

Blood - Vascular Conditions in Psychoses (1). By ISABELLA
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(This communication forms part of a Report to the Medical Research Council.)

IN a previous communication (1) I presented certain observations on the leucocytic reactions which occur in the normal and in the psychotic individual following ingestion of milk, and also as the result of various physical and chemical stimuli.

The technique, which is very important, was described in detail. There is, however, one point which requires further emphasis.

Before any stimulus was applied to the subject, two initial counts were taken at intervals of 10 or 15 minutes. In the event of the two initial counts differing a third count was taken, and if leucocytic variations were still noted the experiment was abandoned.

The response to ingestion of 200 grm. of cold milk by 100 fasting normal subjects was a leucocytosis, chiefly a polymorphonuclear leucocytosis, accompanied by either a slight rise or no alteration in the arterial blood-pressure.

The response to ingestion of 200 grm. of cold milk by 90 fasting subjects, all of whom were well established cases of mental disorder, was a leucopenia in 88%, a leucocytosis in only 11%. This leucopenia was accompanied by a fall in blood-pressure in over 50%, and in the majority of the cases there was an absolute and relative decrease of polymorphonuclear leucocytes, a relative and in some cases an absolute increase of lymphocytes, and an absolute and relative increase of large mononuclears.

The third group of subjects comprised 275 early psychotic cases, varying from the milder neuroses to the more acute forms of mental disorder and including a large number of adolescents of the dementia præcox type. In this group 49% reacted by the hæmoclastic crisis, 12·5% showed an indeterminate reaction, and 38·5% reacted normally by a leucocytosis.

The fact that physiological leucocytic variations do occur has caused certain observers to conclude that the leucocytosis or leucopenia noted after milk is merely the expression of the phase of the normal leucocytic curve at the time the test is done. The leucocytic changes have recently been investigated by Dr. A. F. Bernard Shaw (2), who does not consider that either a digestion leucocytosis or a digestion leucopenia does occur.

The reaction he obtained in normal persons after ingestion of milk he divides into four groups: (1) leucopenia, (2) no effect, (3) leucocytosis, (4) paradoxical.

(1) A paper read at the Quarterly Meeting held in London, February 10, 1926.

The subjects examined numbered 23, of whom 8 were tested once, and 15 two or more times, usually on successive days. The total examinations made were 40, and taking these as a basis, there was a leucopenia 20 times (50%), leucocytosis 7 times (18%), and no effect 13 times (32%).

The first three groups consisted of 17 subjects. Of these 9 reacted by a leucopenia, 5 showed no effect, and 3 reacted by a leucocytosis. In each of the 9 subjects who were subsequently examined a similar type of reaction was obtained, a leucopenia 5 times, no effect twice, and a leucocytosis twice.

His table illustrating paradoxical results contains figures derived from 6 cases. In 3 cases a leucopenia was obtained on one occasion, and no effect on another occasion. In a fourth case a leucopenia was noted on the first occasion and no effect on two subsequent occasions. A fifth case on one occasion showed no effect, and subsequently a marked leucocytosis. The last case, which on two occasions reacted by a leucopenia, on a third occasion showed the following figures: 6,000 (initial), 10,000 (20'), 5,300 (40'), 4,600 (60'). This last reaction is similar to the reactions which I have called indeterminate, and in 50% of which I have obtained a leucopenia on later examination, and which I have therefore included amongst the cases which reacted to ingestion of milk by hæmoclasia.

The reaction of 6 normal subjects to local application of cold was investigated, with varying results. The results of my own investigations on the local application of both heat and cold have shown that the effect of heat is to cause a leucocytosis, but that if the heat be sufficiently intense a leucopenia will occur, and similarly the effect of cold is to produce a leucopenia, but that if the cold be prolonged, a leucocytosis will be produced.

The reaction of 7 normal subjects to 400 c.c. of distilled water was a leucopenia in 6 and a leucocytosis in the seventh. My investigations on the effect of ingestion of 200 grm. of water showed negligible variations of the leucocytic level, either in the normal or pathological subject.

As the result of investigations on the leucocytic variations during physiological rest, Shaw concludes that leucocytic equilibrium is not necessarily maintained in the absence of alimentary stimulation. His figures show that during the first hour a fall occurred in 3 cases, a rise in 1, and in 6 the leucocytic content remained stable. Consequently he considers "that there is neither a 'digestion leucocytosis' nor a 'digestion leucopenia,' the results recorded as such in the literature on hæmoclasia being simply the expression of the phase of the normal curve at the time the test is done, a

descending phase being registered as a leucopenia and an ascending one as a leucocytosis."

I should like to draw attention to certain figures I have quoted from this paper. Following ingestion of milk, in 50% of the normal subjects a leucopenia was noted, in 18% a leucocytosis, and in 32% no effect, whereas consideration of the leucocytic variations during physiological rest shows a leucopenia in only 3 cases, or 30%, and an unchanged leucocytic level in 6 cases, or 60%.

Feinblatt (3), as the result of an investigation on the alimentary leucocytosis in 80 healthy students, found a definite leucocytosis in all of them. Wilson (4) also records a leucocytosis within one hour in 30 students after 200 grm. of milk. In my own series of 100 normal subjects, I always found a well-marked leucocytosis, though in a few cases it was comparatively slight.

That physiological leucocytic variations do occur both in the normal and in the pathological subject is beyond doubt. There is also evidence to show that the leucocyte count may be affected by psychic and emotional disturbances, and that these variations may be both rapid and intense. But in spite of these facts, it is possible with a sufficiently accurate technique, and under experimental conditions where every cause of disturbance is reduced to a minimum, to obtain leucocytic equilibrium during the course of one hour.

From a consideration of the figures I have quoted I remain unconvinced that the work of Dr. Shaw and of other critics has in any way detracted from the fact that the hæmoclastic crisis is a specific leucocytic reaction.

HÆMOCLASIA AND ENCEPHALITIS LETHARGICA.

Amongst the early psychotic cases at the Maudsley Hospital were 15 cases of encephalitis lethargica. In 13 of these cases a definite hæmoclastic crisis was obtained, the remaining two reacting normally by a leucocytosis. These findings are in agreement with those of most observers who note the occurrence of the hæmoclastic crisis both in cases of encephalitis lethargica and paralysis agitans. A further group of 8, 4 women and 4 children, all of whom were undoubtedly cases of encephalitis lethargica, was selected for investigation. This investigation consisted of repeated examination, on several days, of the leucocytes of these cases following ingestion of 200 grm. of milk, the effect on the leucocytes of the administration of hyoscine, the effect of hyoscine on the hæmoclastic crisis, and finally the effect of adrenalin on the hæmoclastic crisis.

In addition a group of 6 children suffering from chorea was

similarly investigated, for comparison with the results obtained from the encephalitic children.

The following table gives the results of the ingestion of milk on the leucocytes of these cases.

		Initial counts.	20'.	40'.
Encephalitic children	1.	(5,850) 5,950	5,250	4,950
	2.	(4,900) 4,950	4,650	4,000
	3.	(7,750) 7,650	7,650	6,900
	4.	(6,800) 6,850	6,850	6,950
Encephalitic cases (women)	5.	(11,200) 11,000	5,850	7,550
	6.	(12,000) 12,300	12,300	9,100
	7.	(10,900) 10,750	9,250	9,300
	8.	(12,400) 12,400	12,800	11,150
Chorea cases (children)	1.	8,300	9,400	9,850
	2.	8,100	9,600	8,800
	3.	12,050	9,750	10,300
	4.	7,800	9,750	8,750
	5.	5,800	5,600	6,050
	6.	7,050	6,550	6,900

The actual figures varied on different occasions, but a similar type of response was obtained in the same subject on successive days. In none of the encephalitic cases was a leucocytosis obtained, though one case on one occasion showed no change, and on two other occasions a leucopenia. A definite leucocytosis was obtained in 3 of the chorea cases, a definite leucopenia in one, no change in 1, and in the remaining case the leucocytes were slightly decreased after 20 minutes, returning to the original level after 40 minutes, *i.e.*, a rather indefinite hæmoclasia occurred.

Glasser (5), and Schiff and Stransky (6), have shown the occurrence of hæmoclasia in a certain percentage of normal children and infants, and the occurrence of the leucopenia in the two choreic children is not abnormal. The occurrence of a leucopenia on practically every occasion in the encephalitic children, however, definitely exceeds this percentage.

The effect of subcutaneous injection of *hyoscine* on the encephalitic cases resulted in a leucopenia in all but one. In this one case, a child, it was followed by a slight leucocytosis.

In the chorea cases, the effect of administration of *hyoscine* was a well-marked leucocytosis in 4, a slight leucocytosis in one, and a leucopenia in the sixth case.

The tendency, therefore, is for the effect of *hyoscine* to resemble that of the response to milk in each case, but this does not hold absolutely.

The effect of *hyoscine on the hæmoclastic crisis* was then observed. Immediately following the ingestion of milk a subcutaneous injection of hyoscine was given to the subject, and the leucocytes counted 20 and 40 minutes later, the initial leucocytic level having been previously noted. In only one of the encephalitic women was a reversed reaction found, though in two others there was a tendency towards reversal, while the fourth was entirely unaffected. Following administration of hyoscine, 2 of the encephalitic children showed a reversed type of reaction to ingestion of milk, while the other 2 remained unaltered.

Of the 6 chorea cases, in 4 the reaction was unaltered, and of the two who did show a reversed reaction, one had previously responded to ingestion of milk by a leucopenia, the other by a leucocytosis.

Adrenalin—mij 1 : 1000 solution of adrenalin chloride—was given subcutaneously to be followed by an increase in the number of leucocytes, to a maximum about 15 minutes after the injection. As in the previous investigation of the influence of adrenalin on the hæmoclastic crisis in dementia præcox, milk was given 10 minutes after the injection of adrenalin. Leucocytes were counted before injection of adrenalin, and 10 minutes, 30 and 50 minutes later. Three days later a similar injection of adrenalin was given, and the leucocytes counted before and 10 minutes after the injection. Milk was then taken immediately by the subject and the leucocytes again noted 20 and 40 minutes later. Comparison of these two curves showed that in every one of the cases of encephalitis lethargica examined, the effect of the adrenalin had been to abolish the occurrence of the hæmoclastic crisis and to replace it by a more or less normal response, a leucocytosis.

HYDROGEN ION CONCENTRATION OF THE BLOOD.

At Dr. Golla's suggestion an investigation was undertaken to demonstrate changes in the hydrogen ion concentration of the blood, and to correlate these, if any, with the varying types of leucocytic response to physiological and pharmacological stimuli. The hydrogen ion concentration of the blood following ingestion of milk was investigated in a group of normal subjects, and in a group of psychotics who had previously shown a marked hæmoclastic crisis.

This necessitated frequent samples of blood, and a micro-method differing only in a few details from the colorimetric method of Cullen (7), was adopted. The diluting fluid (.9% NaCl plus a sufficient amount of phenol red solution) was rendered CO₂ free and kept in a Pyrex flask under oil. This was renewed each day.

Sörenson's phosphate mixtures were also renewed at frequent intervals. The indicators were prepared daily by adding 0.1 c.c. of the appropriate phosphate mixture to 2 c.c. of the diluting fluid. The tubes used were of neutral glass and of uniform size, 3 in. by $\frac{1}{4}$ in.

The blood was collected, under oil, from the finger. Oil was drawn into the pipette, and 0.1 c.c. of blood was collected in the pipette and a drop of oil drawn up. The blood was then run into tubes containing 2 c.c. of the diluting fluid, covered with oil, and the blood and diluting fluid mixed by stirring with a fine glass rod. The tubes were then filled with oil and gently centrifugalized. The corpuscles settled to the bottom of the tube, leaving a clear fluid, which was matched against the indicators. The accuracy of this method was found to be under 0.02 pH, provided that no air was introduced.

Hawkins (8), who used whole blood instead of serum, and introduced it straight into tubes containing saline and phenol red, states that whole blood and plasma show either no difference or only 0.02 pH. difference.

Blood was collected at intervals of 20 minutes during one hour from fasting subjects, both normal and psychotic. The pH was estimated, and was found to be constant within the limit of experimental error in the same individual.

The pH of the blood was again estimated at intervals of 20 and 40 minutes after ingestion of milk by fasting subjects. Two groups, 4 normal subjects and 4 who showed a marked hæmoclastic crisis, were selected. In both groups the hydrogen ion concentration of the blood was found to remain constant during this time.

DISCUSSION OF RESULTS.

In a previous communication it was shown that the hæmoclastic crisis does not occur in the normal healthy subject, but that it does occur in a large percentage of psychotics. Analysis of the group of 90 well-established cases of mental disorder shows that 94% were schizophrenic in type, 85% were cases of melancholia, and 75% chronic mania.

In 260 early psychotic and neurotic cases, a hæmoclastic crisis was found in over 60%, it was noted that the greater number of these were psychotic, chiefly of the schizophrenic type, and that most of the neuroses included in this 60% were anxiety forms. Consideration of the subsequent progress of 148 of these cases showed that 55% of the positive cases were reported as worse, 24% were better, and that 70% of the negative cases were reported as better and only 10% worse.

It was pointed out that these figures were probably inaccurate. Consideration of the subsequent progress of many of these cases during a further period, and of many who were not included in the first list, shows that there is very little change in the proportion of cases included under the different headings. The revised list shows that 61% of the positive cases are reported as worse, 22% as better, and that 67% of the negative cases are reported as better, 11% as worse.

The results in both groups of encephalitis lethargica cases show that hæmoclasia occurs in 90% of these cases. This hæmoclasia can be prevented by previous administration of adrenalin. The effect of hyoscine is much less constant, a reversed reaction or a tendency to a reversed reaction being found in only 60%. No correlation, however, was possible between the effect of hyoscine on the hæmoclastic crisis and the clinical effect of hyoscine on the subject.

Another point of considerable interest is that hæmoclasia occurs in 97% of diabetics following ingestion of glucose, but in less than 50% following ingestion of milk. Glucose, however, does not cause hæmoclasia in psychotic cases who exhibit it after milk.

In investigating anaphylaxis it was established that certain phenomena either occurred with or immediately before the onset of the anaphylactic symptoms. The most important of these were a fall in the leucocyte count, a fall in the arterial blood-pressure, hypercoagulability of the blood and a diminution of the refractive index of the serum. The presence of this crisis was demonstrated in asthma, paroxysmal hæmoglobinuria, epilepsy, etc.

Widal (9) suggests that the colloid constituents of the body-fluids are normally in a condition of equilibrium. In a sensitized individual minute quantities of an incompatible colloid, or even a crystalloid, may disturb this equilibrium. This colloidoclasia is accompanied by the changes in the blood described as the hæmoclastic crisis.

The test for liver function arose out of the foregoing theory. It was thought that an impaired liver would be likely to allow imperfectly metabolized proteins to pass into the systemic circulation, that these would be likely to produce a mild colloidoclasia, and that this would be recognized by the appearance of the hæmoclastic crisis.

Widal and certain other workers have demonstrated the presence of the hæmoclastic crisis in practically all cases of liver disease, and consider that the test is specific for liver inefficiency, not for the liver function in general, but for the proteopexic function of the liver.

The majority of writers on this subject do not find that the hæmoclastic crisis is a test specific only for liver disturbance, and the balance of opinion, therefore, is against regarding it as a specific liver function test. It is more or less generally agreed, however, that hæmoclasia does occur in anaphylactic conditions.

Anaphylactic shock is not due to a specific poison, but can appear as the result of a physical process. A toxic process is essentially specific. The condition which is produced by antigen, crystalloid, cold, is not intoxication or destruction of the cellular chemical equilibrium, but colloidoclasia, or disrapture of the physical equilibrium of the colloids of the organism.

It has been shown (Schiff (10)) that a marked eosinophilia occurs in the blood during anaphylactic shock, and those workers who have investigated the eosinophil cells during the occurrence of the hæmoclastic crisis have found an eosinophilia, thus emphasizing the similarity of the blood picture during hæmoclasia, and the blood picture which is found following anaphylactic shock.

In both conditions a fall of blood-pressure is generally noted.

These facts, therefore, indicate that there is a marked similarity between hæmoclasia and anaphylaxis.

Another factor of considerable importance is the effect of adrenalin on hæmoclasia. Glaser (5) finds that after an active dose of adrenalin or atropine, the leucopenia following ingestion of milk can be converted into a leucocytosis. He also finds that administration of pilocarpine to a normal subject converts the leucocytosis into a leucopenia. He therefore considers that the cause of the hæmoclastic crisis is a change in the equilibrium between vagus and sympathetic tonus. Stocker (11) also notes that previous injection of adrenalin prevents the occurrence of the hæmoclasia, and considers this to be due to the increased resistance brought about by the raising of the sympathetic tonus by the adrenalin. Similar experimental results and conclusions have been reported by Tinel (12), who concludes that susceptibility corresponds to a special state of vago-sympathetic equilibrium, the vagotonic state exaggerating and the sympathetic-tonic suppressing the influences which produce hæmoclasia.

My observations are in agreement with those findings, as in every case investigated the administration of adrenalin (and atropine, though to a less extent) was to prevent the subsequent appearance of the hæmoclastic crisis.

From a consideration of these facts it would seem reasonable to suggest that in a large percentage of psychotics, especially those of the schizophrenic type, and in a large percentage of the anxiety neurotics, ingestion of milk is followed by a colloidoclasia, the

occurrence of this colloidoclasia being dependent on a change in the equilibrium between vagus and sympathetic tonus which occurs in these individuals.

There is, however, another fact of considerable importance. An abnormal response to postural change was found in 87% of the psychotics. This response was purely a vaso-dilation. It was not possible, however, to influence this reaction by adrenalin injection.

In view of the reversal of reaction in response to ingestion of milk by adrenalin, these results with postural change would appear paradoxical if the reactions have the same origin. It may be that the ultimate result may depend upon adequate adrenalin dosage, or that in postural reactions one is dealing with a simple vaso-dilatation and simple volume circulatory disturbance, whereas in the hæmoclastic reaction there is probably a second factor of the nature of a colloidoclasia.

This work has been conducted in the Central Laboratory of the London County Mental Hospitals, Maudsley Hospital, and I would express my indebtedness to the Director, Dr. Golla, for his helpful criticism and advice, and to Dr. Mapother and his medical officers for facilities to examine their cases, and to the volunteers from the hospital staff who have provided me with normal controls.

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Suggestions on the Psychology of Mental Deficiency⁽¹⁾. By HUBERT C. BRISTOWE, M.D.Lond., Medical Officer to Yatton Hall Institution for Mental Defectives, Somerset County Council.

IN his *Creative Evolution*, Bergson sets out to prove the thesis that instinct and intellect tend to develop along parallel lines, and that instinct only develops at the expense of intellect, and intellect only develops at the expense of instinct. Though this appears to me to be undoubtedly correct, it does not include the complete truth. For I find on studying the matter more deeply that intellect

⁽¹⁾ Being the Presidential Address to the Bath and Bristol Branch of the British Medical Association, June, 1924.