Remarks

ON

THE PRESENT POSITION OF THE PROBLEM OF PSYCHIATRIC PATHOLOGY.*

BY

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THE mental case is too often an unwelcome addition to the anxieties of the busy practitioner. Apart from nursing difficulties the whole process of ingravescant mental disorder seems to him so ill-defined, even mysterious, that he scarcely knows where to begin. He finds it far from easy to persuade the relatives that early removal to a special hospital is desirable, although he assures them that thus only can the patient receive proper treatment. This is a most generous attitude on his part, for he knows that, except for moral control and outdoor exercise, the case will receive much the same symptomatic treatment as he himself is well able to supply—chiefly laxatives and sedatives. But it is undesirable that any case of illness should present itself to a medical man as a nuisance, and for this those who practise and teach psychiatry are largely to blame. The limited time available in a crowded curriculum precludes the teacher from directing the attention of the senior student to the physiological and neurological aspects of mind, so that, coming fresh from more exact histological and biochemical laboratory methods, he is given “nothing to get hold of.” We may as well admit our ignorance—we cannot teach what we do not know; for, let there be no doubt about it, theories of the causation of mental illness are highly problematical. But the best way to tackle a problem is to set up a theory and then proceed to demolish it, until from the ruins a sounder edifice can be erected. There are no mental diseases properly so called, there is only disordered action of the brain cortex; there is no essential difference between the neuroses, the psychoneuroses, and the psychoses; the diseased processes which result in mental illness are just those which we are accustomed to recognize in physical disorders, and that the clinical presentations are so different is more a social than a medical problem. Therefore I believe that the general practitioner could help the psychiatrist beyond measure if he had time to make a note on his clinical cases of all the slight mental changes which occur from day to day—the attitude, facial expression, mental outlook expressed in conversation, memory, attention, interests, dreams, reaction to pain, and so on, carefully correlated to the somatic signs present. This address is frank propaganda; its object is to seek the help of our medical colleagues in furthering the great cause of mental welfare, one important aspect of which is the pathology of mental disorder. It may enlist their interest if I mention a few of the almost innumerable problems upon which we should like light to be thrown. These are not selected quite at random, but because over forty years of clinical experience suggest to me that some of them may ultimately yield useful results in furthering the cause we have at heart.

The efforts of Pinel, Tuke, Conolly, and others at the beginning of last century and earlier were devoted to the social amelioration of the insane rather than to the scientific side, so that France and England lagged behind Germany; nor had the United States, where of late years more work has been done than anywhere else, yet entered the lists. But for nearly a century a long roll of distinguished workers in the Wakefield Asylum laboratory has kept alive the spirit of research—Sir William Ellis, Sir David Ferrier, Dr. Henry Maudsley, Sir James Crichton-Browne, Dr. Herbert Major, Professor Bevan Lewis, and the present president of the Royal Medico-Psychological Association, Professor J. Shaw Bolton. Nowadays, of course, nearly every mental hospital and psychiatric clinic has its laboratory, and, especially since 1918, an enormous stream of literature has poured forth, applying to mental cases nearly every clinical or laboratory test which has

been suggested for use in general medicine. And withal I think we must confess that no special light has been thrown upon the genesis of mental disorder. Not that all these efforts have been wasted; on the contrary, a negative deduction is of value in eliminating one more source of error.

Within the last two years the Royal Medico-Psychological Association, recognizing that one great reason for failure has been diffusion of effort, and that more and more in the future team work will be necessary, has, mainly through the enthusiastic drive of one of our recent presidents, Colonel J. R. Lord of Epsom Mental Hospital, appointed a comprehensive committee to co-ordinate investigation. We do not expect miracles, we realize that none of those at present alive are likely to see a solution of our difficulties, but we do at least hope to make a beginning, to build up effort gradually, until in the end some such body as the Medical Research Council, or even the League of Nations, takes up the work. But right at the beginning it seems to me that it would be a mistake to start with such abstruse problems as schizophrenic conditions; we are more likely to advance by means of the simpler emotional and toxic psychoses. It is true that the lamented death of Sir Frederick Mott left incomplete his work on dementia praecox and the endocrine glands, but I think he wanted really to establish a standard, for he often expressed to me the hope that biochemical work on the action of the vegetative nervous system in connexion with the emotions would follow upon his anatomical findings. And so I confine myself here to the manic-depressive or toxic psychoses, and suggest a pathology which will serve as well as any other as a cock-shy; for what excites opposition may also, in some corner or other, stimulate investigation.

The mention of the word toxæmia is apt to raise a smile, yet I doubt if anyone questions its importance in disease. Many, perhaps most, families of micro-organisms, aerobic and anaerobic, produce by their life-processes hæmolytic or neurolytic non-specific poisons, chiefly in the intestine, but also in mouth, fauces, accessory sinuses, or genito-urinary tract, less often in joints, lungs, or skin. These toxins are normally dealt with by the portal system, principally the liver, but if this barrier fails they may reach any part of the body in the blood stream. Before they can affect the neurones of the central nervous system they must reach the cerebro-spinal fluid through the reticulo-endothelial system of the choroid plexuses, and only then can a psychosis be produced. The actual method of production, as suggested by the work of Marinesco, Mott, and others, seems to be a toxic anoxæmia by inhibition of the neuronal oxidases, so that the state of synaptic resistance is altered and the cortical pathways disorganized, for synaptic resistance is the anatomical basis of all regulated nerve action. But, further, the pathways in the basal ganglia, hypothalamus, and mid-brain are liable to become confused, with disastrous consequences to the vegetative and extrapyramidal reflex systems. And so it may come about that the basic emotional feeling-tone which determines the character of the psychosis may be due, not to any difference in the nature of the original toxæmia, nor to any primary variation in the quality of the endocrine secretions, but only to the manner in which these are influenced by the sympathetic system, and so ultimately to the directional manner in which the built-up emotion is presented to the cortical analysers. Therefore I suggest that five essential fields for research are: (1) the bacteriology of the intestine and accessory sinuses; (2) the proteolytic functions of the liver; (3) the histology of the basal ganglia, mid-brain, and hypothalamus; (4) the influence of toxic agents on the cortex; and (5) the permeability of the choroid plexuses.

BACTERIOLOGICAL PROBLEMS.

Clinically we have a good deal of negative knowledge of toxæmia in the psychoses. We meet sepsis in all its forms in mental hospitals; in fact, the helpless social habits of our patients constitute one of our worst surgical troubles; but we never find a septic infection arousing an acute mental exacerbation in a chronic case. I have never seen an acute puerperal psychosis arising primarily in a mental hospital confinement—that is, in a patient already

* Made at a meeting of the Staffordshire Branch of the British Medical Association, May 16th, 1929.

under treatment for some delusional or chronic mental illness. We all know that in a very small percentage of cases of almost any bodily disorder, exanthematous or otherwise, a psychosis may arise, and this quite independently of the degree of severity of the illness. On the other hand, many diseases have their specific mental side, such as thyroid imbalance or pellagra. That toxæmia has a very real connexion with the psychoses is indicated by the improvement when sources of sepsis are removed, especially by a course of autogenous vaccines. Some pathogenic organisms are highly virulent, and produce a toxin demonstrable by a specific reaction, but most intestinal groups are of low virulence, and produce mixtures of non-specific ptomaines whose influence on the host varies extraordinarily under different conditions of susceptibility, etc. This at once suggests some abnormal deviation in a group normally indigenous to the bowel.

At Cheddleton Major F. H. Stewart, working with aerobic methods, has studied the formation by coliforms of phenol and tyramine from tyrosine, and has established the following position.

1. Carriers of N.L.F. coliforms (*paracolon mutabile*) are four times more common among acute mental patients than among sane controls on the same diet.

2. Bacteria forming phenol from tyrosine in alkaline media are much more abundant in the faeces of acute psychotics than of sane controls; these were chiefly (a) the Morgan group (in 25 per cent. of mental cases and 9.5 per cent. of controls), (b) *B. phenologenes* of Berthelot—that is, a generic term for any phenol-forming coliform.

3. Fifty per cent. of acute psychotics yielded from faeces in tyrosine media over 0.015 per cent. of phenol; no sane controls reached this amount; many yielded none. Of course, no one supposes that phenol itself is the toxic agent, but it is a measurable indicator of some more complicated abnormal product.

4. Intravenous autogenous Morgan vaccination will remove this bacillus from the stools without immediate mental improvement, but bodily symptoms may be relieved—that is, headache, dyspepsia, anaemia, loss of weight.

5. In relapsing cases thus treated the place of Morgan in the intestine is taken over by one of the phenologenic group.

Those interested in the subject will find Stewart's work set forth in detail mostly in recent numbers of the *Journal of Mental Science*. What interests us here is not scientific labelling, but solely the question, Does this or that organism produce a toxin? If so, under what conditions, and what is its biochemistry?

Dr. Ford-Robertson at St. Andrew's Hospital, Northampton, has been working on the anaerobic groups, especially the diphtheroid-lepto-streptothrix types, and believes that subtoxic anaerobes play an important part in chronic focal infections, principally in the intestine, but also in teeth, tonsils, sinuses, and cerebro-spinal fluid. Special forms of anaerobes have been found in mental cases which are rare in sane controls, and it would appear that to some groups the central nervous system is especially susceptible.

The work of Dr. F. A. Pickworth, pathologist to the Birmingham Mental Hospitals, is well known from his publications on the bacteriology of the accessory sinuses. Some of his beautifully mounted specimens show bacteria from the sphenoidal sinus passing through the thin bony septum and invading the pituitary fossa and substance of that gland. Many of the patients treated at the Birmingham mental hospitals for sinusitis by Mr. W. S. Adams are stated to have lost their more urgent symptoms—headache, malaise, and depression—and to have been able to return home and resume work.

Finally, in connexion with bacteriological problems, many believe that the organisms actually at fault are filterable viruses, possibly commensal with some which can be readily recovered from the intestine and other body cavities.

Liver Efficiency.

It is not without significance that mental diseases have been associated with liver disturbances since the dawn of medicine; the word melancholia reminds us of the connexion. Clinically a large percentage of recent and acute psychotics show marked digestive upset, chiefly the manic-depressive types, the so-called "toxic" or "toxæmic"

class. It is the usual thing for chronic cases subject to periodical acute relapses to usher these in with a "bilious" attack. In recent melancholia we find anorexia, flatulence, gastric discomfort, constipation, often slight jaundice; in early mania, headache, furred tongue, foul breath, or vomiting; all these, of course, are traceable to disturbance of the involuntary nervous system. But there are so many other disorders apart from mental illness which exhibit similar troubles that we want all the information we can get about the emotional side of such functional upsets as seasickness, migraine, vertigo, tinnitus, nystagmus, headache, and the large class of neuroses dubbed "neurasthenia," as well as those included under such headings as "the chronic abdomen." No doubt the intact intestinal mucosa ought to prove an efficient barrier against the entrance of toxins into the portal circulation, but enteroptosis, liver cirrhosis, jaundice, appendicitis, cholecystitis, atheroma, and countless other disorders are evidence of the universality of toxæmia. The functions of the liver are so numerous and ill defined that it is difficult, even theoretically, to devise efficiency tests. The glycogenic function is about the only one which has been seriously attacked in connexion with mental states in this country. S. A. Mann at the Maudsley laboratory, and Drury and Farren Ridge at Stafford, have estimated the blood glucose in a series of cases, and the former in another series used the levulose reaction. Everyone admits that sugar storage is disordered in mental disorder, especially in melancholia, but Mann concludes that the pancreas rather than the liver is at fault. I hardly think his cases were very well selected; what is wanted is not a haphazard group of mental patients, but rather an intensive study of a few cases, correlating the results with the varying mental states. Isabella Robertson has dealt somewhat fully with the homoclastic crisis of Widal, and here again the results are indeterminate, although certainly a leucopenia is much commoner in psychotics than in normal controls. But the connexion of the haemoclastic crisis with liver functions is still undetermined. The various papers of the above workers may be found in the *Journal of Mental Science*, July, 1925. I cannot find any record of a systematic series of van den Bergh reactions in mental cases; it would be trying to the patients to bleed them sufficiently often, and this procedure alone would tend to vitiate results. In some cases at Cheddleton we have obtained encouraging results, but it has only been used where some suspicion of hepatic defect was otherwise excited. It would appear that the efficiency of the liver cells varies from hour to hour, and that the reserve of efficiency is very large. There are some diseases where degeneration of liver and central nervous system occurs simultaneously, such as in Wilson's disease. Also one occasionally, in mental hospitals, meets with cases of pernicious anaemia and subacute combined sclerosis which develop a psychosis, and this may be either excitement or depression.

Mid-brain and Hypothalamus.

Our knowledge of the mid-brain, hypothalamus, and tegmentum is still most imperfect. The parts are not easy of access in the experimental animal, small lesions are misleading and easily fatal, the paths are short and lend themselves badly to degenerations, and the systems are very complicated and not strongly marked. The main connexions of the red nucleus have been fairly well established; it can be studied phylogenetically, and its position as a great co-ordinating centre of extrapyramidal and cerebellar functions is clear. But other grey masses still elude us, and for further advance we must trust to careful records of clinical cases. In this way we are beginning to learn something of two great ganglia—the substantia nigra and the corpus Luysii. It would appear that the neurones of the former are greatly reduced in Parkinsonian degeneration, whatever other centres may be in addition, those of the latter in chronic chorea. Now these two degenerations are associated with somewhat specific mental states. In advanced Parkinsonism euphoria is the rule, although not always seen in early cases. This euphoria is real mental satisfaction and contentment in the patient, and is not merely loss of power over the facial muscles hiding the expression of a dysphoria; the patient enjoys life and entirely fails to realize the gravity of his condition, and a

similar feeling-tone is described in lenticular degenerations. In chorea another change is seen—gross instability of emotional tone. Dr. Pindon Martin¹ has found that nearly all recorded cases show such mental changes and that they are associated with degeneration of the corpus luteum. Just as in acute chorea the muscular movements are entirely purposeless and belong to a low physiological level, so in chronic chorea the patient is apt to be impulsive, irascible, and uncontrolled. This is well seen in Huntington's chorea, such families being notable for illegitimacy and drink.

The broad view to take of the mid-brain, hypothalamus, and bulb is to look upon the grey masses not so much as nuclei of origin of nerve impulses, but rather as great reflex relay stations between cortical and striothalamic functions; and if it can be shown that different focal lesions are accompanied by uniformly varying feeling-tones the possibility is opened up that emotional variations depend, not so much on the nature of endocrine, sympathetic, and other afferent elements, as on divergences of the paths of presentation to the thalamus, and ultimately to the cortex. The Lange-James theory of the emotions depends upon results produced through afferents from somatic muscle, but we now realize that this is only a small part of the picture, for plain muscle everywhere produces a like effect upon the elements of an emotion. Not seldom one comes across manic-depressive cases whose relapses are sometimes into excitement, sometimes into depression—this from similar sets of causes and without regular sequence. People gravely ill from, say, puerperal or other sepsis vary greatly; some are petulant and fearful, some unreasonably buoyant. And the same occurs in advanced phthisis. Until we know what happens to the sympathetic afferents after they enter the cord, and until we know whether the pain fibres in the posterior columns are unmyelinated or not, it would be premature to formulate definite theories; but if differences in synaptic resistance in the subthalamus and neighbouring parts can be produced by neurotoxins, then the whole mass of glandular, vascular, respiratory, and postural elements which go to build up the complete emotional picture may depend upon geography. Such a line of thought leads straight to Pavlov's theory of sleep; internal cortical inhibitions spreading to the great basal relay stations would remove at once the necessity for predicated a sleep centre in the hypothalamus; synaptic resistances would produce the same effect.

The Action of the Brain Cortex.

The two principal directions in which the human cortex transcends that of lower phylae are the more extensive association areas round each primary centre and the growth of the supragranular layers. Both these have really one objective—the multiplication of neural paths. Supragranular axons are associational only, within the cortex, and each individual path is quite short; infragranular axons form the corticofugal side of the two-way paths to lower nervous levels. The granular layers are, in some sense, reception centres, such as the visuosensory, so numerous as to form a duplicated line, and in final transmitting centres, such as the precentral, so few that the area has been called "agranular." Granule, or stellate, cells are, wherever they occur, the jack-plugs of the switchboard; their dendrites form synapses with the collaterals of distant neurones; their axons break up at once and form synapses with the dendrites of the next neurones in order. They are the actual anatomical means whereby multiplication of neural pathways can be utilized; they are essential elements in the structure of mind. It is sometimes not easy to realize that mind is merely an anatomical arrangement of intensely complicated cortical pathways, and that numerically the neurones can account for all the phenomena displayed. There are a good many platitudes which as neurologists we recognize but as psychiatrists we jib at. Yet there is only one kind of nerve action, whatever it is. A neurone can only discharge, on the "all or none" principle, go through a refractory interval, and slowly recover. There is not one kind of excitation stimulus and another kind of inhibition stimulus; it is all a question of paths. Many years ago Professor McDougall formulated

his "neurine" hypothesis, and it has never been improved upon, although possibly he laid too much stress on the passive aspect. Then there is the law of dynamic polarity: the synapses are one-way valves. How they act we know not, but probably it is a matter of slight variations in the hydrogen-ion concentration from moment to moment. Again, serial representation occurs everywhere, as has actually been demonstrated in the visual pathway. So mental images and ideas are slowly built up by repeated experience of different degrees of stimulus. Every concept involves the whole of the nervous system, if only by reference to unconscious memory habits; but not every stimulus causes every neurone to discharge, even in the epileptic fit, the nearest approach to a mass discharge which we know. The convulsion, however, is sufficiently near it to indicate the nature of coma, and, conversely, to suggest that consciousness is a state of receptivity of the cortex to incoming stimuli unimpeded by generalized inhibition, which latter is, as Pavlov points out, sleep. Attention is a directed concentration of neural paths, generally determined by the emotion of the moment. All life is one vast complication of conditioned reflexes at every physiological level, and the unconscious are to the conscious as a million to one. By the law of summation of stimuli repetition lowers the synaptic resistance of a given path, hence instinct, habit, custom. Some paths are biologically very old; thus, the vagus system has altered little since the time of Silurian invertebrates. Other paths are exceedingly evanescent, such as women's dress fashions. Free will is a figment of the imagination: every human action is guided by an almost endless chain of previous conditioned reflexes—biological, racial, hereditary, educational; and the only reason why an experience is never exactly repeated is that life is not long enough. We flatter ourselves that we are guided by reason, but the only difference in mentality between civilized man and savage is that the conditioned reflexes of the latter are on lower physiological levels; they are not grided by recent knowledge, and so we call them superstitions.

Neurotoxins and the Cerebro-spinal Fluid.

The central branches of the cerebral arteries supply the choroid plexuses, the cortical branches send tiny loops into the surface grey matter of the hemispheres. The cerebro-spinal fluid is secreted by the choroidal epithelium, and to a small extent also is a serous filtration into the perivascular lymphatic spaces of the brain. This latter is not a reversible action within physiological pressure limits. L. H. Weed in America has for many years investigated this matter, following the original work of Dixon and Halliburton; a summary of Weed's views is to be found in *Physiological Reviews*, 1922. Having escaped through the foramina in the roof of the fourth ventricle and reached the cisterna magna the fluid capillarizes up the arachnoid network, chiefly through the Sylvian fissure, over the hemispheres, tends to pool along the great longitudinal fissure, and gradually enters the superior longitudinal sinus, picking up in its course the products of neuronal disintegration. If it is very toxic it may produce death of many supragranular neurones, which is dementia. If the toxicity was prenatal the growing neurones are nipped in the bud, hence amentia. In any case the irritation of the fluid gradually, as age advances, excites the lymphatic hyperplasia which we call the Paccanion bodies. It may be asked why we do not in an acute psychosis necessarily get motor paralyses, blindness, anaesthesia, and other gross lesions. Such a question loses sight of the essential nature of cortical action. The cortex is, after all, only the highest level of the nervous system; its object is an exquisitely delicate selective release; it does not concern itself with the means by which a movement is performed so much as the reasons for that movement. Even if no movement results, the idea of movement, which older psychologists called ideation or conation, is still there. Besides, the toxic injury is only slight: if it were not so, we should get unconsciousness in some form—in other words, coma. We can no more have an active psychosis with a fully paralysed cortex than we can have athetosis with a wholly destroyed pyramidal tract. The lower mechanisms are older and

sturdier, and they are less directly exposed to the wash of a neuro-toxic cerebro-spinal fluid.

The nature of an insane idea may be illustrated by the sign of "past-pointing." Here a lower mechanism, whether cortical or subcortical, has by instinct and habit established a conditioned reflex of movement and posture which is presented to the cortical analysers as a composite picture or *schema*, as Head calls it, representing the attainment of a certain position in space arrived at in a certain definite manner. When the lower mechanisms are at fault a different picture is produced, which is again accepted by the cortical analysers at its face value, regardless of the fact that the real value has altered. In the insane idea the composite picture is much more complicated, more largely cortical, each component having its own innumerable subschemes derived from every lower physiological level. Thousands of experiences crowd in from every side of our personality—biological, genetic, instinctive, habitual, educative, social; orderly conduction along the millions of paths which constitute normal reason is disturbed by the toxæmia, and the result reacts upon conduct. The details of the process are infinitely complicated, but the mode of action is fairly understandable in the light of our present knowledge.

It is evident that in health the choroid plexuses form a barrier which prevents deleterious substances—for example, organic arsenical preparations—from entering the cerebro-spinal fluid, but I do not know that there is much experimental evidence concerning permeability to tissue poisons. Büchler² of Budapest dealt with the subject, and Walter³ of Rostock Gelsheim devised a bromide permeability test. Measured doses of sodium bromide are given for five days, and a ratio called the "permeability quotient" is set up between blood bromine and C.S.F. bromine. But probably the P.Q. varies from hour to hour according to blood pressure, serum protein content, buffering, and so on; further, permeability to a crystalloid is no index of the behaviour of the much larger colloid molecule. Nor can we separate out the effects of the accumulation of toxins which produce the acute hallucinations occurring in the endurance trials on American speed tracks after days of continuous driving with practically no sleep from those produced by low oxygen tension, and which result in the depression, confusion, and irritability seen in many from continuous high flying or mountain climbing. The cranium is for practical purposes a closed box wherein in health an equilibrium is maintained between the arterial, venous, and cerebro-spinal fluid pressure; the less of any one of these, the more of the others. When the total pressure exceeds physiological limits there comes a time when the amount of arterial blood is insufficient to supply oxygen to the neurones.

I have dealt with mental disease from the physiogenic side. Are there not, then, psychogenic causes as well? Certainly there are, and they often yield to psycho-therapeutic measures, which are, whatever form they take, a deliberate modification on the part of the physician of the patient's higher conditioned reflexes. But their effects are only indirect; the concentrated attention and emotional unrest called worry produce loss of sleep and appetite through endocrine and sympathetic upset, and toxæmia follows. From this stage onwards physiogenic and psychogenic causes march hand-in-hand. I realize that I have given no really practical explanation of mental pathology, but, to tell the truth, we cannot get much further without the intensive work of the biochemist, and the public do not often see the necessity for giving adequate remuneration to a scientific worker who cannot, at a moment's notice, produce rabbits from his hat. The psychiatrist is not wholly to blame for his own ignorance; old legal traditions are powerful, and the state of the law is a heavy drag on our efforts. Nor are our cases easy to manage; they are often restive and always unreliable; they resemble children in that the subjective side of diagnosis is more or less absent, and in many mental conditions even the material obtained for laboratory examination is merely misleading.

REFERENCES.

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HAEMOSTATIC THERAPY IN HAEMOPHILIA

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THE value of most haemostatic drugs can be demonstrated either *in vitro* or by means of an experimental animal. It does not follow, however, that similar good results will follow in the treatment of pathological states. The value of haemostatic drugs in these conditions rests largely on clinical reports based on impressions unsubstantiated by actual measurements. Furthermore, it is highly probable that a drug which might be completely efficacious in dealing with one form of haemorrhage might be quite useless in the case of another. Our conclusions are therefore strictly confined to haemophilia.

In each case the value of the therapeutic agent has been assessed by its effects on the coagulation time. This can be accurately estimated by the Dale-Laidlaw method. Using this method the average normal coagulation time is 1 minute 45 seconds. Values below 1 minute 35 seconds or above 2 minutes are considered to be abnormal. The bleeding time was also taken in each instance, but in haemophilia it is such a variable quantity that it is of little help in diagnosis and quite useless for assessing the value of treatment. It is quite common in haemophilia to find a normal bleeding time.

Inasmuch as the bleeding from a simple needle puncture in a normal subject often stops before clotting can have occurred it follows that other factors besides clot formation must be involved. Two possible mechanisms are: (1) contraction of the capillary walls, and (2) aggregation of platelets sealing the injured wall (Tidy¹). In haemophilia there is no known damage to the capillary walls and the platelet count is normal. It is not, therefore, surprising that the bleeding time is often normal. The prolonged bleeding times sometimes found are probably due to puncture of larger vessels, in which case the formation of a clot is necessary to supplement the action of the above two factors. The condition in thrombocytopenic purpura is in direct contrast to this. Here the capillaries are easily damaged and the platelet count is low, and so, despite an almost normal coagulation time, the bleeding time is markedly prolonged.

CASE REPORTS AND RESULTS.

Four cases of haemophilia were investigated.

CASE I.—Male, aged 6. No family history of "bleeders" was obtained. Of two brothers, one was normal and the other had a coagulation time of 2 minutes 18 seconds. The subject himself had frequent haematomas and haemorrhages into his joints. The blood platelet count was 243,000 per c.mm. The Wassermann reaction was negative.

CASE II.—Male, aged 2; an only child. There was no family history of bleeding. He has had several effusions, presumably haemorrhagic, into his joints. While in hospital he cut his tongue and bled for six days, losing much blood. The platelet count was 245,000 per c.mm.

CASE III.—Male, aged 9½. Family history of "bleeders" obtained. He had been in hospital twice before, once for a small wound, and once for teeth extraction.

CASE IV.—Male, aged 5. Family history of "bleeders." On two previous occasions he had been admitted for haemorrhages. Once transfusion was necessary before bleeding stopped, and once injection of his mother's serum controlled the haemorrhage (technical data not available). On the present occasion it was necessary to extract a tooth, and, despite all the usual local treatment, haemorrhage could not be controlled.

In all these cases the bleeding time showed marked variation without any relation to either the coagulation time or the therapeutic substance used. Most of the values obtained were normal. The following figures show the range of the bleeding time in each subject:

Case I	...	...	...	30 seconds to 12½ minutes.
Case II	...	...	...	1½ minutes to 4½ minutes.
Case III	...	...	...	15 seconds to 4½ minutes.
Case IV	...	...	...	45 seconds to 3½ minutes.