THE ENUMERATION OF THE BLOOD-PLATELETS IN MENTAL DISORDERS.*

By D. K. Bruce, M.B., Ch.B., D.P.M.
Storthes Hall Mental Hospital.

Introduction.

On looking through the literature relating to the blood-picture in various types of mental disorders, one finds that most workers have confined themselves to the red and white cells only. Relatively little attention has been given to the study of the third element of the blood, namely, the blood-platelet. It is now almost universally accepted that the blood-platelet is a constant element in normal blood, and it has been shown both clinically and experimentally that in health and in disease the platelets fluctuate independently of the red and white cells. In toxic conditions there is agreement that the platelets fall in the acute stages, and that during convalescence their numbers tend to increase, after which there is a gradual fall to the normal limits. This constant behaviour of the platelets has been observed in certain acute infectious diseases, in pneumonia and in typhoid fever. Certain writers think that the platelets have an important function in eliminating foreign bodies from the blood, or play some part in establishing a state of immunity to infection. This part played by the platelets in the sterility of the blood-stream suggests an explanation for the reduced numbers in acute infections. Diminution would be due to the using-up of the platelets in removing and destroying the infective agents or their products. The present work gives the results of an attempt to show that this same relation between the platelets and toxins also exists during certain phases of mental disorder and, in these particular cases, a toxin from a focus of infection can be assumed to be the causative agent in producing the psychosis.

Historical.

The existence of the platelet as a third morphological element of the blood has been repeatedly affirmed and denied. The earliest observers were Donne and Arnold (1) about the middle of the last century. Bizzozero (2), who gave the platelets their name, described them as they appeared in the mesenteric

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vessels of the guinea-pig and his observations were confirmed by others, notably Ebert and Schimmerbusch (3). Marino (4) failed to observe them in blood which was allowed to flow into absolute alcohol, but Downey (5) showed that 100% alcohol readily distorted the platelets and rendered them difficult to stain and demonstrate. Many theories have been advanced to explain the origin of blood-platelets, and the theories which hold that the platelets are primary forms of red blood-corpuscles have long been discarded. Schilling (6) believes that the blood-platelet itself is the entire modified nucleus of the younger erythrocyte, partly detached and only becoming free in the circulation, e.g., by blood-platelet thrombosis. The same author concludes that they are not fragments of leucocytes because specific granules are always absent, and that the theory that they are pieces of erythrocytes is contradicted by the fact that hæmoglobin cannot normally be demonstrated. In his classical work Wright (7) has demonstrated that platelets are portions of megakaryocyte cytoplasm of the bone-marrow which, after segmentation, are detached and carried off in the blood-stream. In support of his theory Wright has pointed out the parallelism which exists between the number of platelets in the circulation and the number of megakaryocytes in the bone-marrow. In pathological states megakaryocytes have been found in the spleen, lungs and blood stream, and they are present in all stages of development in the bone-marrow. The youngest cells are non-granular and have a single nucleus, which matures to become larger and more complex, until ultimately several nuclei are formed (8). The cytoplasm also increases in size and becomes full of fine granules, which Wright (7) and Downey (9) consider peculiar to the platelet and the megakaryocyte. Thus the fully-developed cell is very large and has a greater cytoplasm containing a number of nuclei. It is only in the adult stage that megakaryocytes can produce platelets. Wright also points out that platelets do not appear in the embryo before the appearance of the megakaryocytes, and that they are only found in mammals in which megakaryocytes are present. Platelets and megakaryocytes are both increased in the blood following toxæmia, inflammatory states, and in experimental lesions following the injection of anti-platelet serum (10), or of diphtheria antitoxin (11). Both are diminished in pernicious anæmia (12) and after exposure to X-rays (13).

From the foregoing it appears that the platelet normally arises from the megakaryocyte of the bone-marrow. Brown and Bunting (14) assume that in time of stress platelets may arise from mononuclear and transitional cells of the bone-marrow, spleen and glands.

The term "thrombocyte", introduced by Dekbuyzen to describe the spindle-shaped cells found in the blood of amphibians, is now frequently used for all elements of the blood which are smaller than erythrocytes. It includes the blood-platelets of mammals and the small nucleated corpuscles of birds and the lower vertebrates (15).

Destruction of Platelets.

Bedson (16) concludes that the younger cells of the reticulo-endothelial system, of which a large number are situated in the spleen, are normally responsible for the removal of platelets from the blood, and he also reports an increase after splenectomy. In health the spleen contains a large number of platelets, and in disease it has been found to contain a relatively large number of these elements when their numbers are diminished in the blood (17). Mackay (18) concludes that the life of the platelet is short and that a large number are produced and destroyed each day, while Duke (19) considers that circulating platelets degenerate within three to five days.

Numerical Variation of Blood-platelets in Health and Disease.

Cacurri (20) reports that after exercise there is a diminution in the platelet-count lasting a few hours only, due to fatigue liberating harmful products. No change was observed during sleep or lying down. Wittkower (21) notes an increase after a hot bath.

In disease, variations are more marked than in health, and occur during a single illness, according to the stage, whether acute or convalescent. Furthermore, the behaviour depends on the reactive power of the bone-marrow. It can be stated in a very general way that platelets are diminished in leukæmia, acute tonsillitis, lobar pneumonia (pre-critical stage) and pyæmia. They are normal or very slightly increased in scurvy, diabetes mellitus and hyperthyroidism, while in secondary anæmia (post-hæmorrhagic), lobar pneumonia (convalescence), acute rheumatism, nephritis, malignant disease and chronic forms of tuberculosis they are normal or increased (22). The platelets show a rise following parturition and after operation (23).

In acute cases of toxæmia there is a tendency for the platelets to be diminished, and during convalescence the numbers tend to increase, after which there is a gradual fall to the normal limits. This constant behaviour of platelets has also been observed in many acute infectious diseases, e.g., in diphtheria (26), the common cold (27), and smallpox (27*a*). The most comprehensive observations on the platelets in a typical acute infection are those of Reimann (24). He found that in the majority of a series of cases of pneumonia the platelets were considerably reduced during the pyrexia, and began to rise shortly after the crisis, reaching a maximum in from 6–9 days and returning to normal in a further similar period. He further noted that when complications occurred there was a further drop in the platelets. Kemp, Colhoun and Harris (25) state that during the course of typhoid fever the number of platelets is normal or subnormal. "If the fever breaks by crisis, there is a rapid and striking rise in the platelets. If this rise does not occur it suggests a masked serious complication." Duke (26), describing experiments

with diphtheria toxin, killed typhoid bacilli, X-rays and benzol, found that while all these depressed the platelet count, in small doses they frequently caused an elevation.

Certain writers think that the platelets have an important function in eliminating foreign bodies from the blood, or play some part in establishing a state of immunity to infection. Bull (29), in a series of publications, reports that streptococci and pneumococci, unless extremely virulent, were rapidly removed from the blood of experimental animals. He further observed that typhoid and dysentery bacilli of the Flexner group were agglutinated in the blood stream. In both cases the agglutinated organisms were rapidly removed and destroyed in the visceral capillaries. Any bacilli not so agglutinated remained in the blood and produced a septicæmia. Dalrez and Govaerts (30), following up the work of Bull, demonstrated that, in the blood-stream of a rabbit, staphylococci and *paratyphosus B* bacilli adhered to the platelets. This adhesion was associated with the disappearance of bacteria and a diminution of the number of circulating platelets. Two minutes after injection mixed masses of platelets and organisms were found in the capillaries of the spleen and liver. Continuing these investigations, Govaerts found that intravenous injections of washed platelets accelerated the elimination of typhoid bacilli from the blood.

All the above work suggests that the platelets play a part in the sterility of the blood-stream, and it also suggests an explanation for the reduced numbers in acute infections. Diminution would be due to the using up of platelets in removing and destroying infective agents. Dawburn, Easlam and Evans (31), summarizing the literature on the effect of sepsis on the platelet, report : " There is a very definite measure of agreement as to the fall in the acute stages and the rise in convalescence on the platelets in acute generalized infections."

Focal Infections and Mental Disorder.

For years past intensive investigations have been carried out on the study of nerve disorders based upon alterations in the blood and glands, and from the results of these it is realized that infection plays a large part in the causation of mental disorder (Hunter (32), Cotton (33)). Mapother (34) reports Cotton as saying : " Mental disorders are due to a combination of many factors, but the most constant one is the intracerebral biochemical cellular disturbances arising from circulating toxins originating in chronic foci of infection situated anywhere throughout the body, associated probably with secondary disturbances of the endocrine system."

Moynihan (35) reported cases of mental disorder relieved by operation for chronic appendix, gastric ulcer and gall-bladder. He concluded that the infective agencies which appear sometimes associated with mental diseases are the teeth, the facial sinuses, the alimentary tract and gall-bladder ; and

that infections, wherever arising, are apt when they reach the cæcum and ascending colon to remain there long after the primary focus has ceased to be active. His work shows that mental instability and insanity may sometimes be relieved, and apparently cured, by the eradication of a focus of infection, or the removal of the disease that it has originated.

Graves (36) stresses the frequency of sinus infection, and claims that the treatment of these conditions is followed in a very large number of cases by physical and mental improvement, even in cases that have been in a stationary or progressive phase of mental deterioration for so long as to be considered hopeless.

Watson-Williams (37) has shown that a septic focus in the teeth, tonsils, prostate gland or gastro-intestinal tract may be the cause of remote systemic disorders, and the work of Rosenow has been of great value in helping to explain the mechanism of these processes. Rosenow speaks of the elective localization of micro-organisms, and this may be decided by qualities of the soil no less than of the seed.

Clarke (38), though not entirely confirming Graves's results, concludes that focal sepsis can predispose to, and exaggerate the development of, mental symptoms; infections of the ear, nose and throat are likely to be particularly potent in doing so; the incidence of ear, throat and nose infections in the insane is considerable.

Many important psychiatrists have called in question the results claimed, and the alleged "proven relationship" of sepsis and mental disorder, chief among whom are Henderson and Menzies. Henderson challenges the findings of Hunter and Graves. He states (39) that Kopeloff and Kirby examined 120 patients, dividing them into two groups as nearly identical as possible. One group was treated surgically, while the other group had no surgical treatment. The percentage recovery-rate of the manic-depressive patients in the two groups was equal, while patients with dementia præcox showed a slightly lower recovery-rate in those operated upon than in those left alone.

Menzies agrees that the incidence of chronic sepsis is no more frequent in the insane than in the sane (40), sepsis is, as a rule, a secondary cause of mental disorder, the recovery-rate has not been materially raised by antiseptic measures, the use of autogenous vaccines has proved disappointing, and serological, metabolic and endocrinological tests have all given results that are not at all specific. However, it is not denied that the end-result from severe attacks of septicæmia may be mental disorder.

The mode of action of toxins in the causation of mental disorder is conveniently reviewed by Ford Robertson (41):

"If a toxin is circulating in the blood, it will fix itself on any substance for which it has a chemical affinity. There are many toxins, and some of them of bacterial origin, that have a special affinity for nerve-cells. The liability to be injured by such neurotoxin is, however, not the same in all nerve-cells.

There are wide local and individual differences dependent upon congenital and acquired qualities. Special vulnerability to toxins on the part of nerve-cells of the association centres in some stocks appears clearly to be at least one important factor included in hereditary predisposition to insanity. Two distinct effects upon the association centres must be recognized. During the height of the toxic action the metabolic processes occurring in these centres are seriously disturbed: mental reactions are correspondingly disordered, and consequently there is confusion, excitement, depression and stupor. If the toxic action subsides, there may be complete recovery on the part of the tissues, in which case the mental reactions again become normal. In other cases there is irreparable destruction of many neurons, and the centres are permanently damaged; the mental reactions, therefore, remain more or less abnormal. Thus regarded, mental disorders are abnormal reactions of an associative mechanism that is damaged by active, or former, disease, or by traumatism, or that is defective owing to some developmental fault."

From a consideration of the literature and clinically and experimentally there is a great deal of evidence in support of the contention that focal infections are capable of causing serious mental disturbance, and that they cause the most serious effects at a distance.

METHOD.

It is to be regretted that there is no standard method of counting the blood-platelets. With each technique different counts are obtained, and some workers consider the method which gives the highest figures to be the most accurate. Platelets are easily damaged; they can be disintegrated by the pressure of a cover-slip; they also clump very easily, either to each other or to the red blood-corpuscles. It is of the utmost importance to employ methods that do not damage the platelets and also prevent their clumping.

Throughout the work reported upon in this paper I have used the method described by Cumings (42). By this technique the results are more accurate and stable, the platelets are evenly distributed over all the fields, they show no evidence of clumping and they are not damaged in any way because their shape, size and outline are distinct. By other methods I found counting was rendered extremely difficult, owing to mass clumping of platelets, while in stained films platelets adhering to red cells and clumping gave rise to inaccuracies in the results.

Cumings claims that the absence of clumping in his method is partly the result of using paraffin containers, also that small platelets are not damaged but well preserved owing to the addition of mercuric chloride to the diluting solution. Using this method Cumings's findings conform to those of Flossner and Dameshek Olef, who obtained figures from adult males of about 600,000 per c.mm.

The actual technique employed is as follows:

Two solutions are required :—

Solution A :

Sodium chloride	0·8%.
Calcium chloride	0·02%.
Potassium chloride	0·02%.
Sodium bicarbonate	0·1%.
Sodium acid phosphate	0·005%.
Magnesium chloride	0·01%.

To prevent contamination, add to above solution mercuric chloride 1/10,000.

Solution B :

1% mercuric chloride in normal saline.

Immediately before use add 5 parts of solution A to 1 part of solution B, without filtering either fluid. Blood is obtained from the ear by pricking through a drop of diluting fluid, without using local pressure, and allowing the blood to flow directly into the diluting fluid, which is in a small paraffined bowl (about 1 in. × ½ in. × ¾ in.). By means of a paraffined rod, or better, by means of a piece of glass tubing coated within and without with paraffin, through which air can be blown by means of a rubber teat, the contents are thoroughly mixed. The exact degree of dilution is that which, by experience, is shown to give the greatest enumeration—usually about 1–400. The ear is carefully dried and blood taken for a red corpuscle-count, which is performed in the usual manner.

By means of the paraffined glass mixer a drop of the diluted blood is placed on a counting chamber, and the cover-slip applied. After the red cells and platelets have settled, usually in ten minutes, the platelets are counted against the red cells, a thousand of the latter being enumerated, using a high power eye-piece (× 8) and a dry lens (⅙ in.). It is convenient to have about 150 red cells in a field, and the original dilution of the blood should be such as to give this figure. The count should always be performed within half an hour of collection. The counting chamber should be kept specially for platelet counts, and very carefully cleansed before use ; if found scratched it must be discarded. A drop of the diluting fluid should always be examined each day before starting to see that no free particles, such as might resemble platelets, are present.

The platelets are easily recognized as highly refractile particles, varying in size from about one-eighth to one-half the diameter of a red cell. Their shape is round, oval or oblong, with well-defined edges, and they show no movement once they have settled in a counting chamber.

The results to be described are of male cases only ; the patients chosen were mainly new admissions, except for a number of cases of schizophrenia ; all were under 55 years of age and all were free from intercurrent disease, thus eliminating the fallacies that might be due to menstruation (in the female), to diseases of the blood and organs, especially arterial degeneration and nephritis, and to senility. The examinations were performed at the same time each morning, four hours after breakfast, and no medicine was administered for twelve hours previously. The patients were kept resting in bed all the morning, so that no fallacy could arise from fatigue and exercise.

The cases—95 in number—will be subdivided into groups, which will be considered separately.

Manic-Depressive Insanities.

Twenty-eight of the patients come under this category, namely, 17 maniacs, 7 melancholics and 4 cases of alternating insanity.

Examples of four cases of mania will be given first, as in these cases a blood-platelet enumeration was performed each day during the full course of the acute illness.

Case 1.—T. W—, aged 53, admitted August 23, 1934. Weftman, married.

Past history.—Fourth attack; previous attacks 1921, 1923 and 1927. No illnesses, except influenza and "chronic sniffles" during the winters. Wife and friends noticed that he was getting sleepless and restless for two weeks.

Family history.—Negative.

Condition on admission.—Temperature 98·4° F., pulse 80, respirations 20. Pale, rather toxic looking, but colour of membranes and lips good; edentulous (all teeth extracted when last certified and in this hospital; at that time had pyorrhœa, and teeth were carious). Gums apparently healthy and show no evidence of gingivitis. Tongue furred. Chest and abdomen: nothing abnormal found. Blood-pressure 120. All reflexes normal.

Wassermann, Meinicke and Widal tests negative.

Urine: S.G. 1024, acid, negative for sugar and albumen.

Mental condition.—Admitted in an acutely maniacal condition. Was greatly excited and generally uncontrolled. He was distractible, and his attention could only be sustained for a few seconds. Talked incoherent nonsense, switched from one subject to another and, at times, shouted, sung or cried in turn. Very restless, mischievous, and inclined to be destructive and depraved in his habits.

Progress and course:

August 24: Continually shouting and talking nonsense. Required to be under special supervision. After paraldehyde 2 drm. slept for five hours.

August 25: Uncontrolled in his thoughts and actions. Maintains his excitement and restlessness. Slept little.

August 26: Restless and excited behaviour continued.

August 27: Takes his diet when spoon-fed. Manifests distractibility and "flight of ideas". Slept five hours overnight. Still requires special supervision.

August 28: Given hypodermic of morphine and hyoscine; slept for five hours.

August 29: Patient in a condition of stupor; is more settled in his behaviour. Taking diet and sleeping better.

September 1: Has gained control over himself and is more rational in his talk and conduct. Slight amnesia and confusion for the events of the past few days.

September 3: Well orientated; realizes that he has been ill mentally. Conversation normal and attention good. Sleeps well now.

Date.	Erythrocytes per c.mm.	Platelets per c.mm.
August 24	6,000,000	410,000
,, 25	6,200,000	410,000
,, 26	6,250,000	420,000
,, 27	6,000,000	430,000
,, 28	6,000,000	425,000
,, 29	6,200,000	300,000
,, 30	5,500,000	550,000
,, 31	5,750,000	520,000
September 1	5,500,000	620,000
,, 2	5,750,000	600,000
,, 6	5,600,000	600,000

CASE 2.—L. T—, single, aged 21, motor driver, admitted January 22, 1934. First certification.

Family history.—History of intemperance on mother's side.

Personal history.—Suffered from no illnesses except common colds and bronchitis since childhood.

Present illness.—Very sudden onset. Was apparently well until the day previous to admission.

Physical state.—Temperature and pulse normal. Tongue coated and tonsils inflamed. Teeth fairly good. Nothing abnormal in chest and abdomen. Reflexes normal.

Urine: S.G. 1020, acid, no abnormal constituents.

Wassermann, Meinicke and Widal negative.

Mental state.—Wildly excited, noisy, resistive, distractible, rambles incessantly and incoherently in his talk.

Progress and course.—For four days his excitement continued, and injections of morphine and hyoscine had to be administered.

January 26: In condition of stadium debilitatis. Knows all that is going on around him, amenable, manageable.

January 29: On the whole much better. Realizes that he has been ill and his mental symptoms have disappeared.

February: Made satisfactory progress and was discharged recovered.

Date.	Erythrocytes per c.mm.	Platelets per c.mm.
January 23	6,000,000	300,000
,, 24	5,600,000	260,000
,, 25	5,700,000	500,000
,, 26	6,200,000	540,000
,, 27	6,000,000	500,000
,, 28	5,700,000	690,000
,, 29	5,500,000	600,000
,, 30	5,700,000	625,000
February 9	5,750,000	635,000

CASE 3.—S. C—, male, aged 35, chimney sweep, married. First certification.

Family history.—No history available.

Physical state.—Fairly well nourished. Normal pulse. No gross lesions of the major viscera. Advanced pyorrhœa and teeth carious.

Urine normal. Wassermann negative.

Mental condition.—Rambling and incoherent in his statements, which follow each other with extreme rapidity. Exalted, with delusions of persecution. Restless and mischievous.

Progress and course.—For four days after admission had to be confined to a side room and required special supervision.

January 31: Extreme symptoms subsided, was somewhat stuporose, but was amenable and controlled in his conduct.

February 2: Showing more interest, association of ideas normal, well orientated and has insight.

Maintained a steady progress.

Date.	Erythrocytes per c.mm.	Platelets per c.mm.
January 28	5,800,000	300,000
,, 29	6,000,000	420,000
,, 30	6,000,000	450,000
,, 31	5,500,000	500,000
February 1	5,800,000	520,000
,, 2	5,500,000	600,000
,, 3	5,600,000	700,000
,, 4	5,600,000	610,000

CASE 4.—G. M—, single, aged 25. First attack.

Has chronic rhinitis. Anæmic and toxic-looking on admission. No evidence of organic disease, and urine and blood examination negative.

Mental state.—Uncontrolled in thoughts and actions for four days. Afterwards became manageable and amenable, and in seven days had recovered from his acute symptoms. Was discharged recovered.

Date.	Erythrocytes per c.mm.	Platelets per c.mm.
March 3	5,700,000	460,000
,, 4	6,000,000	460,000
,, 5	5,800,000	500,000
,, 6	5,500,000	500,000
,, 7	5,750,000	550,000
,, 8	5,700,000	610,000
,, 9	5,750,000	610,000

COMMENT ON CASES.

The tables show the results obtained in these four cases. On examining the figures it is clear that on the days after admission there was a marked diminution in the circulating platelets of the blood, and that the count remained at a low level during the four days in which the patients were uncontrolled and the mental symptoms were most acute. In Case 1 the count was stationary during the acute phase, and in Cases 2 and 3, although there was a slight increase noted each day the numbers did not reach normal limits. On the next three days, while the patients were in the "stadium debilitatis" there was a rapid rise in the platelet numbers, which increase rose to normal on the third day of this stage. On the first day of the convalescence the platelets exceeded the normal numbers for the one day only, after which they fell to normal and remained at this level.

It is reasonable to assume that in these four cases a toxic influence was the causative agent in producing the rise and fall in the circulating platelets. These findings are conformable to those reported in fevers and generalized toxic conditions, except that, in these four cases of mania, the increase during convalescence lasted the one day only, whereas in generalized toxæmia the increase in the platelet numbers at this stage is stated to last for a number of days. This could be accounted for by the larger amount of toxin absorbed into the blood during the acute stages of the more generalized illness making a greater call upon the defensive forces of the blood and, during the convalescent stages, the activity of the hæmopoietic tissues will necessarily have to be prolonged to restore the blood elements to the normal numbers. That a chronic focus of infection was existent in these four cases is evident from the histories. In Case 1 the patient has had attacks of influenza, and during the winter months suffered from chronic "sniffles", Case 2 suffered from chronic bronchitis, in Case 3 the teeth were carious and the gums showed pyorrhœa, and in Case 4 there was chronic rhinitis.

From a consideration of these cases it is apparent that it was during the "stadium acutum" that the neurotoxin from a focus of infection acting on the cortical cells and causing the cerebral irritation was greatest in its intensity, and that the platelets acting as agents in eliminating foreign substances from the blood were being used up, and were, accordingly, reduced in numbers. In the exhaustive stages, and with the subsidence of the acute symptoms, the rise in the platelet numbers shows that the toxæmia has been counteracted, and the platelets, not being used up in neutralizing the toxin, begin to return to the general circulation. The increase during the first day of the convalescence was merely reactionary on the part of the bone-marrow, and during convalescence the toxin has been completely eliminated and the platelets are therefore found in their normal numbers in the drop of blood examined.

Another feature in favour of the contention that there is a toxin present in the blood in the cases of mania was noted during this investigation. Platelets are generally described as varying in shape and size, some being half the size of a red blood-corpuscle and rounded or pointed in shape, but in the acute stages of the maniacal attack no large or intermediate platelets were observed, all being small, rounded, with well-defined edges and about one-sixteenth the size of a red cell. This would appear to be due to the larger platelets being used up, the observed smaller forms being the new forms from stimulation and response of the bone-marrow. The larger forms returned when the platelet-count began to rise, and during the convalescence their shape and size was normal.

In two other cases of mania, in which the acute symptoms lasted three or four weeks, no fluctuation in the platelets was noted, and they were normal in numbers and appearance until two to three days before the patients became controlled and amenable; then the numbers decreased, small platelets predominating, and they remained depressed until the subsidence of the excitability, when the platelets returned to their normal numbers.

It will be seen from a consideration of the above two cases that the symptoms did not subside until three days after the platelets showed a decrease. It would appear that there was an inability on the part of the platelets from the beginning of the illness to neutralize the toxin, which, by remaining active, caused the acute symptoms. When the platelets overcame the inhibiting action of the toxin, as shown by their reduced numbers and the preponderance of the small forms of platelets, the patients improved mentally.

Four cases of mania which died within a few days of admission only allowed of a platelet-count on the first and second days after admission. In three of these cases the count was decreased, being under 500,000 on the two days, and in the other case the count was 550,000 on the first day, and on the second day, a few hours before death, the numbers rose to 1,000,000.

Owing to the necessity of having to administer sedative drugs to three cases, a count was only possible at irregular intervals, but in these three cases

a decreased count was noted when the blood was examined during the excited phase of the illness.

Normal or slightly increased counts were only found in three of the cases of mania examined.

In one case, which had septic abrasions on his hips, thighs and both arms, caused in a cycle accident four days prior to admission, an increase was noted, but when the patient returned to a normal mental stability and his septic wounds had healed a normal count was recorded.

ACUTE MELANCHOLIA.

Case.	Platelet-count on admission.	Average platelet-count during acute illness.	Duration of acute illness.	Platelet numbers on recovery.	Remarks.
A. S—	390,000	450,000	18 days	650,000	Recovered.
W. B—	400,000	500,000	14 ,,	600,000	,,
F. B—	400,000	400,000	12 ,,	550,000	,,
P. L—	420,000	480,000	28 ,,	625,000	,,
A. S—	800,000	700,000	Died six weeks after admission.		
R. N—	760,000	700,000	6 weeks	650,000	Recovered.
R. B—	700,000	700,000	8 ,,	700,000	,,

In this group 7 cases of typical melancholia were taken and blood-counts were performed on every third day during the acute illness of the patients. From a consideration of the above table it will be seen that in four cases a decreased count was obtained on admission, and in all during the acute illness the platelet numbers remained low. On recovery the platelet numbers returned to the normal limits and no increase was noted during convalescence. In two of the remaining cases the number of platelets was slightly above the normal, and in the seventh case the numbers remained at a stationary level throughout the illness.

It is interesting to know that in the four cases in which a low platelet-count prevailed during the acute stages of the illness, the depression and active symptoms subsided sooner than in those cases in which the platelets remained high, and it can be considered a reasonable assumption that in these cases a toxic factor was present, and that the platelets, by being reduced, were counteracting the toxin.

ALTERNATING INSANITY.

Firstly I will submit one case as a typical example of this group :

G. E. C—, aged 42. Very unstable and unreliable from 28 years. Has periods of depression alternating with attacks of mania. Shows remissions lasting 1–3 months. During his excited phase he is generally uncontrolled and impulsive and, when depressed, is sullen, morose, self-absorbed and seldom speaks.

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Platelet-count per c.mm.

During excited phase :

1st day	350,000.	Uncontrolled.
8th ,, ...	500,000.	Beginning to settle.
12th ,, ...	600,000.	Controlled and rational.

During remission : 650,000.

During melancholic phase :

1st day	400,000.	Profoundly depressed.
10th ,, ...	625,000.	Brighter.
18th ,, ...	700,000.	Depression subsided.

In three other cases in this group findings conforming to the above were found, and in these cases the numbers on the day of relapse were 420,000, 420,000 and 440,000 respectively. With the relieving of the symptoms the platelets gradually rose until they were normal or within normal limits when the patients had regained temporary stability.

Primary Dementia.

In this group twenty cases were investigated, and normal readings or a slight increase in the numbers of the platelets were noted.

Delusional Insanity, Chronic Mania and Chronic Melancholia.

No variation from the normal numbers was observed in these groups.

Dementia : Senile and Secondary.

These cases gave normal findings except in three instances, which showed a marked increase during exacerbation of the mental symptoms. As these three cases could not be followed up no definite conclusions can be arrived at.

Dementia Paralytica.

Ten cases suffering from this condition were examined. The most significant feature was that an altered type of platelet predominated. This was large, irregular in shape and darker than the platelet seen in normal blood. In a general way it may be stated that the more progressive and advanced the disease the more large and irregular platelets were observed.

It is now accepted that many of the symptoms of general paralysis of the insane are caused by the toxic agent produced by the spirochæte, and there can be no doubt that the toxin is acting on the blood and tissues from shortly after the patient has contracted the disease. Schilling reports (43) an increase in the number of platelets in syphilis. All the cases of dementia paralytica reported above gave a history of having been infected for more than ten years previous to admission. This would mean that during all these years the

platelets were increased, were continually being destroyed and that, after a time, the strain could no longer be borne by the platelet-forming tissues and, in consequence, these tissues show exhaustive or other changes. In pernicious anæmia, Gulland and Goodall (44) consider that the abnormal red blood-cells seen in the blood are due to a toxic effect on the bone-marrow, causing a degeneration which may be looked upon as a reversion to the fœtal type of marrow. It is reasonable to assume that in dementia paralytica, as in pernicious anæmia, the constant drain on the platelet-forming tissues, as a result of the prolonged action of the syphilis toxin, leads to a fœtal type of marrow and, consequently, the appearance of the large irregular forms of platelets in the circulating blood. This contention is strengthened by the fact that Schilling (43) reports that in childhood the platelets are increased in size, and Wright (7) has demonstrated that the younger cells are non-granular and become larger on maturation.

General Conclusion.

Valentine (45), in his experiments with staphylococcal infection on human and rabbit blood, concludes that "the comparatively poor development of circulating antihæmolysin in many patients suffering from chronic furunculosis may be due to the fact that the toxin is fixed locally in the tissues and does not therefore stimulate a general immunity. In a deeply-seated abscess the absorption to toxin appears to be easier". It is my opinion that the platelet response to toxins is the same as that of antihæmolysin to infection. I conclude that in the cases of mania, melancholia and alternating insanity which showed a fluctuation in the circulating platelets conforming to that shown in generalized toxic conditions, a circulating toxin was operative and caused the psychotic symptoms, and that the toxin arose from deeply-seated abscesses. Graves stresses the frequency of deep sinus infection in most of his cases, and it will be observed that the cases of mania quoted in this paper show evidence of deep infective processes.

In all the other cases of mental disease reported upon, and in which no fluctuation was noted, a focus of infection may have been present, but the toxin from this may have been fixed locally and caused no reaction in the circulating blood, or the toxins, having been acting over a fairly long period, may have established a general immunity in the patients and, therefore, no change in the blood could be expected.

Summary.

1. In four cases of mania the platelet fluctuation conformed to that observed in generalized toxic conditions. In these cases a toxin from a focus of infection may be assumed to be present.

2. While the platelets remained at the normal level in two cases of mania, there was no change in the mental symptoms, but when the number of platelets fell, indicating a possible neutralization of toxins, the acute mental symptoms subsided.

3. In the cases of mania only small forms of platelets were observed. This would appear to be due to the larger forms being used up in counteracting the toxin, the smaller forms being the new platelets from bone-marrow response.

4. Four cases of melancholia which showed a low platelet count recovered more quickly than cases which showed no platelet response.

5. During the relapse stage in alternating insanity the platelets diminished, probably indicating a body response to a toxin.

6. No variation in the platelet numbers were noted in chronic forms of mental disease.

7. In dementia paralytica a large, irregular type of platelet, darker than normal, predominated, and the more advanced the disease the more these large irregular forms were seen in the films examined. This is probably due to a degeneration of the bone-marrow, from the prolonged action of the syphilis toxin, causing a reversion to a fœtal type of marrow.

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