sympathetic stimulation of an artery affected it locally rather than in the whole of its distribution, and Williams in 1934 showed that, on the evidence of its sympathetic nerve supply, the posterior cerebral was really a branch of the internal carotid.

The most powerful factor controlling peripheral circulation is the presence of metabolites ; this, together with the blood-pressure changes effected by the sympathetic mechanisms of aortic and carotid sinus reflexes and the facial nerve, constitutes the main physiological cause of change of lumen of the cerebral capillaries. It should be noted that the arteries of the brain-stem have their sympathetic nerve-supply distinct from that of the cerebrum ; also that the medial muscular coat of the cerebral arteries is deficient.

Constriction of the cerebral vessels takes place with direct electrical stimulation, which completely occludes the lumen for 15 sec. to 2½ hours after cessation of the stimulus (Wolff). It occurs when the blood becomes hypertonic, when the oxygen content is high or the carbon dioxide content is decreased, with stimulation of the cervical sympathetic, and with adrenaline, provided that the inhibition is overcome by sympathectomy or ergotamine (it has, however,

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no constrictor action on the parietal region (Schmidt)). A slight constriction usually occurs, lasting two minutes, before the dilatation due to fall in blood-pressure, however caused (Fog, 1937). Peterson says that peripheral chilling contracts the cerebral arteries as well as the peripheral vessels, and when so contracted they fail to respond to nerve stimuli. Stavraky has shown that constriction of the cerebral vessels occurs on stimulation of part of the hypothalamic region commonly known as the fear area. Peripheral capillary circulation is controlled by the Rouget cells, each of which has its sympathetic nerve-supply. Williams, however, could find no sympathetic nerves to the cerebral venous capillaries. Generally, vasoconstrictors act on both arterioles and capillaries; a dissociated action is seen in the emotional pallor of the face (capillary constriction)—often a chronic phenomenon in mental disorder cases; and in the cold blue of the extremities with constricted arterioles and dilated capillaries—common in schizophrenia.

Dilatation occurs with increased carbon dioxide (mild asphyxia), trauma, acidosis, vagus stimulation (but not when the seventh nerve is cut close to the medulla), with a temperature of 40° C. (inconstant); with stimulation of the seventh nerve; and with a fall of blood-pressure, however caused (unless vessels are already dilated, when a narrowing of the lumen may occur); with ether, histamine (a very sensitive reaction which, however, does not occur regularly if vessels are already dilated by ether), acetylcholine, amyl nitrite and adenylic acid (a product of cerebral metabolism), and carbon monoxide—which causes long-lasting maximal dilatation (Wolff). The pituitary secretion sometimes causes dilatation, depending upon conditions already acting upon the vessels; in the parietal region it has a vaso-dilator effect (Schmidt). Edinow found that ultra-violet light dilates skin blood-vessels, causing a permanent change, so that months afterwards the irradiated area can be detected by its reaction by dilatation to histamine—an important introduction to the phenomenon of latent affection of cerebral vessels. Stavraky showed that very marked pial dilatation occurs on faradic stimulation of the tuber cinereum, a similar dilatation occurring when this area is pressed upon by a small soft sponge. A dilatation could also be obtained by stimulation of the ventral and medial parts of the thalamus. Rhythmic dilatations of pial arteries (10-sec. or 2-min. intervals) were also noted. Capillary paralysis as demonstrated by von Braunmühl follows excitement. The action of CO_2 on the brain vessels contrasts with its action on the muscle vessels; in the brain its influence in causing dilatation overcomes all constricting influences, whilst in the muscle its constricting influence overcomes all dilators.

Tureen found that inflammatory reaction took place two to three days after ischæmia had damaged the tissues, the tissue becoming normal in 11 days. Hill showed that if the intra-ocular tension be artificially lowered, abdominal pressure caused intra-ocular hæmorrhage—a phenomenon which can be applied in the explanation of the origin of small cerebral hæmorrhages. The flow in the minute capillaries is remarkably constant, and according to Wolff, the vessels do not periodically appear and disappear as in other tissues. More oxygen disappears from the blood in its passage through the brain than through the extremities (Myerson and Hilloran, 1930); jugular blood is more venous than femoral vein blood (Lennox, 1931); as much as 10% of total body utilization of oxygen is consumed by the brain, and the oxygen is chiefly used up in the synapses and not in the ganglion cells (the dorsal root ganglia having no synapses, a poor blood-supply and using little oxygen; whilst lamina IV is rich in synapses, has a good blood-supply and its oxygen consumption is

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correspondingly high). The oxygen requirement of the brain tissue is so great that the difference of the bright red of the arteries and the dark blue of the veins is remarkable; the $Q\ O_2$ *in vivo* is 8·4 = 14 c.c./100 grm./minute (Himwick and Nahum), and 3 seconds is the normal circulation time of the brain as measured by radium emanation. Ten minutes' cerebral anæmia kills the ganglion-cells, and Hill and Mott showed the disappearance of Nissl substance after ligature of the carotid in cats, pointing out that the small cells were the first to die on account of the little reserve material. Too much oxygen, however, is highly detrimental to nervous tissue, which normally has a low oxidation-reduction potential; and the blood-supply of the brain is not so great as many standard text-books would have us believe—a test by my method showing it to be about one-sixteenth that of the kidney.

It was long supposed that the brain arteries were end-arteries (Cohnheim, 1872); Fay (1925) injected cerebral vessels with mercury, photographing them stereoscopically by X-rays, and his results tended to support this. Recent researches of Pfeiffer and Cobb, however, show a wealth of anastomoses in the smaller arteries; and at present it is generally assumed that there are no end-arteries in the brain. When œdema or thrombosis affects a number of anastomotic vessels the possibility of virtual end-arteries must be considered.*

The causes of that ischæmia which results in disintegration of the vascular capillary pattern are spasm, stasis, œdema, diapedesis, capillary hæmorrhages and thromboses. A limitation of blood-flow is imposed by some atherosclerotic lesions, 'aseptic' meningitis, chronic subdural hæmorrhages and cardiac decompensation, whilst hyaline changes in the vessels, perivascular cuffing and intimal thickenings reduce local respiratory exchange.

In 1927 Ricker (18) advanced his theory of prestasis, which supposed a constriction of the smaller cerebral arteries coincident with dilatation of arterioles and capillaries. Hiller added to this a possibility of irregular dilatation of some of the arterioles arising from the same constricted artery, thus diverting the already restricted blood-supply from any undilated capillaries and causing local ischæmia. The harmful effects of prestasis are partly overcome by venous obstruction, and partial compression of the jugular vein might thus become a method of treatment of mental disorder symptoms (Fig. 1). Graves's case of ligature of one internal jugular vein for mastoid complications showed an immediate mental improvement, which was maintained. Hallay (1936) produced lucid intervals in mute catatonic patients by alternate rhythmical compression of the jugular veins. The good results of treatment of obliterative vascular disease by rhythmical (2-minute) increased and decreased atmospheric pressure (19) indicate a hopeful future for mild restriction of the jugular flow in mental disorder cases. Hitzenberger warns us not to exceed a positive pressure of 20 mm. Hg. or thromboses occur, nor a negative pressure exceeding 80 mm. Hg. or hæmorrhages occur. Such secondary changes are shown by my method in brains from mental disorder

* For further recent detailed information the reader is referred to the excellent work published in a long series of papers from the Harvard Medical School, Boston.

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cases, and indicate the natural use of pressure variation as a method of compensation of disturbed capillary (mental) function.

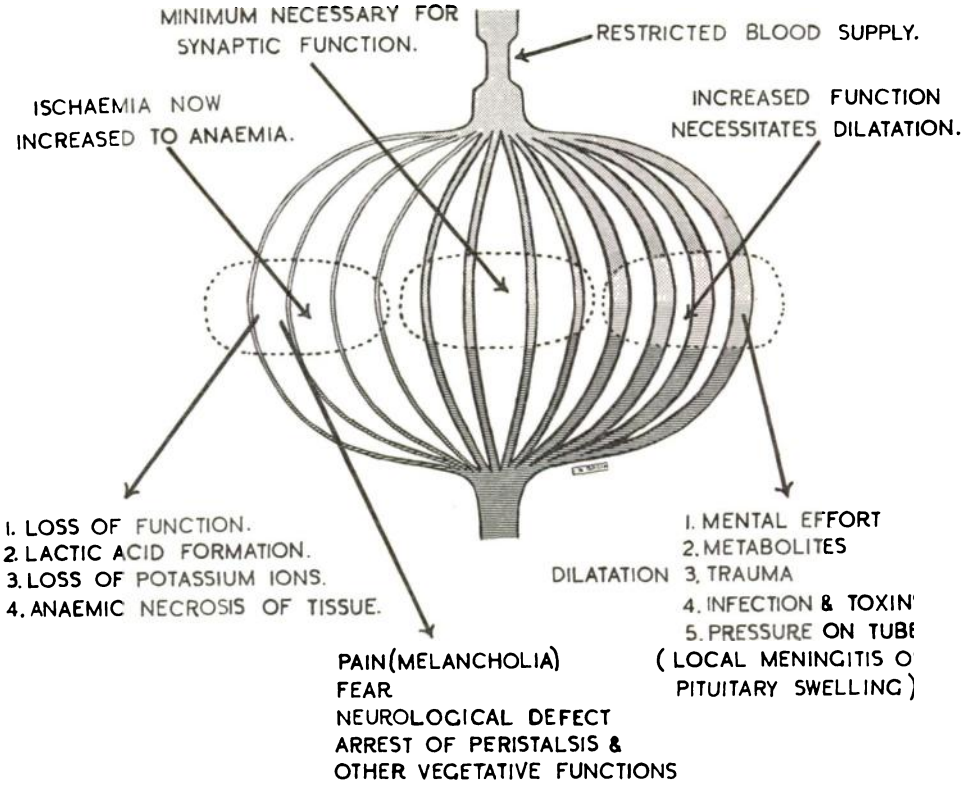


FIG. 1.—Diagram illustrating Rickers' and Hiller's theories. Centre dotted area is normal, any cause of dilatation of capillaries (right) necessitates emptying of capillaries (left) owing to restriction of total available flow. Note: Restriction of venous return would fill up the empty capillaries on left.

DESCRIPTION OF CEREBRAL PATHOLOGY.

Macroscopic.

In addition to the post-mortem findings of œdema, hæmorrhages, softening and atrophy, I have frequently noted pale yellowish areas in the cortex and basal ganglia which are macroscopic confirmations of the ischæmia shown by the capillary stain; vascularized adhesions indicating long-past septic intracranial complications; partial occlusion of the carotid or vertebral arteries by atheroma; and partial thrombosis of cerebral arteries (which is by no means uncommon). In 1925 I collected the carotids of 50 consecutive post-mortems, finding athero-sclerotic lesions at the junction of internal and

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external carotids in every case. In my book, *Chronic Nasal Sinusitis and its Relation to Mental Disorder*, there is figured, opposite p. 32, a specimen illustrative of the long duration of traumatic disturbance of the pia arachnoid. Opposite p. 107 is shown an illustration of latent vascular disease of the cerebellum unmasked by a generalized toxin (adder-bite); it has already been mentioned that ultra-violet light causes a permanent change in the reactivity of vessels to such substances as histamine, and it is therefore changes of a similar nature to the above (which in this particular case were in all probability due to a septic complication from pulmonary tuberculosis many years previously) which are of importance in mental disorder cases. Macroscopic involvement of the carotid artery by contiguous nasal sinus infection is shown opposite p. 32, and also opposite p. 116, where the pathological changes of the artery are actually to be seen through the walls of the sphenoidal sinus. Opposite p. 116 is also figured a specimen of a sphenoidal sinus infection with thickened membrane and a thrombosis of the peri-carotid capillaries on both sides—the effect of this upon the sympathetic plexus needs no exposition. Everyone has noted athero-sclerotic lesions of the cerebral arteries; in some of these a decided restriction of blood-flow is evident, thus constituting a condition of prestasis which under certain circumstances may result in focal ischæmia. Similar lesions are seen in the vertebral and basilar arteries, where the prestatic condition in relation to the posterior cerebral artery is more obvious, since these arteries, although apparently continuations of the basilar, and only connected to the carotid by the small communicating arms of the circle of Willis, nevertheless have their nerve-supply (as Williams has shown) entirely from the carotid sympathetic plexus and not from the vertebral artery. A threatened ischæmia of the lower centres must at all costs be overcome, and thus what might be regarded as an emergency mechanism—that of restriction of blood-supply to a large portion of the cerebral cortex—becomes absolutely necessary, and must be continued permanently so long as the restricted blood-supply of vital centres is barely minimal to support function. Macroscopic pathology of the larger arteries indicates the probability of similar pathology in smaller arteries, and possible interruption of their sympathetic nerve-supply.

Microscopic.

Table I shows the number of brains examined by my capillary stain method, with the more important findings. Some work has been included in this table not satisfactorily out of the experimental stage, so that the whole must still be considered of a preliminary nature. Many more years of patient application will be necessary before the various problems which I have put forward can be settled, but this is the only method so far applicable for the working-out of the slight but chronic departures from the normal physiological

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TABLE I.—*Capillary Stain. Brains from* 171 *Mental Cases. (Total Sections Examined,* 4439.)

	Cases.	Is.	Cg.	Th.	Hm.	Gr.	Lv.	Pvs.
Oligophrenia (A)*	7	6	3	2	5	3	1	2
Schizophrenia (C)	18	16	14	5	9	5	2	7
Paranoia (D)	11	8	6	2	3	2	2	6
Manic-depressive: Mania (Ea) . .	8	8	3	3	6	3	2	2
,, Melancholia (Eb)	7	5	6	1	4	3	3	3
,, Stupor (EaIII) .	1	1	..	..	1	..	..	..
Confusional (F)	23	18	12	3	13	7	5	3
Epileptic (G)	31	28	23	9	19	13	4	11
General paralysis (H) . . .	35	29	19	11	19	6	3	12
Organic brain disease (I) . . .	8	7	3	2	4	3	..	1
Dementia (J)	22	14	10	4	8	8	2	7

Is., ischæmia; Cg., congestion; Th., thromboses; Hm., hæmorrhages; Gr., granules; Lv., loss of vessels; Pvs., perivascular spaces.

* R.M.P.A. classification.

state which we have found to be present in cases of mental disorder. At present I am without any qualified help, but credit is due to the help of a former scholar, Dr. G. M. L. Hobart, and to my assistants, Messrs. Stewart, Rennie and Hindle for the technical application of the method.

In the normal cortex and white matter the regular structure of the vascular arborizations as revealed by my method possess a beauty of form, like that of a pine forest, which can only be appreciated by actual viewing through a binocular stereoscopic microscope (Fig. 2, normal cerebellum; and Fig. 3, normal cerebral cortex). The vessels in healthy animals are normally of even calibre and nowhere show departure from the expected regularity. In all mental cases so far examined and in animals known to be unhealthy when killed, departures from the normal regularity are found.

I have not yet sectioned a large number of brains from non-mental patients because that would not help the problem in its present stage; we are not concerned with averages, but with the absolute clinico-pathological state of undue ischæmia of cerebral tissue, and Nature's attempt at restoration of function in the face of permanent vascular lesions.

Pfeiffer (20) has shown similar conditions of disturbed vascularity of the brain in tuberculosis, where it is probably indicative of the mental changes commonly found in that condition. Old age of itself is not necessarily accompanied by much reduction in the complexity of the capillary regularity and arborizations, as will be evident from Fig. 3, from a case aged 90, which is given as an illustration of the normal for that reason. Some of the irregularities met with are described, with the method, in my paper in the *Journal of Anatomy* (16).

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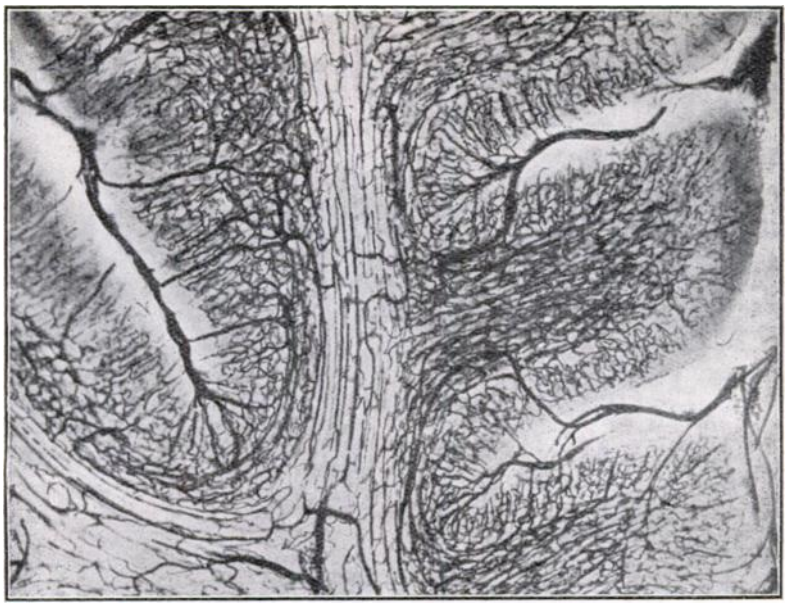


FIG. 2.—Cerebellum—selected area of normal appearance. × 24.

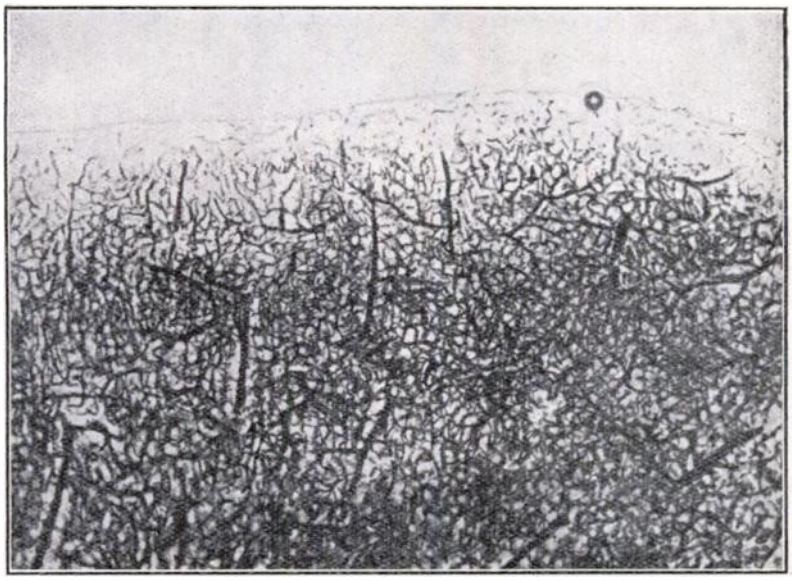


FIG. 3.—Cerebral cortex—selected area of normal appearance. × 25.

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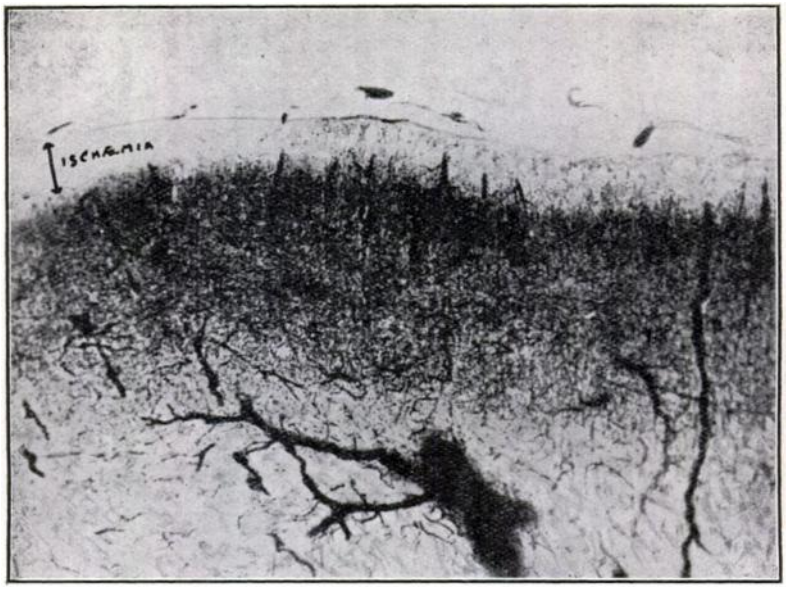


FIG. 4.—Ischæmia of outer cortical layer. (Case of general paralysis.) × 28.

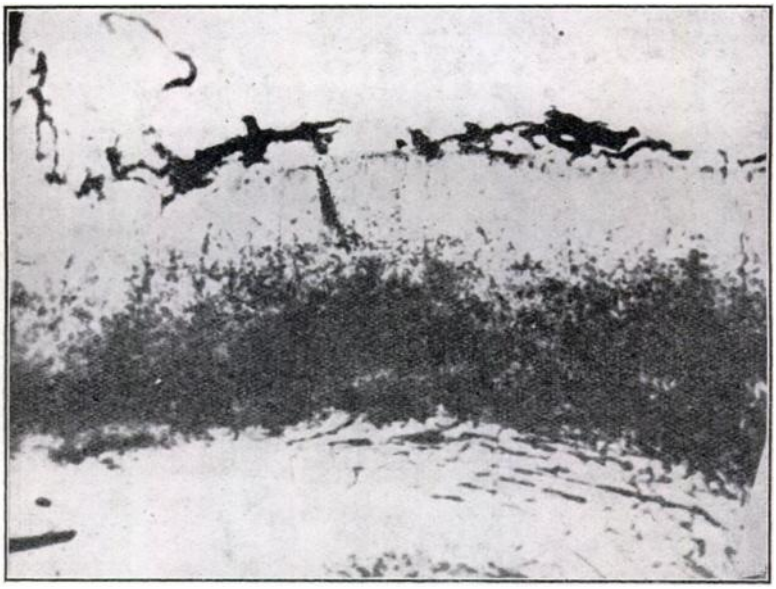


FIG. 5.—Ischæmia of outer cortex with congestion of deeper layers. (Case of melancholia.) × 25.

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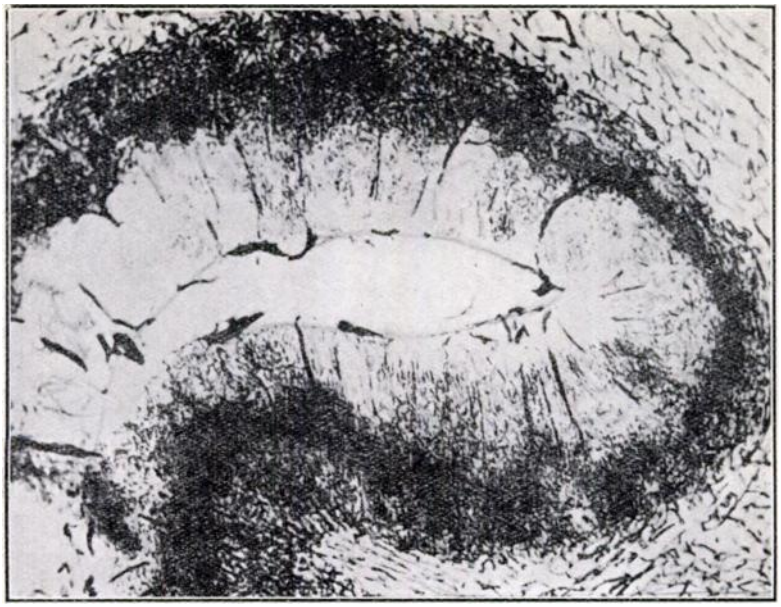


FIG. 6.—Ischæmia of outer layer within a small sulcus. (Case of melancholia.) × 10.

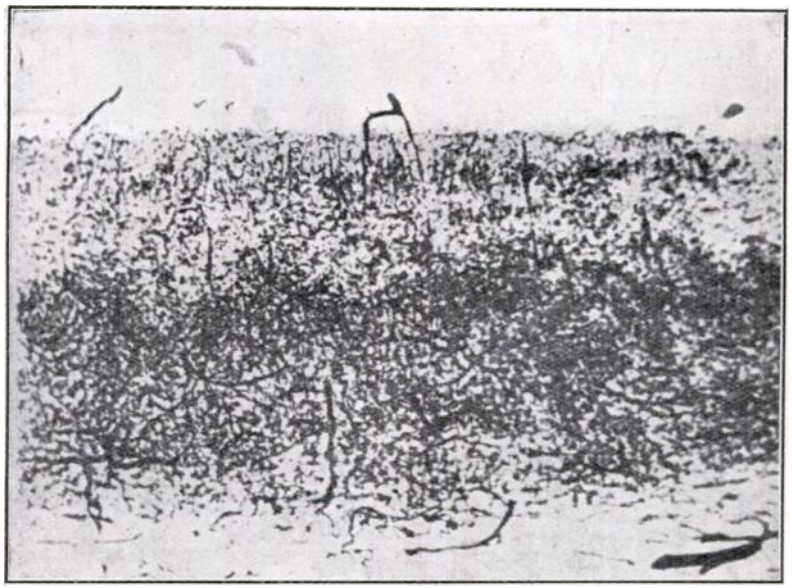


FIG. 7.—Cerebral cortex, congestion of outer layers. (Melancholia following post-lethargic encephalitis.) × 28.

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FIG. 8.—Diapedesis of corpuscles. (Case of epileptic insanity dying in *status epilepticus*.) × 40.

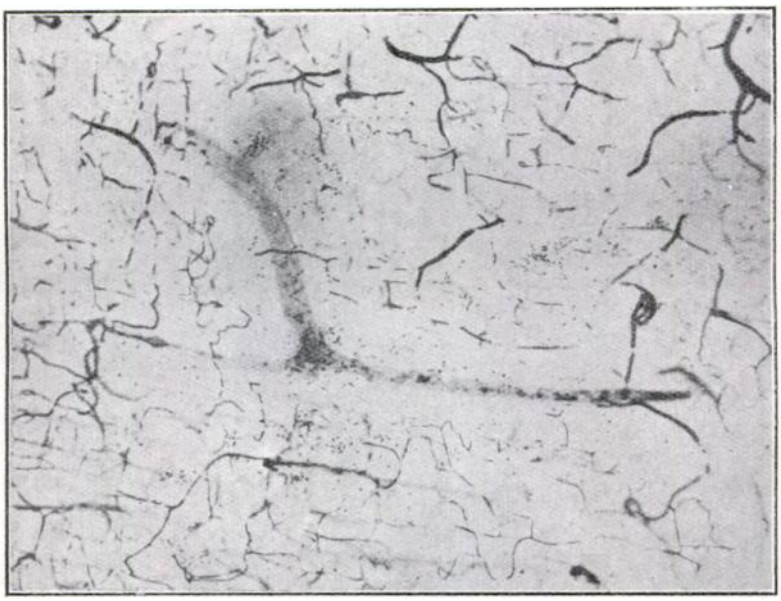


FIG. 9. Thrombosis of capillary. (Case of contusional insanity with lobar pneumonia.) × 40.

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Fig. 4 shows ischæmia of the outer synaptic layer of the cortex; it is from a case of general paralysis. Fig. 5 shows a more extensive ischæmia with congestion of the deeper layers of the cortex; from a case of melancholia. Fig. 6, also from a case of melancholia, shows ischæmia within a small sulcus, and is given to show that these appearances are not due to mechanical interferences during preparation of the section. Fig. 7 shows congestion extending into the outer layer of the cortex and is virtually an encephalitis; it is from a case of melancholia following an attack of encephalitis lethargica. Fig. 8 shows diapedesis of the cerebral capillaries in a case of epileptic insanity which died in *status epilepticus;* he also had a lobar pneumonia. Fig. 9 shows thrombosis of some of the capillaries in a case of confusional insanity.

The table given shows that evidences of vascular disturbances can be obtained from all the brains examined in mental disorder cases. Further work is in progress, and it is hoped to correlate certain localizations of vascular defect with the major mental symptoms and with neurological conditions which the patients have shown during life. The theory which I have put forward of the limitation of synaptic function by the vascular state can be proved or disproved by a further application of the method, and besides opening up a more hopeful outlook in the barren field of treatment of certain neurological conditions, it requires that psychiatric cases should be treated as suffering from vascular instead of nerve pathology.

Correlations.

The use of focal ischæmia of the cerebral synapses as a common denominator of mental and medical science will now be illustrated.

Mental phenomena.—It has long been accepted that local ischæmia of nervous tissue means functional paralysis. Mott showed that temporary or permanent dementia could be produced in animals by carotid ligature. The Assyrians compressed the carotids of their young men to relieve the pain of castration. Trotter, with regard to cerebral hæmorrhage, says that irritative symptoms mean congestion and paralytic symptoms mean anæmia. Mental effort results in an increase in the oxygen and a decrease in the carbon dioxide of the jugular blood, i.e., a dilatation of cerebral capillaries. Gildea and Cobb described a loss of intelligence and a bizarre activity of cats whose vertebral artery had been ligated. Drugs producing volubility, exhilaration or motor hyper-activity (ephedrine and benzedrine) belong to the class of drugs specifically acting upon blood-vessels. Ferris denervated the carotid sinus, and some patients after the operation could see better and felt better, and colours appeared brighter. Royle cured irritability and bad temper by cervical sympathectomy—which effected a change in the cerebral circulation, and von Braunmühl showed excitement to be associated with capillary stasis.

Neurological.—Cerebral vascular spasm is said to be the cause of cerebral

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anæmia, eclampsia, migraine, functional hemiplegia, aphasia and amaurosis. Cortical ischæmia is considered to be the cause of the familiar Babinski sign (25) and the cerebral malformations in Pick's disease. Mott showed that firm pressure on the upper cord did not prevent nerve-impulses passing from the cortical leg area to the muscles, but light pressure in the lumbo-sacral region sufficient to cause ischæmia of the grey matter completely obstructed even the strongest impulses. The widespread functional loss in many nervous lesions (infantile paralysis) later recovers as the ischæmia caused by œdema is relieved. In addition to the relief of symptoms of mental dysfunction by cerebral stimulation, the associated contortions of torticollis, parkinsonism, etc., are also temporarily relieved; such clinical demonstrations show that not only mental disorder but many neurological conditions are caused by functional rather than structural disorder of the cerebral neurones, the synaptic pattern remaining normal under such diseased conditions, but a functional inhibition is imposed by deficiency in the blood-supply of the synapses. Stammering is illustrative of interruption of synapses by ischæmia where the neuronic patterns are obviously intact, and the locomotion and oculogyric crises of post-encephalitis show how activity of contiguous synapses may sometimes allow sufficient oxygenation of the ischæmic synapses to permit temporary direct function (also illustrative of the reason for the peculiar associated behaviour in both conditions). Failure to recognize the vascular regulation of synaptic function as being the basis of conditioned reflexes has led to difficulties in neurological research, such as the necessity for extraordinary precautions and unnatural isolation of animals during investigation.

Physiological.—The physiology of alternative reactions to the same stimulus is explicable by my theory of vascular regulation of synaptic function; for example, the same olfactory food stimulus can be a source either of attraction or repulsion, depending upon the full or empty state of the stomach, the visceral impulses presumably influencing the vascularity of alternate cerebral synaptic paths. In many animals (e.g., the early worm-fishes) olfactory nerves pass from the olfactory region both to the pineal-habenular and the pituitary-hypothalamic regions of the brain (Clark (22)). The reason for olfactory impulses passing to such widely different parts of the brain is difficult to explain by any other mechanism than the synaptic facilitation theory which I have put forward, and which makes the fact that a crab's nerve supplies both flexor and extensor muscles of the joint no longer a curiosity. Many of the discordant results encountered in the study of the action of certain nerve excitations, and of the pharmacological action of drugs, are possibly due to failure to recognize the all-importance of the vascular supply of certain synapses in order to get the desired pattern of reflex response. The lability of reflex pattern response is well shown in, for example, a dog, previously careful and obedient, who at the sight of another dog across the road at once becomes heedless of command and of traffic—the cerebral vascular capillary pattern

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having been "set" by the mental reflex to that which allows only the one nervous synaptic pattern and resultant behaviour.

Emotional.—The emotions of shame and embarrassment are associated with peripheral dilatation, and fear, pain and anger with peripheral vaso-constriction—no doubt a corresponding alteration of certain focal brain areas occurs simultaneously. Stimulation of the anterior hypothalamus in the region commonly known as the fear area contracts pial arteries (Stavraky (23)), and pain inhibits function and peristalsis. Obliterative endarteritis is distressingly painful, and thus cerebral vascular spasm may be evidenced by melancholia. Continued pain may be compensated by vascular adjustments similar to the extinction of the sound of clock-ticking; in such conditions the collateral paths of the pain-impulse which cause vascular spasm may persist—in chronic nasal sepsis a facial pallor is commonly noticeable. Similarly mental effort and metabolism may be inhibited by chronic pain stimuli, where the actual sensation of pain has, by reason of its duration, ceased to enter consciousness.

Endocrines.—That endocrine secretions affect the vascularity of the brain has long been known, and Cushing's (21) demonstration of the intra-ventricular action of pituitrin is very convincing. Schmidt (17) has studied the elective action of certain endocrine secretions (pituitrin, adrenaline) upon different parts of the cerebrum and brain-stem. Although endocrine activity has no direct relation to the insane condition (as evidenced by cases of extreme endocrine hyper- and hypo-activity without mental disturbance), yet its effect upon a case with a disintegration of the capillary pattern is of the utmost importance. This is best illustrated by contrasting the maniacal behaviour in some cases of hyperthyroidism (in which the endocrine secretion is acting upon an already disintegrated cerebral capillary pattern) with the sexual behaviour of an animal having a normal brain, but with total removal of gonads and genitalia, on injection of the sex hormone.

Stupor.—In stupor and hibernation, function and production of metabolites are minimal and the synapses are accustomed to less oxygen requirement. A blood-supply adequate to support existence in hibernation would probably result in anoxæmic necrosis of tissue in the normal state of function. Stupor and apathy are means of forced economy of the cerebral blood-supply under conditions where it is limited by spasm or disease.

Mental deficiency.—The anthropologist Hrdlicka (24) said that man had not yet progressed to his full mental capacity because the development of the cerebral vessels had not kept pace with the development of the brain. It follows from this that any additional lack of development of cerebral vessels must necessarily cause a degree of mental defect depending upon its locality and extent. Early traumatic or toxic disturbances of the fœtal cerebral circulation inhibit growth of embryonic cells which, owing to their period restriction (Needham), cannot later develop even should the circulation be

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later restored. Evidences of such are seen as "stigmata of degeneration", and a restricted locality is indicated by "idiots savants". After birth the conditioning of environment influences the cerebral vascular supply by the constant buffetings of emotional and digestive upsets, and to these may be added dietetic and infective causes of vascular disease, also the later vascular diversions of puberty, menstruation and courtship. Vascular spasm persisting during development (such as from otitis, sinusitis, naso-pharyngeal sepsis, etc.) necessarily inhibits mental development, and such cases, even although passing as normal, would have been superior mentally and physically had such accidents not occurred.

Psychiatric.—The individual personality is built up by neuronic patterns which are conditioned by social demands, and it follows that when such pattern is disrupted by chronic ischæmia, the behaviour will change away from such properly conditioned types to inferior or antagonistic (asocial or negativistic) reactions. The naughtiness of post-encephalitis is a typical example. In my work I frequently find atheromatous changes in the vertebral and basilar arteries, sufficient to form a prestatic condition of the lower vital centres; ischæmia of these centres would occur by dilatation of branches of the posterior cerebral artery, which, as Williams showed, has its sympathetic nerve-supply from the carotid and not from the vertebral. Since the dilatation in such conditions must be overcome by a vascular agent of constriction, stimulation of the fear area has a clinical significance.

In addition to the pale yellow areas in the basal ganglia and cortex, which I have noted are universally present in mentally disordered cases and which afford naked-eye evidences of ischæmia, the following associations are of interest: *Epileptic insanity* may be regarded as invariably associated with cerebral vaso-lability, and parenchymatous degeneration in certain brain areas (cornu ammonis) has long been recognized by Spielmeyer and others, as due to cerebral vascular spasm. Mott obtained epileptic phenomena by moderate stimuli of the motor cortex in animals also suffering from experimental cerebral ischæmia. Kausmaul and Tenner compressed the carotids of six persons, two having epileptic fits. Hughlings Jackson thought epilepsy was due to vascular plugging of small cerebral vessels. Kennedy noted blanching of cerebral capillaries during epileptic tonic spasm with engorgement in the clonic phase. Penfield says the constant visible phenomenon in the brains during a seizure is the cessation of arterial pulsation in a focal area. *Schizophrenia* shows peripheral capillary phenomena comparable with ergot or histamine poisoning as pointed out by Bayard Holmes; Hollander and Rouvroy described thickening or atrophy of walls of minute vessels. Gottlieb ascribed the static vascularity present to an irresponsiveness of the sympathetic system. *Manic-depressive* insanity shows coagulative necrosis of nerve-cells (Marburg)—probably due to ischæmia; Bouman and Brouwer found dot-like hæmorrhages in the cortex, hyperæmia of the pia, and thrombi

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partly extending from the pial veins to the large cerebral sinuses in two cases of acute delirium. In *confusional insanity* Damaye and Poirier described a meningo-encephalitis similar but of less intensity to that of general paralysis. The vascular lesions of *general paralysis* are exceptionally severe, as shown by my method. Winkelman and Eckel remark on the similarity of the vascular lesions of syphilis and sepsis. As the pathological causes of ischæmia increase, neighbouring ganglion cells may become destroyed, resulting in dementia or permanent neurological lesion. *Dementia* is of two types: The one due to ischæmia of synapses and clinically distinguished by an ability to show temporary recovery or cerebral stimulation; the other due to ganglion cell necrosis, distinguished histologically by atrophy and thinning of widespread cortical areas.

The success of the various treatments of general paralysis in most cases depends upon their ability to alter the vascularity of certain brain areas. My work with the capillary stain method has led me to suppose that mental disorder syndromes are due to pathological obliteration or disruption of the vascular capillary pattern upon which the nervous synaptic pattern depends for normal function. A bizarre conduct ensues when function is compromised by unusual nerve routes, and secondary degenerative changes, which occur when the ischæmia is widespread, result in acidic and excitatory changes, causing irregular stimulations of the sensorium or impulsive behaviour. The various psychiatric syndromes can be assumed to depend upon the anatomical localizations, the multiplicity of areas involved, the age of onset, the duration and the oscillatory vascular changes consequent upon attempts at overcoming any ischæmia of vital areas, which must at all costs function to preserve life itself.

Biochemical.—Local cerebral ischæmia causes œdema, which shuts off anastomoses, and therefore the brain suffers both oxygen lack and accumulation of metabolites; one of these, adenylic acid, has been shown by Drury to cause capillary dilatation. Under conditions of ischæmia lactic acid is produced, which physiologically reduces the oxidation-reduction potential of the nervous tissue, with protective cessation of function; it is probably for this reason that there are naturally alkali (ammonia)-producing enzymes in the brain. Under pathological conditions of ischæmia the acidity may exert a poisonous effect upon neighbouring tissues, causing fatty changes in the cells, as found by Cotton, or mucin accumulations (Buscaino); mucin has been found by us in the brain of a case of myxœdema. Anoxæmia also causes loss of potassium ions, which have a powerful effect in inhibiting adjacent nerve-function, and the finding of an increase of potassium in the cerebro-spinal fluid in 8 out of 20 cases of schizophrenia by Katzenelbogen (26) thus indicates cerebral ischæmia.

Bacteriological.—Repeated bacteriæmias of chronic sepsis, such as established by Parish and Okell and Round and Kirkpatrick, are related to ischæmia and vascular clogging by well-known bacterial reactive mechanisms, such as adhesion of organisms to the cerebral capillary wall (found by me in a

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case of acutely excited dementia præcox), which, but for the rapid disappearance of organisms (about four days), would be much more frequently found; the tissue fixation of organisms (Menkin); the inflammation caused by antibodies and antigen uniting in the tissues (Opie); the progressively increasing local reaction to repeated doses of the same antigen (Arthus); the clogging of vessels with antigenic material (Kahn); and the peculiar reaction to 24-hour spaced injections of bacterial filtrates (Schwartzmann). A chance involvement of a certain local tissue renders it liable to become a *locus minoris resistentiæ* in the event of similar bacteriæmias on a future occasion. The same occurs from contiguous diffusion of neighbouring infection. A new field is opened up for the action of toxins upon the vascular supply of special focal areas of the brain.

Atherosclerosis.—Arteritis may be caused by typhoid fever, diphtheria, measles, scarlet fever and small pox. My researches on the Widal reaction show that a significantly high proportion of mental patients (including defectives) have had infection with dysenteric or food-poisoning organisms. Atheroma the cerebral arteries is commonly found, often with partial thrombosis of t larger arteries; in one case a complete thrombosis of the carotid artery from t junction with the external carotid to its intra-cranial termination was fou Lead poisoning causes arterio-sclerotic changes by reason of the vascu spasm; it is probable that other causes of spasm, such as the referred pain chronic sepsis of the ear, nose and throat may similarly be related ætiologica to the atherosclerosis commonly found. Many specimens of nasal sinus also show athero-sclerotic changes of the internal carotid artery, and are fu described in my book.

Nasal sinus sepsis.—At Birmingham the incidence of nasal sinusitis a its association with mental disorder has been investigated and a valua collection of museum specimens made. The lymphatic drainage of the na sinuses passes into the deep cervical chain in relation to the superior cervi and the carotid artery; contiguous toxins diffusing into the ganglion perivascular sheaths affect the cerebral circulation by spasm, stasis and thro bosis in a manner analogous to that shown experimentally by Orr and Ro Pituitary gland swelling due to contiguous sphenoidal sinus sepsis may pr upon the tuber, thus causing a reflex dilatation of the pial vessels.

Focal cerebral ischæmia thus forms a useful connecting link between men and medical scientific research, and opens up new possibilities in the preventi and treatment of mental disorder and defect.

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Discussion.

Prof. F. L. GOLLA said he was sure all must admire the courage and industry of Dr. Pickworth, perhaps especially his courage. That gentleman had done what very few members dared to do. All, no doubt, kept some sort of note-book of things which could be philosophized about, but there the matter usually stayed. It was a pity it should so stay, and many of the points which Dr. Pickworth had brought out and which could be thought about were those with regard to which Dr. Pickworth might be right, and he might be wrong. As a technician Dr. Pickworth had shown superlative skill. Many of the demonstrations given by him were not to be regarded as final; they might be taken as suggestions of what might happen if certain views were adopted. Understood in that spirit, he was sure all present would have learned much from his most interesting lecture and demonstrations.

Dr. J. H. MACDONALD said that what had been given to the meeting to-day had been extremely interesting, and perhaps it had been informative too. It was a very old question, and was one of those which Ford Robertson, senior, and himself were interested in when they were doing histological work on the degeneration of the nerve-cell. It was striking to him, the speaker, as a pathologist, how often he came across vascular disturbances in cases of neuronic disease. Were these changes in the cell primary, or were they secondary? Could he be told whether these toxæmias were acting primarily on the nerve-cells, or on the capillary vessels? Should they be regarded as vascular changes, or as neuronic? That was, he thought, still an unsettled question. In many cases, however, one was able to find evidence of circulatory changes, and workers were beginning to lay great stress on the presence of ischæmia.

Prof. Golla had uttered a very important warning when he spoke of the defective methods of estimating the circulation in a particular cerebral area. It was very important to reflect on the ischæmic changes which followed concussion and also emotional shock. Many suffered periods of concussion, others suffered enormous emotional upsets. Because they had such experiences he would not consider it showed they were on the way to becoming lunatics, via these ischæmic changes.

Another point which struck him as important was the reference to epilepsy and the changes in the cornu ammonis, which could be interpreted as ischæmic. He asked what was the interpretation of the epileptiform convulsions in general paralysis, where the changes were regarded as congestive rather than ischæmic? Gross congestion seen might be accompanied by local ischæmia; but the picture of an epileptiform convulsion was not one of ischæmia. There existed a striking want of co-ordination between these pathological and histological findings in reference to the clinical conditions. What was seen could easily be explained wrongly. The clinical and pathological pictures did not fit in with each other sufficiently to warrant a general conclusion yet. As Prof. Golla had just said, it was necessary to be very careful about the conclusions based upon these findings otherwise one might very well be led astray.

Dr. J. H. BIGGART expressed his congratulations to Dr. Pickworth on the

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amount of work he had done. Four years ago he would have been much more interested in it. He had been examining 300 brains a year, and while at first he was inclined to explain dementia on pathological findings and on the vascular disease which he found, he soon came to the conclusion that he was finding in non-demented patients vascular pictures equivalent to those in the demented: atheroma, arteries sclerosed, and areas of ischæmia, with infarcts; in fact all the vascular lesions which Dr. Pickworth showed to-day could be found in routine examinations of brains of patients dying in a general hospital who did not suffer from dementia.

He had been very interested in the application of Dr. Pickworth's stain, but the view of that gentleman was anatomical more than pathological. There were many artefacts in reference to the pathogenic aspect of mental disease. There was the handling of the brain itself, and there were the agonal changes. He had a patient in hospital who died from asphyxia due to a large retro-sternal goitre. Her brain showed many vascular pictures resembling those which Dr. Pickworth showed, but because she had sudden terminal asphyxia no evidence was forthcoming in regard to those vascular changes and the possible cause of her dementia præcox. Therefore it was necessary to view with great caution any explanation of mental disease which was based upon these pictures. Other explanations brought forward included swelling of the sphenoid. He had found that often in ordinary mental cases, but not causing any symptoms which could be associated with any damage to the tuber. It was known that damage to the tuber produced gonadal atrophy and diabetes insipidus, and these cases of sphenoidal sinusitis with pituitary œdema did not come into this category. He challenged the reader as to whether there was tuberal damage, causing damage to the tuberal vessels.

His experience in examining 400 control brains made him sceptical about the conclusions which might be based upon implication of the sinus. He felt there might be an association. He owed much to Dr. Pickworth, who had been very brave, but he, the speaker, did not feel positive about it. He felt himself to be in a position of negativism with regard to a possible explanation.

The PRESIDENT said that Spielmeyer had retracted all he had previously said about the effects of functional disorder of the vascular system. A good deal was taught about toxæmia in mental disease. He always said that it depended, first of all, on the amount of the toxin, and, secondly, on the constitution of the individual. If twelve men were placed in a row and half a glass of whisky was given to each, not much difference might be noted in the effect it appeared to have. If, however, the quantity was increased to two or three glasses, one noted that some of the men got confused, then garrulous; one might become arrogant and wish to fight; another became unduly affable and familiar. Later the alcohol caused sleep. Clinically one could produce different effects according to the quantity taken, and eventually very small amounts might be injurious. Because a great variety of clinical conditions could be demonstrated it must not be said that the lesions were connected with mind; they were connected with motor and sensory areas which controlled functions in other parts of the body, such as the endocrine glands. He did not see how any kind of injury could produce a specific mental symptom.

Dr. PICKWORTH, in reply, dealt first with Dr. Macdonald's remarks on agonal changes. He, Dr. Pickworth, had compared the results in cats which had been killed in various ways, such as by strangulation, decapitation, cyanide or gassing, and he thought the agonal changes soon disappeared, and that the ischæmic areas which he had demonstrated were chronic changes.

With regard to the question whether a toxin acted on the vessels or on the cells, if the toxin acted on the cell the latter was unlikely to recover, and if it did one would not expect it to revert later to the identical toxin-impaired state in the same way as the mental state reverts after temporary restoration of sanity by methods of cerebral stimulation. If one gave an excess of CO_2 a patient would

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become mentally normal for a short period, but shortly after the effects of the stimulus passed off the original state was resumed. It could therefore not be an effect on the nerve-cells as the functional capacity of nerve patterns in mental disorder remained normal.

Another point was that ischæmia was not necessarily a permanent change. There were exhibited slides illustrating regeneration of vessels. One had always been taught that nerve tissue could not regenerate, though vessels could do so; ischæmia could be a temporary change. A physiological conditioning of the mental state or emotion by a definite capillary mosaic allowed of a definite neuronic pattern by inhibiting unwanted synaptic paths. There were millions of nerve-cells, with countless millions of synapses, but as long as only one capillary pattern existed, motor response to stimuli could only be along the one path left open for it.

With regard to general paralysis, he had never found a case of it without marked cerebral ischæmia, though congestion occurred at the same time.

Almost half his paper was devoted to the correlation of the clinical with the pathological for which speakers had asked.

Referring to Dr. Biggart's remarks, dementia also could be associated with ischæmia, but was of two types, one recoverable, the other permanent with destruction of nerve-cells. Spielmeyer and others had shown that there could be ischæmic necrosis of tissue, and there must be a consequent dementia, because the nerve-cells had gone. That could be seen best in cases of G.P.I., where the atrophy of the brain was evident to the naked eye.

With regard to changes in the tuber, it was not his intention to infer there were any permanent changes there. Any contiguous sphenoidal sinusitis might cause inflammatory changes affecting the local blood-supply, and a very small change might produce sufficient ischæmia to cause functional inhibitions. It could be shown that light pressure on the tuber caused dilatation of the pial vessels.

Referring to the President's remarks, he, Dr. Pickworth, placed the whole theory of mental and emotional states on the capillary patterns. An individual personality resulted from labile changes in capillary pattern, conforming to circumstances and allowing appropriate behaviour. The synapses might normally become adjusted to one pattern, but that pattern changed conformably to emotional reaction, mental effort or to any instinct, or any hormone which affected the vascular capillary pattern of the brain. Mental changes were not necessarily associated with insanity, even if they were due to pathological ischæmia; and pathological changes could arise from undue prolongation of physiological causes. No doubt even alcohol acted primarily on the cerebral capillary circulation, because one of its effects was to cause inconvenient changes in the capillarity of the face.

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