A STUDY OF THE HAEMOCLASIC CRISIS TEST FOR LIVER FUNCTION:

WITH SPECIAL REFERENCE TO THE LEUCOCYTIC
CHANGES.

BY

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IN 1920 Widal, Abrami, and Ivanescu¹ described a new test for liver function under the title "digestive haemoclasis." From experiments on dogs they claim to have proved that during protein digestion the peptones absorbed from the intestine are arrested by the liver ("proteopexic function") and do not reach the general circulation. In the normal dog the protein meal excites a digestion leucocytosis. On the other hand, intravenous injection of peptone into the systemic circulation in a fasting dog immediately provokes a "haemoclasic crisis"—namely: (a) leucopenia with a relative lymphocytosis; (b) fall of blood pressure; (c) hypercoagulability; (d) decrease of the refractometric index of the serum. These data were then applied as a clinical diagnostic test for hepatic insufficiency in man, on the theory that in liver disease the proteopexic function is impaired or destroyed and allows a haemoclasic crisis to develop after a protein meal. In practice the test is extremely simple, serial leucocytic counts being all that are required according to Widal. Estimations of blood pressure, coagulation, and refractometric index are not essential for diagnosis.

Preliminary starvation of the patient is essential (five hours at least). A leucocytic count is done and the standard test meal, which is 200 c.cm. of milk, is immediately given. The counts are repeated every twenty minutes for one hour. In liver disease a leucopenia of 30 to 70 per cent. with a relative lymphocytosis develops and reaches its maximum in twenty to forty minutes after the test meal. A leucocytosis appears about one and a half hours after the milk. Associated with the leucopenia there is a fall of blood pressure (10 to 20 mm. Hg), hypercoagulability, and a fall in the serum index. With 8 grams of dried casein (=200 c.cm. milk) the reaction is intense and precocious. Widal found that in 39 cases of definite liver disease 38 gave a positive reaction. He claims that the test is extremely sensitive, being capable of detecting "latent hepatism" and also liver damage due to salvarsan compounds. It is negative in acholuric jaundice. In 11 normal persons the test was negative; in 9 a leucocytosis appeared and in 2 no appreciable change; in all the blood pressure rose 10 to 30 mm. The reaction was also negative in diseases of the alimentary tract and in other conditions in which the liver was intact.

In criticism of Widal's work it may be said that although the accuracy of the test depends entirely on the technique employed in counting and the interpretation of the results therefrom, yet he omits to describe his technique and gives no protocols of his counts. Only one count is done before the test meal, and this is accepted as a fixed point on which to interpret the subsequent variations; but this assumes that in a starving person the number of leucocytes is either constant or if fluctuations occur they are so small as to introduce no serious error. The extensive literature provoked by the test is open to the same criticism, and is itself sufficiently conflicting to throw doubt on the value of the reaction as a means of clinical diagnosis in hepatic insufficiency.

Observations on the Haemoclasic Crisis.

My own observations refer to the leucocytic changes in (1) cases of liver disease, including acholuric jaundice and persons treated with novarsenobillon (N.A.B.), after 200 c.cm. of milk; (2) normal persons after 200 c.cm. of milk; (3) normal persons fed with substances other than milk; (4) normal persons after the local application of cold; (5) normal persons during physiological rest. Blood

pressure readings were taken in some cases. No records were made of coagulation or serum refractometry.

Conditions of Experiment and Technique.—All subjects were starved of food and fluid overnight. To eliminate possible effects of periodicity, temperature, and exertion the zero count was made between 9 and 9.30 a.m. in a room of uniform temperature. Patients were examined in bed; normals were kept in a position of complete rest for at least half an hour before zero count.

No. 1 Laennec's cirrhosis. Male. 54 years. Confirmed post-mortem.

Time	0'	20'	40'	70'	Remarks
Total leucocytes	4450	4600	3700	3700	Leukopenia = 17% in 40'

Differential Count. Relative increase of polymorphs by 6% at leukopenia with relative and absolute decrease of lymphocytes.

No. 2 Obstructive Jaundice. Female. 57 years. Post-mortem—cancer head of pancreas; obstruction of common bile duct; metastases in liver.

Time	0'	20'	40'	70'	Remarks
Total leucocytes	4150	4700	3450	5400	Leukopenia = 17% in 40' Leucocytosis in 70'

Differential Count. Slight and irregular oscillations throughout but no evidence of lymphocytosis.

Blood Pressure. Rise of 6 mm. at leukopenia otherwise no change.

No. 3 Catarrhal Jaundice. Male. 24 years. Recovery.

Day of disease	0'	20'	40'	70'	Remarks
13 th	7200	6300	5950	7350	Deep jaundice. Leukopenia 17% in 40'
22 nd	8050	8200	8000	8900	Slight jaundice. Leucocytosis in 70'
34 th	7100	6900	7000	7750	No jaundice; Urine—no bile constituents Leucocytosis in 70'
2 months later	6500	5150	5300	6750	At work 2 months. No jaundice. Urine—nil. Leukopenia = 21% in 20'

Differential Counts. On 13th and 22nd days showed irregular oscillations but no lymphocytosis.

No. 4 Acholuric Jaundice. Female. 6 years. Anaemia, splenomegaly; increased fragility of red cells. Urine—excess of urobilin. No other bile constituents. Two tests on consecutive days.

Time	0'	20'	40'	70'	Remarks
Total leucocytes	9000	7050	8200	8500	Leukopenia = 22% in 20'
"	9000	7350	8150	7150	Leukopenia = 16% in 20'

Differential Count. There was a slight relative lymphocytosis (4%) coinciding with leukopenic phase in first test.

No. 5 Jaundice after N.A.B. Male. 26 years. Primary syphilis. Course = 2.2 grms. N.A.B. Jaundice appeared 6 months later.

Time	0'	20'	40'	60'	Remarks
Total leucocytes	4100	3300	3650	3600	Deep jaundice. Leukopenia 19% in 20'

Blood Pressure. No appreciable change.

No. 6 Jaundice after N.A.B. Male. 27 years. Course = 2.2 grms. N.A.B. Jaundice and ascites appeared 2 months later. Post-mortem—advanced subacute atrophy of liver. Tested three times; the second test 4 days after the first and the third 16 days after the second.

Time	0'	20'	40'	60'	80'	Remarks
Total leucocytes	2300	2250	1600	1600	1800	Leukopenia = 30% in 40'
"	2300	1500	1450	2250	2200	Leukopenia = 36% in 40'
"	3050	2400	2450	2750	—	Leukopenia = 21% in 20'

Differential Counts. In first test a relative increase of polymorphs by 10% at maximum leukopenia. In second test an absolute and relative decrease of polymorphs and a relative lymphocytosis (7%) at time of maximum leukopenia.

Blood Pressure. Maximum depression was 4 mm. and did not coincide with leukopenia.

No. 7 Primary Syphilis before and during N.A.B. course. Male. 34 years. Primary chancre otherwise in good health. No evidence of liver disease; never had jaundice. Urine—nil.

Time	0'	20'	40'	60'	70'	Remarks
Before treatment	6550	5100	5800	—	5850	Leukopenia = 22% in 20'
3 days after 0.45 grms N.A.B.	6650	6650	6500	—	6750	No change
1 day after a total course of 1.5 grms N.A.B.	6550	5500	6200	5450	—	Leukopenia = 16% in 20'

Blood was taken from the ear with the usual precautions. Preliminary experiments with the Thoma-Zeiss counting chamber showed that this apparatus is subject to considerable error. All readings were made with the Fuchs-Rosenthal counting chamber and Thoma-Zeiss leucocytic pipette. The blood was diluted 1 in 10; it was shaken vigorously for three minutes. The cells on ten squares were counted, this number being one-fifth of the total in 1 c.mm. of undiluted blood. The cover-glass designed by Allport² was used; owing to its thickness (4 mm.) there is no risk of bending and it can be placed in position with formation of Newtonian rings before the counting chamber is charged. The error with this technique does not exceed 2 per cent., but variations of less than 10 per cent. from the zero count were accentuated

as indicating no alteration in the number of leucocytes. The zero count was made immediately before ingestion of the test meal. For differential counts 500 cells were registered.

The Reaction in Liver Disease and after Novarsenobillon.

Observations were made in 7 cases with 200 c.cm. of cold milk, the maximum leucopenia recorded within one hour being taken as a positive result. The clinical details of the cases and the results of the test were as shown in the protocols (p. 914).

Examination of the protocols shows that in 4 cases (Nos. 1, 2, 5, 6) of obvious liver disease the test gave consistent results as indicated by a leucopenia of 17 to 36 per cent. in twenty to forty minutes, although in the severe and fatal case of obstructive jaundice (No. 2) the reaction is not very convincing, an echelon curve being present, which Widal regards as indicating improvement in liver insufficiency. The serial tests in catarrhal jaundice (No. 3) are conflicting. There is a positive reaction during the period of severe icterus, followed by a negative at a time when it is extremely doubtful if the liver function has been restored to normal, while two months later haemoclasis recurs in the absence of any clinical or urological signs of hepatic disturbance. The attempt to assess the value of the test during arsenobenzol treatment (No. 7) was frustrated by the presence of a positive reaction before treatment was commenced and in the absence of any signs of impaired liver function. The positive result in acholuric jaundice (No. 4) is contrary to Widal's statement that haemoclasis is absent in this disease.

Although continual fluctuations appeared in the differential counts there was no evidence of a consistent lymphocytosis, and in none of the cases in which blood pressure readings were taken did a hypotension develop. The results, on the whole, discount the value of the test as a means of diagnosis in liver insufficiency, and further investigations have been directed to elucidating the mechanism and significance of the leucocytic variations in the haemoclasic test by a study of the reaction in normal persons subjected to various stimuli.

The Reaction in Normal Persons.

The majority were student volunteers; only those were accepted who gave no history of liver disease and in whom the urine contained no bile constituents. The total examined numbered 23, of whom 8 were tested once and 15 two or more times, usually on successive days. The test meal was 200 c.cm. of cold milk, and the result was registered on the percentage variation in one hour. As the leucocytic response varied not only in different persons but sometimes in the same person from day to day, it was necessary to divide the results into four groups—namely:

(1) leucopenia, (2) no effect, (3) leucocytosis, (4) paradoxical. The protocols of these are shown in Tables I, II, III, and IV. The total examinations made were 40, and taking these as a basis there was a leucopenia 20 times (50 per cent.), leucocytosis 7 times (18 per cent.), and no effect 13 times (32 per cent.)—proportions which correspond fairly closely with the results of Schiff and Stransky³ in infants. Consequently alimentary leucopenia is not peculiar to infancy, as suggested by Glazer,⁴ but appears to occur as frequently in adults.

In the leucopenic series the extent of the fall varies from 10 to 28 per cent., often corresponding in the same person on consecutive days (Nos. 2, 3, 4, and 102). Usually the fall reaches its maximum in twenty to forty minutes, but in some cases the decline has set in or even reached its apogee ten minutes after the milk. Occasionally it is evanescent and only registered at one examination. The subsequent course of the curve is also variable, the count returning to the initial level or the fall persisting. The appearance of a leucocytosis after an hour is inconstant. Obviously in this group the curve is quite comparable in its general characters to that in liver disease, and it can be concluded that many normal persons react with a haemoclasic leucopenia. This agrees with Eisenstadt,⁵ who found a leucopenia in normal adults (number not recorded) after 200 c.cm. of milk, in spite of the fact that he accepted a variation of less than 17 per cent. in the count as due to experimental error. However, in 4 normals (Zehnter⁶) and in 3 normals (Mauriac and Ragot⁷) there was no leucopenia after

20 c.cm. of milk. Unfortunately the authors do not state what other change took place. Whether the leucopenia can be attributed to the milk at all seems extremely doubtful. In 32 per cent. of my tests the count remained more or less constant for an hour or longer, and in several cases reacting with leucopenia the response to a second test showed that the milk had either no influence or appeared

to produce a leucocytosis. Similarly it is difficult to accept the view that the milk produces a "digestion" leucocytosis—that is, a chemotactic response to the products of digestion. Only in 18 per cent. of tests did a rise, which sometimes was evanescent, develop in one hour. The leucocytosis which Widal found to appear in about one and a half hours is not confirmed by my protocols, as the results in seventy to ninety minutes are quite variable—a rise only occurring in about half the cases. If the rise represented a true reaction to the milk products absorbed during digestion it should appear in every normal person within a definite period of time. Its absence cannot be attributed to the small amount of milk given, for in 6 normal persons fed with 400 c.cm. the leucocytic response was similar to that following half the amount. Moreover, the times selected for doing the counts

TABLE I. Illustrating leucopenia after 200 cc. milk. (9 cases).

Case No.	0'	10'	20'	30'	40'	50'	60'	70'	80'	90'	Percentage Fall
2.	9400	—	7100	—	7200	—	—	9300	—	—	24% in 20'
"	9000	3900	—	4100	—	4400	—	4300	—	—	22% in 10'
3.	5600	—	5150	—	4350	—	5150	—	5700	—	18% in 40'
"	5800	5150	—	4900	—	5000	—	5150	—	—	15% in 30'
4.	8050	—	6050	—	6250	—	—	6250	—	—	25% in 20'
"	9650	7850	—	7250	—	—	—	7550	—	—	25% in 40'
5.	3600	—	3350	—	3250	—	3200	—	—	—	10% in 40'
"	4050	3450	—	3300	—	—	3700	—	—	—	19% in 30'
10.	4000	—	3850	—	3600	—	—	3750	—	—	10% in 40'
"	3950	—	3200	—	2850	—	—	3400	—	—	27% in 40'
12.	4300	—	3450	—	3550	—	—	3650	—	—	20% in 20'
13.	7650	—	5700	—	—	5500	—	6050	—	—	28% in 20'
14.	6450	6650	—	—	5650	—	5650	—	—	—	12% in 40'
23.	3650	—	4200	—	5050	—	5050	—	—	5700	25% in 20'

TABLE II. Illustrating no effect after 200 cc. milk. (5 cases).

Case No.	0'	10'	20'	30'	40'	50'	60'	70'	80'	90'
8.	5550	—	5350	—	5500	—	—	6150	—	—
"	5000	—	5050	—	4850	—	5000	—	—	—
19.	6000	6000	—	6200	—	6450	—	—	6300	—
24.	7350	—	6750	—	7450	—	—	7600	—	—
103.	4300	—	5300	—	4850	—	4300	—	—	4500
"	4800	—	5150	—	4700	—	4350	—	—	4300
18.	3300	—	3000	—	3150	—	—	2800	—	—

* Gradual fall to 5100 at end of 3 hours

TABLE III. Illustrating leucocytosis after 200 cc. milk. (3 cases).

Case No.	0'	20'	30'	40'	50'	60'	70'	80'	100'	Percentage Rise
11.	6100	6200	—	—	7700	—	—	6600	—	26% in 50'
"	6000	5900	—	—	6950	—	—	6600	—	16% in 50'
104.	4900	6150	—	—	5900	—	5300	—	4600	25% in 20'
7.	7050	6400	—	7800	—	8000	—	—	—	10% in 40'
"	7350	7650	—	7300	—	8900	—	—	—	12% in 60'

TABLE IV. Illustrating paradoxical results after 200 cc. milk. (6 cases).

Case No.	0'	10'	20'	30'	40'	50'	60'	70'	80'	90'	Result
1	7300	—	6100	—	5850	—	5100	—	5450	—	Leucopenia = 20% in 40'
"	4750	5350	—	4750	—	5050	—	6350	—	—	No effect. (Leucocytosis after one hour)
6.	3850	—	3750	—	4000	—	3900	—	—	—	No effect
"	3900	4050	—	3250	—	—	3550	—	—	—	Leucopenia = 17% in 30'
100.	3650	—	6150	—	4250	—	8900	—	3700	—	Leucocytosis = 68% & 144% in 20' & 60'
"	3500	—	3300	—	3350	—	3850	—	4400	—	No effect. (Leucocytosis after one hour)
9	5300	—	4500	—	4700	—	4700	—	—	—	Leucopenia = 15% in 20'
"	4350	—	4700	—	4650	—	5150	—	—	—	No effect. (Leucocytosis after one hour)
101	7000	—	6200	—	5400	—	6750	—	5900	—	Leucopenia = 25% in 40'
"	6700	—	7250	—	7000	—	10850	—	7350	—	No effect. (Leucocytosis after one hour)
"	6850	—	7200	—	6800	—	—	9300	—	—	No effect. (Leucocytosis after one hour)
102	7300	—	5800	—	5600	—	6100	—	8600	—	Leucopenia = 25% in 40' (Leucocytosis after one hour)
"	5800	4500	—	4500	—	5000	—	4900	—	—	Leucopenia = 22% in 10'
"	6000	—	10,000	—	5300	—	4600	—	5200	—	Leucocytosis = 67% in 20'

being arbitrary, it is difficult to avoid the impression that the oscillations are often more rapid than the observations indicate, and possibly the results in some cases might have been different if the counts had been made at shorter intervals, though technically it was impossible to do this and ensure accuracy.

In 10 cases selected from the three types of response the differential count revealed qualitative changes similar to those found in liver cases—that is, there was no schematic alteration. The blood pressure taken in 4 cases (2 leucopenia and 2 leucocytosis) showed oscillations of a few millimetres bearing no relation to the leucocytic curve. However, there are some investigators who find that leucocytosis does develop in normal persons. Holzer and Schilling⁸ say that a digestion leucocytosis follows 200 c.cm. of milk or an equivalent amount of carbohydrate in normals. Feinblatt⁹ tested 80 normal adults with 200 c.cm. of milk, and in every case a leucocytosis appeared, reaching its maximum after an hour. All the curves were surprisingly similar in character, and though the first count was made half an hour after the test meal a fall below the initial count was never registered. C. M. Wilson¹⁰ also records a leucocytosis within one hour after 200 c.cm. of milk in 30 normal students. Nevertheless, in my observations there is no evidence that the ingestion of 200 to 400 c.cm. of milk produces a specific effect on the leucocytic content of the peripheral capillary blood, either in the form of a "digestion leucopenia" or a "digestion leucocytosis."

The Reaction in Normal Persons to Other Substances.

1. *Distilled Water.*—Under usual conditions of experiment 7 normal adults were given 400 c.cm. of cold distilled water. The results (Table V) show that one case reacted with a rise which reached its maximum of 23 per cent. in forty minutes, and in 6 cases a leucopenia of 11 to 32 per cent. developed in twenty to forty minutes. The differential counts in 4 cases gave similar results to those obtained in the milk cases. Evidently there is no essential difference in the response of normal persons to milk and water, as both substances give contradictory results and the curves are similar in their degree and periodicity of variation. There can hardly be any question of a chemical

TABLE V. Illustrating leucocytic variations after 400cc. distilled water.

Case No.	0'	10'	20'	30'	40'	60'	70'	Result.
10.	4400	-	3650	-	3650	-	3200	Leukopenia = 11% in 20'
12.	6300	-	4300	-	4250	-	3700	Leukopenia = 32% in 40'
13.	8000	-	6100	-	6450	-	6300	Leukopenia = 24% in 20'
14.	8050	7700	-	6200	-	7300	-	Leukopenia = 23% in 30'
16.	6200	-	4500	-	4350	-	3600	Leukopenia = 30% in 40'
17.	4950	-	3900	-	3700	-	4250	Leukopenia = 25% in 40'
25.	4850	-	5800	-	5950	-	4850	Leukocytosis = 23% in 40'

action as the cause of the leucocytic fluctuations following distilled water, and blood dilution is eliminated by the development of a rise in Case 25, and also by comparing the reaction to 200 c.cm. of milk and 400 c.cm. of distilled water in the same person. This was done in 4 cases (Nos. 10, 12, 13, 14). All reacted with a fall to both substances, but in Nos. 10 and 13, the comparative curves of which are shown in Chart A, the fall was greater with milk than with water. These results agree with the work of Moutier and Rachet,¹¹ who tested 10 persons with distilled water. A fall followed in 6 and a rise in 4, while in 9 of the cases the milk curve ran parallel to the water curve.

2. *Casein.*—Three normal adults were fed on 30 grams of dried casein (=800 c.cm. of milk). In 2 cases there was a fall of 10 and 20 per cent. in twenty and forty minutes respectively, followed by a definite rise in seventy minutes in both of them. In the third case the count remained constant until the examinations ceased in eighty minutes.

3. *Butter-fat.*—One normal adult was fed on 30 grams of butter-fat. The leucocytic count remained unchanged during the test of seventy minutes. Therefore the tests with casein and butter-fat confirm the opinion that the leucocytic fluctuations do not depend on a chemical stimulus following absorption of the milk products.

The conclusions drawn from all the experiments are that

the leucocytic variations are quite independent of the ingestion of food or fluid in the amounts given, and do not represent either a response to any chemical stimulus provided by the products of digestion or the effect of blood dilution following absorption of fluid.

The Reaction to the Local Application of Cold.

It is generally thought that the external application of cold, such as a cold bath, produces a leucocytosis. But Widal, Abrami, and Brissaud¹² maintain that exposure to cold is followed by a haemoclastic shock identical with that occurring in hepatic insufficiency. In dogs immersed in a bath at 2-3° for fifteen to forty-five minutes the crisis developed in ten to fifteen minutes from the moment of immersion and persisted for half an hour to an hour. Tinel and Santenaise¹³ say that after freezing the finger with ethyl chloride for a few seconds there is an immediate fall in the leucocytic count by 2,000 to 4,000, but whether this occurs in the peripheral circulation generally or only in the domain of application is not made clear by the authors. On the other hand, Jolly and Saragea,¹⁴ working with rats, found that leucopenia followed exposure to hot air. In my experiments the arm was immersed for twenty-five minutes in a water-bath at 8° C., a leucocytic count having been done previously from the finger. At the end of twenty-five minutes another count was done with the arm still in water; subsequent counts after removal from water. All counts were done locally—that is, from a finger of the

TABLE VI. Illustrating leucocytic variations after the local application of cold.

Case No.	Before Immersion	Immediately after	10'	30'	40'	50'	60'	70'	80'	Result
74.	6650	7350	-	7700	-	6650	-	-	-	Leukocytosis = 16% in 30'
53.	5350	5800	5200	5650	-	5700	-	-	-	No effect
54.	5100	6100	7050	-	5800	-	-	8100	-	Leukocytosis = 40% in 10'
55.	6050	4750	4500	-	3950	-	5350	-	5700	Leukopenia = 35% in 40'
56.	8150	6500	6900	7050	-	7350	-	-	-	Leukopenia = 20% (immediately after)
57.	6050	6250	6700	-	7250	-	8350	-	7850	Leukocytosis = 38% in 60'

immersed limb. Percentage variations were reckoned on the alterations appearing between zero and up to one hour from the time immersion ceased. Six normal adults were tested (Table VI). Three reacted with a leucocytosis, two with leucopenia, and in one there was no appreciable change. In 4 cases (Nos. 54-57) the differential counts revealed no consistent alterations. It is evident that under the conditions of experiment employed the local application of cold has no specific effect on the number of leucocytes—the cases falling into the three categories which have been described in connexion with alimentary stimulation. The results also appear to eliminate the possibility of the milk

CHART A. Leucocytic curves after 200cc. milk and 400cc. distilled water in same person.

or distilled water, which were given cold, exerting any specific influence on the leucocytic count by means of their low temperature.

Leucocytic Variation during Physiological Rest.

The conflicting results obtained suggest that there must be some other factor wholly or partly responsible for the oscillations observed after the various stimuli used. It has already been said that Widal—and indeed nearly all writers on the subject of haemoclasia—has assumed that during physiological rest the number of leucocytes in the peripheral blood remains practically constant until the alimentary or other stimulus is applied. Consequently they have accepted a

single pre-test count as representing a fixed point, subsequent variations from which are held to be the response to the stimulus. But my observations show conclusively that leucocytic equilibrium is not necessarily maintained in the absence of alimentary stimulation. I have examined 10 normal adults during physio-

logical rest over periods ranging from eighty minutes to two hours and twenty minutes, the protocols of which are shown in Table VII. To make the readings comparable to my other observations the zero count is taken as a fixed point and the percentage variation calculated during the succeeding hour. If, however, the difference between the maximum and minimum counts over the whole period of observation is taken, the variation, in some cases, would be greater. The protocols show that during the first hour a fall occurred in 3 cases, a rise in 1 case, and in 6 cases the leucocytic content remained stable. Therefore each case falls into one of the three groups found after stimulation. Moreover, when oscillations occur during physiological rest, they are similar in rapidity and extent to those following milk, etc. This is confirmed by comparing the "rest" curve and "stimulation" curve in the same person, which was done in 7 cases. In 4 cases the milk curve and the "rest" curve ran parallel in 2, while the distilled water curve and the rest curve were similar in one of the three cases tested. This is illustrated in Chart B. Evidence of

oscillation during physiological rest also appeared in persons subjected to the haemoclastic test. In all my protocols only one pre-test count has been recorded, but in 7 cases two counts were made at intervals of fifteen to twenty-five minutes, the test meal being given immediately after the second count. The percentage difference between the two counts in the 7 cases was: -13%; -10%; -9%; +16%; -7%; +4%; +30% (the minus sign indicates that the first count was the higher of the two; the plus sign the reverse). If the first count had been accepted as representing the leucocytic content immediately before the test meal the results would have been altered in 5 of the 7 cases.

Fluctuation in the number of leucocytes apart from food has been noted by several observers. Mauriac and Cabouat,¹⁵ examining the leucocytic variations in two normal adults, not in absolute physiological rest, over a period of fifteen hours at intervals of thirty minutes, found considerable and sudden oscillations in the count. Servantie, Panzatz, and Monod,¹⁶ in one normal person during starvation, record fluctuations of 2,000 to 3,700 in counts done every ten minutes. Kobryner¹⁷ concludes, from numerous observations made over long periods, that

during physiological rest there is a leucocytic curve composed of large waves, which in their course show subsidiary variations, the latter sometimes exhibiting considerable oscillations. It is obvious, therefore, that the single count before stimulation cannot be accepted as necessarily indicating a state of equilibrium. Frequently it is only an index of the number at the particular moment, and represents nothing more than a point on one of the oscillations of the physiological rest curve.

Furthermore, a study of the total series of pre-test counts in my observations indicates that the particular result obtained in the haemoclastic test depends on the phase of the normal curve at the moment of test. The

lowest counts were between 3,000 and 4,000, the highest between 8,000 and 9,650, and these represent the extreme limits of undulation in the series of normal persons. In every count above 8,000 the test was followed by a considerable fall—that is, at the time when the curve was presumably at its zenith—while the variable results

following low and intermediate counts appear to be due to the particular direction pursued by the curve during the period of test. But my observations also show that phases of equilibrium do occur, and are associated more especially with relatively low counts. Possibly this may explain why Friedemann and Nubian¹⁸ failed to obtain a fall in cases of leucopenia due to various causes and in which they concluded a permanent state of haemoclasia existed. Even assuming that the stimuli I have used do influence the number of leucocytes, the result must be considerably modified by the physiological variations, and it would be necessary to eliminate the latter to arrive at the effect of the stimulus. But it has been shown that the two curves are so similar as to be practically identical, and therefore I think that the stimuli employed have no effect on the number of leucocytes in the peripheral blood—the variations recorded in the experiments being nothing more than the fluctuations of physiological rest. Kobryner's work confirms this, for he has shown that food, fluid, movement, etc., do not influence either the total leucocytic curve or its

phases. Consequently I think that there is neither a "digestion leucocytosis" nor a "digestion leucopenia," the results recorded as such in the literature on haemoclasia 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.

CONCLUSIONS.

1. Widal's haemoclastic test for liver function lacks a theoretical basis, and in practice is of no value in the diagnosis of hepatic insufficiency.

2. During physiological rest the number of leucocytes in the peripheral blood is subject to considerable and rapid fluctuations, though there are phases in which a state of equilibrium exists.

3. There is no evidence that the ingestion of milk, casein, butter-fat, and distilled water in certain quantities, or the local application of cold, influences the leucocytic content of the peripheral capillary blood, the oscillations following these stimuli being the same as the physiological variations during rest.

4. The phenomena of "digestion leucocytosis" and "digestion leucopenia" described in connexion with the

TABLE VII. Illustrating leucocytic variations during physiological rest.

Case No.	0"	20"	30"	40"	50"	70"	80"	90"	100"	110"	120"	130"	140"	Result.
15.	5550	—	3750	—	4300	—	4050	—	—	—	—	—	—	Fall = 32% in 30"
	4750	—	3600	—	4150	—	4400	—	—	—	—	—	—	Fall = 24% in 30"
16.	6650	—	4700	—	5550	—	5200	—	—	—	—	—	—	Fall = 30% in 30"
17.	4200	4000	—	4250	—	—	5250	—	—	4850	—	5350	—	No change in first hour
18.	3200	3100	—	—	3250	3600	—	—	3400	—	—	—	—	No change
21.	5300	5300	—	—	6100	—	—	5900	—	—	—	—	—	Rise = 15% in 50"
23.	4400	4100	—	—	4650	—	—	4350	—	—	4550	—	—	No change
24.	6700	—	6200	—	6850	—	6500	—	5900	—	6150	—	—	No change in first hour
25.	5700	5650	—	5150	—	5500	—	—	—	5700	—	—	5250	No change in first hour
26.	8600	7600	—	—	6900	8050	—	—	7550	—	—	8100	—	Fall = 20% in 50"
30.	4450	—	4550	—	4450	4250	—	—	4550	—	—	—	—	No change

CHART B. Leucocytic curve during rest compared with curve after 200 cc. milk or 400 cc. water in the same person.

haemoclastic test are simply physiological variations and not the response to ingestion of foodstuffs.

5. The conflicting conclusions as to the value of the haemoclastic test arise from a failure to recognize that normally the leucocytic content is in a state of flux, and consequently that a single count made before the test does not represent a state of equilibrium.

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ACTINOMYCOSIS OF THE PLEURA.

AN ACCOUNT OF TWO CASES, WITH PATHOLOGICAL FINDINGS,

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THE two cases here recorded differ considerably in type, but the clinical features are worthy of study, as also are certain considerations which the cases raise as to the vexed question of the etiology of this disease.

CASE I.

A woman, aged 20, an assistant in a drapery shop, had always lived in Newcastle. In October, 1921, she complained of pains in the back and general malaise, and about a fortnight later was laid up with "pleurisy" on the left side and pain in the left shoulder. She appeared to get over this, but, not gaining strength, reported to her doctor late in November, and was found by him to have a coarse pericardial friction rub over the base of the heart. She was seen in consultation with Dr. S. Worthington on December 10th, on account of the development of a lump above the left breast. She was pale and somewhat hectic, had a temperature of 100° F., and a pulse of 120. There was an oval swelling about half the size of a hen's egg in relation to the anterior end of the second left rib and second interspace. The swelling was tender, elastic in consistency, not red and not hot; the skin could be moved freely over it, but it was fixed to the deeper structures. There was no pulsation, nor impulse on coughing. Immediately under the swelling there was some diminution of the breath sounds and of the vocal resonance and fremitus, otherwise there were no abnormal signs in the lungs. At the right border of the sternum, in the second and third interspaces, a well marked systolic bruit was audible, the characters of which suggested that it was exocardial. The heart appeared normal in size and position, and there were no other murmurs. Nothing abnormal was found in the other organs.

No definite diagnosis was made and the case was admitted to hospital. Slight fever continued, and the lump gradually increased in size. At the end of a fortnight the lump had doubled in size, and the skin was becoming stretched over it and red in places. The swelling was then explored with a hypodermic syringe, and a little blood withdrawn, but no pus. The site of the needle puncture failed to heal, and within forty-eight hours began to discharge typical oily pus, containing opaque greyish-white granules. Stained specimens revealed the branching mycelia of actinomycetes, and there was also definite evidence of clubbing. No other organisms were found, and pure cultures were obtained anaerobically in 2 per cent. glucose agar, growth being obtained in all of six tubes inoculated. The organism also showed feeble powers of growth under aerobic conditions, two colonies developing on the surface of one of two agar slopes inoculated. A few spores occurred in the stab cultures on the fourteenth day.

The swelling continued to increase rapidly in size, and discharging sinuses appeared in several places; the breast became invaded, and the appearance shown in the photographs was gradually assumed. Surgical intervention was discussed, but abandoned by the surgeons in view of the evidence of involvement of the

FIG. 1.—Early stage.

FIG. 2.—Later stage.

mediastinal tissues. As alternatives various lines of treatment were followed, namely—

1. Ionization of the growth with potassium iodide.
2. An autogenous vaccine of the streptothrix was prepared from the discharge and administered in increasing doses for many weeks.
3. Potassium iodide was given by the mouth in large doses for several months: 60 grains three times daily were taken for a week at a time, followed by four days without the drug. No signs of iodism appeared at any time.
4. In place of ionization a long course of x-ray treatment was given. In all eighty-one applications were given with a 10-milliampère Coolidge tube and a 2 mm. aluminium filter, the tube distance being 12 inches.

None of these measures had any appreciable effect, the local condition remaining more or less stationary while general cachexia and emaciation advanced. Considerable glandular enlargement appeared in the left axilla, and two additional swellings appeared, one behind the right ear and one at the lower end of the left scapula. The former burst and discharged pus and then healed; no actinomycetes was obtained from the pus. The latter also broke down, and continued to discharge a small amount of pus. Gradually dullness developed over the greater part of the left lung and numerous crepitations were heard; immediately beneath the growth breath sounds were absent. For several months remittent pyrexia of moderate degree continued, and by January, 1923, the patient's condition was desperate. The spleen became enlarged, the anterior edge descending a handbreadth below the costal margin; the lower edge of the liver reached to the umbilicus. The urine contained a considerable amount of albumin, and there was intermittent diarrhoea. Cough, which had been almost entirely absent, increased a little, but there was very little sputum throughout.

Blood films showed secondary anaemia and a slight polymorphonuclear leucocytosis. Oedema of the left upper limb developed, and death occurred on March 8th, 1923.

Post-mortem Examination, March 9th, 1923 (Dr. A. F. Bernard Shaw).

On reflection of the skin containing the growth a wide area of suppuration was found extending from the left breast, the pus being green and odourless; the suppuration involved all the tissues of the chest wall, and the periosteum of the ribs was stripped and the bones eroded; the necrotic tissues were soft and ochre-yellow. There was gelatinous oedema of the anterior mediastinum, and the pericardial sac was obliterated by adhesions, which were not very dense. The left pleural sac contained abundant loculi of greenish pus, and the rest of the sac was obliterated by dense adhesions. The left lung was collapsed and airless, but contained no actinomycotic lesions. The glands at the root of the right lung were congested, and there was a small area of invasion of the hilus of this lung by the actinomycotic process. No other evidence of actinomycosis was found throughout the body. Though the liver and spleen were markedly enlarged, neither these organs, nor the heart or kidneys, showed naked-eye evidence of amyloid change, and the iodine test for amyloid degeneration was everywhere negative. Smears from the pus in the left pleura showed numerous streptothrix colonies.

CASE II.

A shipyard labourer, aged 42, was admitted to the Royal Victoria Infirmary complaining of "abscesses" over the right lower ribs, which had been present for three months.

History.—The patient stated that he had an attack of pleurisy six months before admission and that he had never been well since. At first he was off work for five weeks, and on attempting to start again he developed a second attack of pleurisy. Some time after this second attack the skin condition commenced with

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