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A NEW OUTLOOK ON THE PHYSIOLOGY AND PATHOLOGY OF MENTAL AND EMOTIONAL STATES *

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(WITH SPECIAL PLATE)

The Present Impasse in Mental Disorder Research

The central nervous system contains a large number of neurones each with cell body, dendrites, axon, collaterals, and synapses, connecting with one another in a manner similar to the communication lines of a number of automatic telephone exchanges; the physiology of the relation of this complicated system of neurones to mental function, emotional reaction, and conduct is, however, obscure. Eminent scientific men have spent their lives in this research, but their work has merely added to our already vast store of knowledge without solving the main problem. At the recent Royal Society of Medicine discussion of the relation of endocrines to mental disorder no agreement was come to regarding this, and for various reasons the discussion was not published; at the psychiatric section Dr. E. Goodall in his presidential address lamented the fact that in spite of enthusiastic work over the last half-century little real progress in either aetiology or treatment had been made. He said: "We have in my opinion made no advance in our knowledge of the pathogenesis of the psychoses." In America, Freeman (1937), after ten years' intensive research in psychiatry, says: "Little more is to be gained from the study of the anthropologic, nosologic, or pathologic-anatomic features of the body in persons suffering from mental disorders." Hoskins (1937), with reference to schizophrenia, states that "the morphologic pathologist has sought in vain for a basis of the disorder." Fulton says that although physiological functions have a cerebral localization few would venture to localize the higher intellectual functions; Lashley says, "I am coming to doubt the validity of the reflex arc hypothesis even as applied to spinal reflexes"; and Professor Golla in his 1937 Maudsley lecture said the physiological make-up of personality does not admit of description in purely scientific terms.

The biogenetic deteriorated-neurone theory of germ-plasm defect, with possibly a few rare exceptions, can no longer be upheld, since the evidence upon which hereditary theories have been based—apart from the conditioning of environment—has been shaken by Paterson, Penrose, and Findlay. The success of various shock treatments (malaria, hyperpyrexia, and insulin)—although this therapy is possibly on the right lines—is without approved explanation. The toxin-impaired-neurone theory, which we have

cherished so long and expended so much energy upon, is untenable for reasons which I shall give later; and the work of Pavlov's school on conditioned reflexes involves almost incredible precautions in the isolation of animals during experiment, in order to eliminate the hypothetical investigatory reflex—precautions totally out of proportion to what we know from our own observations and experience are necessary to establish conditioned reflexes in ourselves or animals, suggesting that the theoretical basis upon which they are working is incomplete. Sherrington (1933) says: "We have to regard the relation of mind to brain as still not merely unsolved but still devoid of a basis for its very beginning." The question naturally arises whether the physiological conception of mental and emotional states upon which research is based is lacking in some fundamental quality. Superstition demands an infinitely more complex control of the already complex nervous system, and thus hinders study of a humbler control by the vascular system.

Higher Reflex Action in Relation to Mental and Emotional States

Neurones transfer energy by electrical impulses† which cease at the next receptor organ or dendrite after having there effected an electro-chemical ionic change (liberation of potassium ions). In the higher animals this change results in a synthesis of a transmitter substance which, if quantitatively sufficient, effects a motor response or a discharge of the neurone with which it is in contact, the new electrical impulse thus set up having different characteristics from the original impulse. A sensory impulse is thus transmitted by alternate physical and chemical agencies, the latter (but not the former) often reinforced by other impulses, till eventually an end-organ is excited (motor response), or it becomes lost by reason of quantitative insufficiency of some synapse in its path. Stimuli reaching the central nervous system and the nerve potentials there built up are annihilated within a fraction of a second; even the central excitatory and central inhibitory states (Sherrington school) attain their maxima in 0.006 and 0.05 second respectively (traces only remaining as long as 0.015 and 0.2 second respectively); all such are instantaneous in comparison with the time duration of mental and emotional states (hereinafter referred to as m.e.s.). The brain itself is incapable of

* An amended lecture read to the Midland Mental and Pathological Society, October, 1937.

† Chemical diffusion along an elephant's motor nerve would take geological time to effect a response.

originating nerve excitation, and the widespread faulty appreciation of this fact in relation to the anatomical "centres" of physiological function in the brain has resulted in the appearance in the literature of erroneous statements of hormones "stimulating" brain centres.

Mental states, although physiologically associated with the central nervous system, possess a somewhat different function and characteristics; attempts to identify them have been and always must be failures. Sherrington (1933) says that "the history of the brain seems to suggest mind as at the outset a sort of adjunct to the nerve management of motor behaviour." Parker (1932) says the dawn of intelligence is seen in the capability of a primitive animal to refuse food when engorged. The word "mind" is best limited to such differential control of alternate nerve pathways (see Fig. B) influencing behaviour, and includes also subconscious function. The distinction between subconscious and conscious varies in the one direction with evolution, growth, and age; and in the other with learning, training, or physiological defect, although limited in the latter respect. The conscious attempt of the child in its first walk contrasts with the adult's conscious attempt at directing any part of the walking phenomena—which decreases rather than increases efficiency; and the brilliance of an artistic performance may be enhanced by a slight general mental inhibition (alcohol). Skilled movements, such as those of pianists and typists, are due to a finely detailed control of synapses; a really expert skilled worker can read, talk, and otherwise pay little conscious attention to his work whilst at the same time doing it quite efficiently.

Mental function is usually somewhat vaguely identified with dynamic activities incident to the characteristics of nerve impulse which have been established by the study of isolated muscle-nerve preparations, together with the principles of functional integration of neurones, conditioned reflexes, and supposed, but impossible, long delay paths in the central nervous system. A single nerve impulse is exceptional rather than the rule, what is generally regarded as an impulse being shown by electrical methods to be built up of a large number of successive impulses. The central reflex time is practically instantaneous, being in some instances less than half the total reflex time; motor effects of longer duration can only be due to *repetition* of the original or other stimulus. The time relations of higher reflex action of the central nervous system, assuming the stimulus is not continued or repeated, therefore cannot be conciliated with those of m.e.s. (which take time to develop and persist several minutes, remaining as traces hours, days, or even years afterwards); thus the latter must have a different physiological basis. Apparently no one has previously attached any importance to the fact that m.e.s. are static rather than dynamic phenomena, and that they are potentially independent of the higher reflexes of the central nervous system whose metabolism they control.

Conduct in Relation to Mental and Emotional States

Since motor behaviour (which is the dynamic end-result of higher reflex action) is constantly changing, even in the same individual, a consideration of the controlling influences of m.e.s. upon conduct is necessary. Certain facts are readily ascertainable from our own experiences; for example, the same stimulus may result in different motor effects under different circumstances—that is, with differing m.e.s. The reaction and behaviour to a plate of hot soup at the beginning or end of a heavy dinner typify the most primitive example of the same stimulus

resulting in a behaviour determined by the then existing mental and emotional state; the word "cats" to a dog nearly asleep may evoke partial opening of one eye, but if the dog is alert and there is a near-by rustling, immediate action ensues, involving the *whole* musculature of the animal. Conversely, widely different stimuli may produce similar motor responses: recognition—which is a mental state—can be observed in a dog receiving an olfactory, auditory, or visual stimulus from its master. Stimuli received during any particular m.e.s. have their characteristic limitation of motor response (conduct)—a fact exploited in political gatherings, and shown by the example that a well-meaning harmless intervener in a quarrel may get his nose broken; docile animals when frightened, or in other unaccustomed m.e.s., may scratch, bite, or otherwise harm their keepers.

Many stimuli received during a certain m.e.s. are lost or inhibited by training; all others automatically (robot-like) result in responses (conduct) in conformity with the particular mental and emotional state. A quiet demeanour in a sick-room is essential because the patient is consciously or unconsciously preoccupied with painful stimuli (an increased activity of those synapses which we know subserve the reflex paths of pain being necessarily paralleled by increased local capillary function), and therefore any uncompensated stimulus intensifies shock—the m.e.s. equivalent to subconscious pain. Unexpected loud sounds or strong stimuli cannot readily be compensated, and elaborate precautions are sometimes taken to prevent street noises reaching the sick-room. When an "irritable" mood prevails, the wireless, clock-tick, canary, door-bell, telephone, and animals' and children's noises are stimuli which may and do excite impulsive behaviour, whereas with a good mood such sounds are stimuli to appropriate motor responses.

Emotional states (anger, friendliness, hostility, approval) are clinically recognized by the facial appearance or attitude. A mother's estimation of her child's capabilities is often emotional rather than intellectual; but such distinctions are of little import, since both mental and emotional states are dependent upon the same mechanism, the only real difference being the fewer possible number of capillary patterns in the brain stem (emotional) as compared with those of the cortex (intellectual). Mental states are best visualized by reference to commonplace expressions such as "remembering," "change or frame of mind," "conversion," "discipline," "bias," "opinion," and "temporarily insane." States alternating between normality and senility are illustrated by aged acquaintances, in whom when undisturbed there is lack of expression, with lustreless eyes and slow movements; but on mention of a favourite topic the eyes sparkle, the features show emotion, the facial furrows disappear, and an associated mental acuity develops which reverts to the original state on changing to another topic of little interest.

Conduct in relation to specific stimuli is therefore not due, as often supposed, to a more or less permanent integrated nervous path through the central nervous system, nor is it even due to a large mass-inhibition of unwanted motor responses; it is due rather to a capricious control of *all* the related delicately balanced synaptic paths by a mediator, known clinically as m.e.s., which enables each and every muscle of the body to take its share in the general attainment of some effect—as seen in cinematograph pictures and photographs of professional athletes and sportsmen. Fig. A shows diagrammatically how this happens when the mediator inhibits or facilitates synapses collected in groups.

Integrity of the Central Nervous System in Mental Disorder

In psychiatry none of the present theories of disordered mental states attempts to account satisfactorily for the clinical remissions and resuscitations which are universally recognized. A patient on admission to a mental hospital may temporarily so improve that certification is very hard during the first two or three days. Dr. D. McRae has remarked that mental hospitals would be extremely difficult to manage were it not for the fact that the majority of the patients are comparatively lucid for most of the day. Temporary mental improvement follows any new treatment, a fact which has given bias not only to individualistic conceptions of aetiology but also to the patient and his relatives in the use of patent medicines and palliative home treatments that are quite devoid of real therapeutic value. Dr. A. M. McCutcheon has told me that a patient in his care maintained a mute vegetative existence for sixteen years, during which he "couldn't have been more like a cabbage"; he then had a fatal attack of pneumonia, coincident with which his mental clarity returned and he asked for his friends, with whom he conversed in a perfectly rational and lucid manner. In 1929 Loevenhart discovered that by asphyxiating mute and apathetic cases of mental disorder almost to the point of death there followed a period during recovery when they became perfectly rational and apparently mentally normal; unfortunately, as the state of cerebral stimulation passed off the identical mute apathetic state always recurred. Other methods of cerebral stimulation are known, such as heavy poisoning with sodium amytal, and recently Hallay invented a method of so-called brain massage by which restoration of sanity in a mentally disordered case was possible by alternate rhythmical compression of the jugular veins. Even certain states formerly considered neurological (torticollis and Parkinsonism) are similarly temporarily relieved by such methods of cerebral stimulation, but they always recur to the identical original condition as the stimulation ceases.

The lucidity, which occurs naturally, or after shock treatments (primitive, surgical, protein, insulin, and others), after prolonged narcosis, and during infections or artificial cerebral stimulation, establishes the significant fact that the synaptic connexions of the central nervous system in the mentally disordered states may, in contrast to the permanent dementia that is due to destructive lesions of nerve parenchyma, remain for many years inert but intact and capable of functioning on the normal personality pattern. This anatomical integrity of the central nervous system is illustrated in its simplest form in stammering—where the nerve reflex pattern of speech is obviously intact, but where direct function is in some way inhibited, as by spasm and ischaemia of the cortex; and in the restoration of lost function seen with excitement in cases following epidemic encephalitis. A story relates how an ancient relative rushed into the road and saved a child from a runaway horse-and-cart; for years before and for ever afterwards he was quite unable to walk!

Neurological conditions are occasionally seen in mental hospital cases, but not to the extent generally supposed, and it is believed that application of the differential diagnostic test of cerebral stimulation would show that some of these conditions are not really neurological, in the sense of nerve pathology, but psychiatric (meaning a disorder of the mediator of alternate synaptic functions

—that is, the m.e.s.). When loss of nerve elements occurs the reflexes dependent upon such elements are lost for ever—and gross atrophy of the cortex has long been associated (quantitatively, according to Lashley) with dementia; nevertheless the occurrence of lucidity from natural or artificial means, even if only temporary, firmly establishes the integrity of that part of the central nervous system subserving the recoverable function in mentally disordered and neurological cases, including clinical dementia without gross brain atrophy.

Synaptic Patterns and their Control

Many speculations have in the past been advanced of the identity of m.e.s. with synaptic function. McDougall (1901) says the physical basis of memory is of the nature of a dielectric stimulation at the synapses; in other publications he introduces speculations of synapses as the seat of psychological processes, consciousness being a fusion of many such activities. Pavlov considered the mind as a mosaic of inhibitions and facilitations of synapses, but emphasized its dynamic character. Others have attempted to correlate mental disorder with the pathology of the cerebral vascular system: among these the work of Spielmeyer will always be remembered, even although his later opinion was that the areas of functional ischaemia and necrosis described by him could not usefully be correlated with a fundamental relation to mental disorder. To these workers the extreme vulnerability of the ganglion cells to oxygen lack has been a stumbling-block causing them to abandon some useful preliminary work. For example, a significant experiment was published by my predecessor, the late Sir Frederick W. Mott (1907), who applied a stimulus to the leg cortical area of the brain, at the same time firmly pressing upon the upper cord sufficiently to indent it, and noting that motor impulses were not affected by such pressure; he then applied light pressure upon the lumbar cord, just enough to cause ischaemia of the cellular (actually of the synaptic) area, upon which impulses promptly ceased, even considerable increase of the strength of the stimulus failing to effect any response of the leg muscles.

The transmission of impulse within a neurone follows an "all or none" law; its physical character admits no modification, and it does not suffer decrement, as was formerly supposed, when a portion of nerve fibre is narcotized. Decrement occurs at, and only at, the synapse where the original nerve impulse ceases and chemical transmission takes its place. The dendrites of a neurone have many synaptic connexions, and are influenced by numerous inhibitory states and excitatory stimuli, which, if in an exact time-identical phase, would leave an effective or insufficient physio-chemical resultant. Infinitesimal time differences in the reception of such stimuli, however, are important, since at any instant the resultant may excite the neurone, then briefly but quite refractory to other stimuli, which are then lost. Sherrington (1933) says that "if nerve activity has relation to mind one can hardly escape the inference that nerve inhibition must be a large factor in the working of the mind." Synaptic function can be inhibited by reduction of its blood supply, any such inhibitory delay preventing premature discharge of the neurone and allowing summation of more stimuli, with greatly enhanced value of the motor response. Reflexes which previous experience has shown to be advantageous can be facilitated by increased blood supply to the synapses, and disadvantageous responses inhibited by relative ischaemia of the respective synapses, this control being part of the capillary mosaic and therefore part of the m.e.s. existing at the time.

A slight ischaemia is known to increase decrement to extinction of impulse; emptying the retinal arteries by simple pressure on the eyeball causes total temporary blindness (Barnert); even electrical records of brain activity show the dependence of brain function upon an adequate capillary blood supply (Adrian, communicated privately). Penfield showed that conduction through a synapse is readily abolished by CO_2 .

In the skin and viscera, where the function of small areas is similar, a local rhythmical variation in capillarity normally occurs, controlled chiefly by metabolites. In the central nervous system, where the function of small adjacent areas is widely different, such rhythmical changes would result in confusion of conduct; and therefore this rhythmic characteristic has probably undergone in the brain certain necessary adaptations to the physiological requirements, by selective local control of the smaller vessels, not only by hormones but also by collateral impulses from higher reflexes of the central nervous system and by sympathetic stimuli; the metabolites and hormones sustaining the variations in the mosaic of capillary pattern induced by the more rapidly acting central nervous system (somewhat analogous to Creed's red tonic muscle supporting the rapidly acting pale muscle). Fig. A shows a theoretical diagram of how a mosaic of vascularized areas can determine the facilitation or inhibition of impulses from the various sensory stimuli of light, sound, etc., so that the type of motor response is conditioned by the mental or emotional state of the individual and not by the stimulus. Sherrington says that "a drug may in a second wholly reverse a reflex by tilting the inhibition-excitation balance," this phenomenon being presumably dependent upon the drug acting on the vascular supply of the synapses.

Physiological problems having an important bearing upon the mind are suggested by the anatomical distribution of fibres from a sensory organ to widely different regions of the brain. Fig. B shows the brain of a cyclostome (le Gros Clark, 1932); olfactory fibres pass from

the olfactory region both to the pineal-habenula and to the pituitary-hypothalamic regions, where function is as widely different as can be postulated. Hunger or disgust may represent an alternative choice of use of such possible reflex paths (primitive m.e.s.), and how far this choice is dependent upon the relative capillary blood supply to the respective alternate regions can be proved by direct observation, or by application of my capillary stain, in

crucial test experiments (in states of full and empty stomach, etc.). Potential m.e.s. exist without any concomitant action of the central nervous system—that is, motor behaviour—so long as no stimuli reach the controlled areas. The static quality of m.e.s. and their potential independence of the central nervous system constitute the new outlook, and are of primary importance in the correlation of the mind and its disorders with the medical sciences.

The mental and emotional states can be associated, and in my opinion identified, with the cortical (not only pia mater) capillary mosaic pattern, which provides an efficient mechanism for the actual control of the patterns of synaptic junctions of the 12,000 millions of neurones of the central nervous system. This materially simplifies the bewildering numerical possibilities of interneuronal connexions, which we are told far exceed seconds in geological time or atoms in the universe, and reduces the number to that which experience leads us to expect by variation of sections of the cerebral capillary mosaic.

Physiology and Biochemistry of Synapses and Cerebral Vessels

Woollard has shown us that systemic vasoconstrictor nerves have two origins: (1) proximal from the sympathetic ganglia, and (2) distal by way of the somatic nerve trunks. Villaret, Cachera, and Fauvert (1937) have recorded photographically actual spasms of pial vessels. Stimulation of the sympathetic groups of fibres on the large vessels of the brain has a local or proximal effect upon arteries rather than a general distal effect on the ultimate distribution of the arterioles, and it is possible that the central nervous system contributes locally to the

FIG. A.—1 to 9 are neurones in sensory path and a, b, and c motor neurones. The synapses are collected in areas A to E. Area C transmits (dotted lines). If area B instead of C transmitted, then the same impulses would either be lost or would excite a different motor cell; other impulses—1, 2, and 5—would also excite b. Sensory impulses are related to conduct through mental and emotional states, here shown as a vascular control of synapses in areas A to E.

FIG. B.—Brain of cyclostome. Olfactory impulses reach two brain areas of widely different function.

control of the arterioles as Woollard has shown for the somatic capillaries. The carotid sinus merely determines the pressure distribution between the head and the rest of the body, electrical stimulation dilating the cerebral vessels: the importance of gross interference of function from contiguous sepsis in relation to disturbed mental states should not be minimized until first subjected to histological proofs. Section of the cervical sympathetic increases the number of patent brain capillaries, and mental improvement has followed some of these operations in selected cases (Royle, 1932).

Danders (quoted by Forbes, 1928) in 1850 obstructed the nose and mouth of animals for ten seconds and observed a dilatation of cerebral vessels through an airtight window in the skull, using a magnification of $\times 45$. Constriction* of cerebral vessels occurs when the carbon dioxide is low, when the oxygen is high, when the blood becomes hypertonic, when the cervical sympathetic is stimulated, when the fear area in the hypothalamus is stimulated (Stavraky, 1936), and with adrenaline after sympathectomy or ergotamine. Dilatation occurs with increased carbon dioxide, trauma, acidosis, stimulation of the seventh nerve, fall in blood pressure, gaseous embolism, acetylcholine, histamine, adenylic acid, nitrites, and a number of other local elective substances, including, for example, that of pituitary secretion on the parietal region. Stimulation of the tuber or pressure with a small sponge, or stimulation of the ventral and medial parts of the thalamus, also dilates pial vessels. Himwich (1937) finds that, in contrast to other viscera, the arterial quality of the venous return from the brain in dogs increases parallel with hypoglycaemia, giving a biochemical explanation; another explanation is also possible, since this phenomenon under other conditions is accepted as proof of cerebral capillary dilatation. Experimental pharmacology shows the selectivity of capillary reaction to drugs. Both histamine and CO_2 contract the capillaries of the lungs but dilate those of the brain; urethane dilates capillaries but not arterioles. Strychnine has formerly been supposed to act directly upon the synapses, but Olkon (1930) observed by direct microscopical examination the contortions, kinking, and spasms resulting in brain capillaries from injection of strychnine into animals, a finding which, taken in relation to clinical symptoms, makes a significant contribution to the new outlook I have put forward in this paper.

A fall or rise in blood pressure is accompanied by distinct modification of feeling and thinking (Gordon, 1930). Mental effort causes an increase in the oxygen and decrease in the carbon dioxide of the jugular blood; that is, a general dilatation of cerebral capillaries (Lennox, 1931). The rapidity with which a "change of mind" or emotion can follow sensory stimuli shows that impulses of the central nervous system are of primary importance in adjusting the mosaic of capillary pattern to altered circumstances and behaviour requirements. Once "set," a capillary pattern tends to persist and even to re-form after diversions or sleep.

The controlling influence of the mosaic pattern of capillary activity upon the pattern of facilitation or inhibition of groups of synapses receives support from recent work on the relation of acetylcholine to synaptic function. A nerve impulse releases potassium ions at the synapse, which in cholinergic fibres effects a synthesis of acetylcholine and excites the second neurone. When

an excitor effect is thus transmitted through a synapse by acetylcholine the latter leaks out around the muscle or nerve; potassium ions similarly leak away during passage of a nerve impulse, and both these substances cause severe depression of further responses to subsequent nerve stimuli. The capillary circulation immediately and completely removes any free acetylcholine that is not limited to the synaptic membrane, also restoring altered salt concentrations; such action may be also said to effect a control of synaptic metabolism and function. Repeated stimuli of the cervical sympathetic cause a continuous output of acetylcholine from the sympathetic ganglia, which, however, soon decreases in amount (recognizable clinically by diminution of motor effects and chemically by the lesser amount of acetylcholine in the perfusate), but suddenly increases, as shown both by motor response and by its quantitative increase in amount in the perfusate, when a small quantity of blood plasma or serum is allowed to reach the synapse again. The vascular supply is therefore normally of primary importance in maintaining the local synthesis of transmitter substance (acetylcholine) and in removing such acetylcholine as has leaked away from the synapses into the surrounding tissue, where its effects are distinctly undesirable. The relatively enormous amounts of oxygen consumed at the synapses (amounting to one-tenth of the total body consumption of oxygen) also indicates the dependence of synaptic function upon the blood supply (for further correlations see Pickworth, 1937).

Neurones and the Action of Toxins

The inhibition of function which often characterizes cases of mental disorder, together with the well-known fact that brain tissue absorbs with avidity many kinds of toxins mixed with it *in vitro*, has directed many, including myself, to the attractive theory of direct action of toxins upon the ganglion cells of the brain; and some regions of the brain have been held to be specially vulnerable to the action of toxins (Vogt's pathocllisis).

Intestinal toxæmia has for a long time been associated with mental disorder, and especially with the katonian states: my work on dysenteric infection prior to admission to mental hospitals and institutions for defectives has shown the importance of such infections as aetiological factors in both clinical conditions (Pickworth, 1927). It is known that bacteria can decarboxylate proteins, giving rise to most powerful pharmacological substances, whereas if previously deamidized by the liver the products are harmless. The action of such poisons has been studied by Ferraro and Kilman (1933) and the brain changes described. Usually toxic action upon nerve cells is histologically demonstrated by cloudy swelling, bulbous processes, alteration of staining reaction, shrinking, vacuolization, pyknosis, displacement and extrusion of nucleus, cell disappearance, and rings of phagocytic cells; special cells from the glia appear to take up the fat and debris, and may remain as scar tissue. Spielmeyer showed that there may be a purely glial response to noxious agents in bacterial infections (glial foci also occur in trichinosis).

It will, however, be evident from the preceding pages that degenerative changes in the brain parenchyma, although frequently present and contributing much to the clinical features, especially in institutions for defectives, have only a secondary relation to the actual phenomena of mental disorder, the lesions produced by destruction of nerve tissue being permanent dementia or neurological rather than psychiatric. Even a partial or reversible toxic action upon nerve cells cannot be admitted,

* Observations limited to the straight portions of pial arteries need revision following the demonstration, by Villaret, Cachera, and Fauvert, that spasmodic constrictions are localized to just beyond arterial bifurcations.

because of the difficulty of explaining in such terms the lapse into the identical disordered mental state, which rapidly follows the lucid interval produced by artificial cerebral stimulation (or excitement in the case of alternating normality and senility quoted). Friedemann and Elkeles (1934) have shown that absorption of toxins by the brain from the blood only exceptionally occurs (with such powerful toxins as cobra venom and lamb dysentery toxin) under normal conditions owing to the perfection of the haemo-encephalic barrier; but the action of intestinal and other toxins upon the *vascular supply* of the brain is supported by many concordant observations. The above-mentioned toxic effects upon nerve cells are also seen in simple anoxia, and therefore should be considered secondary to an ischaemia induced by the action of toxins upon the smooth muscle of the capillaries.

The toxin responsible for brain changes in general paralysis is said by Neuberger, Metz, and Wilders to act on the cerebral vessels; and Merriitt, Putnam, and Campbell (1937) say that degenerative changes in general paralysis may be regarded as secondary to anoxaemia from endarteritis of the small vessels. Alcohol, well known in its effect upon the m.e.s., hitherto has been considered to act upon the ganglion cells, but Thomas has shown (1937) that it has a primary action upon the cerebral blood vessels. Orr and Sturrock (1922), by placing staphylococci in contact with the common carotid, found lesions in the distribution of the cerebral arteries *primarily vascular* in nature. Even the clinical features of toxic action, such as loss of strength, loss of weight, digestive disturbances, increased pulse rate, dry tongue, flushing, pallor, circulatory disturbances of the skin, and peristaltic unrest, are indicative of primary action upon the capillaries of the metabolic centres rather than upon nerve parenchyma. The immunity of the ganglion cells of the central nervous system from prolonged toxæmia is demonstrated by dementia praecox cases, where over many years' duration the presence of circulating toxins, resembling ergot or histamine poisoning (Bayard Holmes), is evident from a study of the vascular system; the brain, however, shows no distinctive gross lesion, and Freeman (1933) speaks of the dementia praecox brain as being "particularly normal." The toxin-inhibited neurone theory must therefore give place to the better-substantiated theory of primary toxic action upon cerebral capillaries. Meyer (1936) and others support this opinion in relation both to selective vulnerability and to many pathological findings in mental deficiency, Spielmeyer also having emphasized the importance of an effect via the vascular system.

Action of Endocrine Secretion

"All living cells give off substances into the blood stream which influence the others so that internal secretion is a fundamental vital phenomenon as old as the vascular system itself" (Cowdry, 1934). About two dozen hormones are known which have their action through the vascular system, but little study has yet been made of their selective action upon the capillaries of the reacting organs. Hypothyroidism is associated with fibrotic ischaemia of the thyroid gland, and hyperthyroidism with hyperaemia—and therefore hyperactivity—use being made of this in the local application of ice (generally limited to shortly before surgical operation). The specific hormones of the pituitary which influence growth and activity of the adrenals, the thyroid, and the mammary gland in all probability have a selective action upon the smooth muscle elements of

the capillaries of the respective glands (Jones, 1936, has shown that the capillaries consist of innervated smooth muscle). In practice hyperaemia of the mammary gland is induced by frequent bathing with hot water, with satisfactory results. The recent finding of many closely related adrenaline-like substances and pituitary hormones contributes to the specificity of local capillary reaction in both systemic and cerebral circulations. Schmidt (1935-6) observes a differential response of the cerebral capillaries to the action of pituitary hormones.

The relation of endocrine secretion to the m.e.s. is only vaguely understood, but the new outlook I have put forward has materially simplified the problem. The normal changes of capillary pattern corresponding to the m.e.s. are to some extent dependent upon the selective reaction to the presence of endocrine secretions which Schmidt has shown. Clinically, fear is associated with mobilization of adrenaline; the injection of sex hormone into animals deprived of gonads and genitalia induces sexual behaviour; a moral degradation accompanies some cases of dyspituitarism, precocity occurs with pineal tumours, sluggishness in myxoedema or adrenal insufficiency, and anxiety at the menopause. Advanced endocrine disturbances are only occasionally found in mental hospitals, but minor endocrine disturbances are universally present—limited only by the clinical acumen and enthusiasm of the observer. Fluctuations in the size of the thyroid (girth of neck) are observable in the cyclic states, and the pituitary gland is sometimes involved in septic extensions from chronic sphenoidal affections (Pickworth, 1935).

Harmonic action upon cerebral capillaries, being thus of primary physiological importance in normal changes of the local cerebral capillarity corresponding to the m.e.s., may later be shown to cause at least some of those pathological disruptions of the cerebral capillary mosaic associated with mental disorder. At present, however, we can only assume that some other pathological causes are primary, and that mental symptoms are then intensified by abnormal endocrine activity (such as mania in Graves's disease, and resembling the unmasking of latent character traits by the influence upon the cerebral capillaries of over-indulgence in alcohol).

Pathology of the Cerebral Capillary Pattern

Subdural haemorrhage illustrates simply the inhibitions related to certain motor cortical areas, and subcortical tumours—those symptoms of psychiatric nature, both the results of pressure ischaemia; such symptoms of incipient insanity can, and have been, cured by simple removal of the tumour, and cortical ischaemia symptoms relieved by evacuation of the clot.

Pathological disruption of the normal capillary patterns results from abnormal accumulations of metabolic products when stimuli are continued in spite of poor local blood supply (worry); from chronic pain stimuli (toothache, sinusitis); from bacteraemia of saprophytic organisms which lodge in cerebral capillaries (focal and intestinal sepsis—Pickworth, 1935); from haemorrhages, near-by necrotic foci, and tumours; and from head trauma (commotio cerebri). Pathological ischaemia occurs by reason of spasm, oedema, diapedesis, capillary haemorrhages, emboli, or thromboses—commonly found in brains from mental hospital cases. A limitation of blood flow to large areas is imposed by atherosclerotic lesions, aseptic meningitis, tumours, chronic subdural haemorrhages, and cardiac decompensation; while hyaline degeneration in the vessels, perivascular cuffing, and intimal thickenings reduce local respiratory exchange.

The posterior cerebral artery supplies the walls of the third ventricle, a large part of the thalamus, and the choroid plexus, as well as the visual cortex; in conditions of atheromatous restriction of the vertebral or basilar lumen an activity of those brain areas supplied by the posterior cerebral artery necessarily depletes the blood supply of the medulla, according to Ricker's peristasis theory with Hiller's corollary (Pickworth, 1937). This might result in an ischaemia of the vital centres which must at all costs be avoided, and so activity of the posterior cerebral artery becomes physiologically inhibited. As the control is not (as one would suppose from its morphology) from the vertebral plexus, but from the carotid plexus via the small communicating arteries (Williams, 1936), such vital implications may very well keep the unfortunate sufferer fully occupied with his internal complications—social activities and even feeding instincts becoming unimportant by comparison. A simpler case of spasm of vessels to vital centres probably occurs in reflex pain of toothache, and might be correlated with the associated mental condition of irritability and incapacity.

Ischaemia of peristatic or pathological origin results in confused behaviour and permits working sections of the cerebral capillary mosaic to be wrongly associated with normal or unrelated sections. During such pathological disturbances an untimely activity of, say, the gonads or pituitary secretions upon local sections of the cerebral capillary pattern can reasonably be supposed to be the cause of obscene language not infrequent in mental disorder cases—that is, however inappropriate with regard to external circumstances, the conduct is nevertheless appropriate to the internal but untimely demands of the individual (*Hamlet*, IV, v, 8). Conversely, it is known that frequent changes of m.e.s., as by multiple interruptions of conditioned reflexes in dogs, cause neurasthenia; and examples are only too numerous where a continued repetition of changes of mental content (such as occurs at puberty and the menopause, and in alcoholic indulgence, remorse for crime, or enforced study), when reinforced by bad training, digestive derangements, or a bacteraemia from local septic conditions, has resulted in a derangement of the cerebral capillary pattern and thus a pre-determined behaviour characteristic of mental disorder.

Mental disorder can therefore be identified with a mixing up of normal and abnormal capillary mosaic patterns. Fragments of some pattern may be assumed to persist coincidentally with fragments of other capillary patterns, in which case a stimulus reaching the brain results in a behaviour corresponding with the predominant type of pattern (that is, the m.e.s.), coloured by other fragmentary patterns also existing at the same time.

Military discipline builds up an m.e.s. which enables a soldier in war-time to obey orders an untrained civilian could not, and typifies the automatic robot-like response to command which I have tried to show is determined by the capillary mosaic regulating synapses and therefore conduct. Persistent m.e.s. result not only from training but from pathological changes. It is obvious that when one alternative of two synaptic areas is facilitated by hyperaemia the other is relatively inhibited. In the excitement of sport an injury may be temporarily unnoticed. Excitement, shock, and fear inhibit pain. A mental patient with pathological fixed inhibitive states can actually evulse an eye or testis with little if any shock or pain; and the usual temperature response to lobar pneumonia or pyrexia-producing drugs is sometimes temporarily absent in the active phases of mental disorder.

At post-mortem examinations of mental patients yellowish areas can be found contrasting with the normal reddish capillarity in the cortex and basal ganglia. These yellowish areas are macroscopic confirmations of ischaemia which is revealed by my capillary stain. This stain discloses not only such gross irregularities of blood supply but also indicates slight differences in the vascularity of local areas, or cortical layers, which I have endeavoured to show have some physiological significance. (Injection methods cannot be used for this purpose, as they are unreliable with respect to incomplete filling in some cases and over-distension in others.) Gross local variations of the blood supply and the pathology of the vessels themselves have been described in my previous publications. The sections (Special Plate) from recognizable brain regions are given to show relative differences in vascularity of the same section, the thickness of the selected areas being in each case controlled by stereoscopic comparison: it is generally possible to use parts of the same brain for normal control. Fig. 1 (Special Plate) shows three selected areas from a section of the frontal cortex; it demonstrates hyperaemia (A), normal (N), and ischaemia (B) in a case of epileptic insanity aged 15; ganglion cells are also revealed. Fig. 2 shows a vascular area (A) and an ischaemic area (B) from a section of the motor cortex of a case of delusional insanity aged 68. (Compare also the size of the giant Betz cells seen in the lower part of both photographs with the relative capillarity.) Fig. 3 shows the occipital cortex of a case of schizophrenia: note the relative vascularity of the two areas A and B. The section also shows cells and demonstrates the band of Gennari. Fig. 4 illustrates the cortex of two contiguous lobules of the cerebellum, and shows an obvious difference in their vascularity: I have noted a rarity of gross lesions of the cerebellum—in contrast to the cerebrum—in mental hospital patients, but my technique reveals a pathology long expected but not previously demonstrated. The clinical significance of regional vascular irregularities, however, needs many more years of further patient study.

The study of mental disorder therefore becomes somewhat changed by the new outlook I have put forward. Histological lesions of the central nervous system are to be regarded as of only secondary importance to changes in the mediator of alternate higher reflex paths which I have correlated with the cerebral capillary blood supply to the synapses. Similarly more hopeful lines of treatment can be adopted: (a) preventive, by avoidance of, or by skilled nursing during and after, known causes of capillary pathology (head trauma, acute and chronic infections, dietary deficiencies and irregularities, digestive upsets, food poisons, undue excitement, etc.), and not excluding antenatal care; and (b) in established cases by attention first to the probable cause (for example, chronic sepsis—Graves, 1932; Watson-Williams, and others) and then by a more scientific study and application of drugs and treatments known to affect the capillarity of local brain areas.

Examples of the latter are seen in Poole and Nason's (1935) work with ergotamine causing contraction of dural vessels (its action on pial vessels is irregular), which has been used with success by M. O'Sullivan (1936) for the cure of migraine; Royle (1932) cured incipient insanity by cerebral sympathectomy in suitable cases; Graves's case (personal communication) of ligation of one jugular vein for mastoid complications showed immediate mental improvement, which has been maintained; C. Adler (1936) has used barbitol with caffeine successfully for epilepsy; W. F. Duggan (1937) treated tobacco amblyopia with repeated injections of nitrites and acetylcholine; Barber and Tietz

(1937) gave daily doses of ergotamine tartrate, which they found diminished suicidal, homicidal, and destructive activity (Linderman observed the converse with adrenaline injections—namely, that patients became more subjective and introspective). Such treatments offer great individual and economic hopefulness, provided sufficient further scientific study of their relation to cerebral capillary function is made to render them scientific instead of empirical: in this direction the work of the Harvard Medical School, Boston, is to be highly commended.

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It is announced that one of the main subjects for discussion at the International Congress on Rheumatism now being organized to take place in Oxford in March is juvenile rheumatism. The views of experts from other lands on this serious malady will be of great interest, and meanwhile there is available Professor H. B. Cushing's recent Blackader Lecture (*Canad. med. Ass. J.*, 1937, **37**, 311) on this disease as it occurs among Canadian children. He places acute rheumatism and cardiac disease in childhood as taking "first place as a threatened danger to normal childhood and adolescence in this country," basing this upon figures which indicate that about 25,000 school children in Canada are afflicted with rheumatic cardiac disease. Professor Cushing reviews the possible means of attack upon this malady and describes the interesting results obtained at the Children's Memorial Hospital, Montreal, where for the past three years children with rheumatic cardiac disease have been treated in a special pavilion very much on the same lines as patients with tuberculosis are treated. It is too soon in the experiment for any definite conclusions to be drawn, but the entire staff of the hospital is convinced that the results obtained are measurably an improvement on those seen before this step was taken. Professor Cushing pleads for organized co-operative effort to secure recognition, supervision, and after-care of all cases of rheumatic fever. He sees the need for the improvement of social conditions, particularly as regards general hygiene and housing conditions. Thirdly, he makes the point that since relapses of rheumatic fever follow regularly on infections of the respiratory tract and of the throat efforts should be made to lessen such infections and improve the hygiene of the mouth and the throat of the community.

THE HEALING OF EMPYEMA CAVITIES WITH SPECIAL REFERENCE TO ASPIRATION AND AIR REPLACEMENT AS AN AID TO OPERATION

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(WITH SPECIAL PLATE)

Since the healing of empyema cavities has been investigated by repeated radiographs with lipiodol injection, it has been apparent on many occasions that the original drainage opening, though adequate at first, has during the course of re-expansion of the lung become unsatisfactory. Healing might often have been accelerated by better planning of the drainage opening. It seems that the exact shape and position of the cavity, and the way in which the lung will expand—things upon which the position of the opening must depend—are more difficult to assess than has been supposed. Ideally the drainage tube should pass perpendicularly through the chest into the empyema at a point in the wall which would normally be the last to heal. Although the attainment of this end—a matter of the greatest importance to successful treatment—might appear to be simple, it has in fact been found to present considerable difficulty. In order to place a drainage opening accurately it is necessary to understand the way in which the obliteration of a cavity normally takes place, the factors which govern this, and how they apply to the particular case under consideration.

Factors governing Healing

Healing of an empyema cavity must be distinguished from mere diminution in capacity. When pus is first removed there is in the acute case an immediate and notable diminution in the capacity of the empyema due to the return of the displaced mediastinum, re-expansion of the compressed lung, and elevation of the depressed diaphragm; but true healing is a comparatively slow

FIG. A.—Diagram showing mediastinal displacement, compression of left lung, and depression of diaphragm by a large empyema.

FIG. B.—The results of simple aspiration.

process, which depends upon the gradual and steady adhesion of the visceral and parietal walls of the empyema. The latter results from granulation-tissue formation and fibrosis all along the line of approximation of the two walls. If the pus removed from an empyema at operation is measured and the cavity immediately refilled with an antiseptic solution it is found that the amount of fluid required to fill the cavity is usually only a small fraction of the volume of pus originally present. It would be absurd, however, to suppose that to that extent healing had taken place. Figs. A and B

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FIG. 1.—Frontal cortex. Three areas from same section, showing increased (A), normal (N), and deficient (B) blood supply. Ganglion cells are also shown. (Mag. $\times 32$; 50μ thick.)

FIG. 2.—Motor cortex (case of delusional insanity), showing relatively good blood supply (A), and deficient blood supply (B). Compare the size of the Betz cells (marked by arrows) of both parts with the relative capillarity. (Mag. $\times 32$; 50μ thick.)

FIG. 3.—Occipital cortex (case of schizophrenia). Note normal vascularity (A), and relative anaemia (B). Cells are quantitatively normal. The white band of Gennari is marked by an arrow. (Mag. $\times 32$; 50μ thick.)

FIG. 4.—Cerebellum. Cortex of two contiguous lobules showing difference in vascularity. (Mag. $\times 60$; 250μ thick.)

All the above are untouched photographic reproductions; each figure shows selected areas from the same section, the thickness being stereoscopically controlled. Author's stain technique.