

ON ALIMENTARY LEUCOCYTOSIS IN ITS RELATION TO
THE "CRISE HÉMOCLASIQUE" OF WIDAL.

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(Received for publication, May 29, 1922.)

During the last few years Widal and his coworkers have shown that under certain conditions a characteristic complex of changes occurs in the blood, a complex denoted by Widal as "*crise hémoclasique*," or "*crise colloïdoclasique*."

If a normal animal is injected intravenously with a certain dose of peptone the blood pressure will fall, the clotting time of the blood will be decreased, the number of leucocytes in the peripheral blood stream will decrease, and the refractive index of the serum will change. Widal (1) showed that in the normal dog after a protein meal higher cleavage products of protein, *i.e.* peptones or albumoses, are absorbed from the intestine, and the occurrence of these cleavage products in the portal blood stream can be demonstrated by physiological means. In normal animals these cleavage products cannot enter the general blood stream, since they are fixed in the liver ("*pouvoir protéopexique*" of the liver). If, however, the liver cells are damaged, they lose part of their fixing power, and albumoses or peptones will escape in the general blood stream and will produce changes in clotting time, in refractive index, in leucocyte count, and so forth, and thus a *crise hémoclasique* will ensue. Such a *crise hémoclasique* can also be produced in other ways; *viz.*, by injection of a specific protein into an individual sensitized to that protein (anaphylactic shock), by injections of certain colloids or of drugs, such as salvarsan, to predisposed individuals, etc. The main point of interest, with regard to the work published in the present paper, is the observation of Widal and his coworkers (2) that in cases of hypersensitiveness to certain foodstuffs in men the ingestion of these foodstuffs will produce a *crise colloïdoclasique* even in the absence of any demonstrable damage of

liver cells. The interrelation of symptoms of hypersensitiveness and of those of a *crise hémoclasique* is, according to Widal, so close that in doubtful cases the finding of a *crise hémoclasique* after ingestion of a certain foodstuff will give an indication as to the nature of the causative agent of the symptoms of hypersensitiveness (migraine, asthma, hay fever, etc.) and thus clear up the diagnosis. Since, according to Widal, the most prominent feature of the *crise hémoclasique* is the decrease in leucocyte count within 20 to 40 minutes after ingestion of the foodstuff or drug, in many cases the diagnosis of hypersensitiveness can be made from a series of leucocyte counts at intervals of 20 minutes before and after the ingestion of a certain foodstuff.

Two of the present authors have been interested in the study of the causes and treatment of bronchial asthma. They found that in many cases of bronchial asthma and hay fever there seems to be a relation between hypersensitiveness to tuberculin and hypersensitiveness to the known or unknown causative agent of the acute attacks of asthma, and were able to prove that in many of these cases a cure or a considerable relief of the asthmatic symptoms could be obtained by desensitizing the patients to tuberculin by means of repeated injections of small doses of this (3). In the course of this work, however, they obtained the impression that in some of the asthma patients who were resistant to the tuberculin therapy the cause of the attacks of asthma was to be looked for in the intestine, and later it appeared that in a number of other cases who were benefited by tuberculin treatment an intestinal factor also played an important part. In accordance with the current opinion the outbreak of attacks of asthma in these cases was ascribed to the ingestion of one definite protein (varying from case to case, but being specific for each patient), to which the patient in question was hypersensitive. It may be stated at once that this opinion proved to be incorrect. Observations and deductions on this point will be discussed in another paper. They only wish to emphasize here that they had at that time to face the following problems:

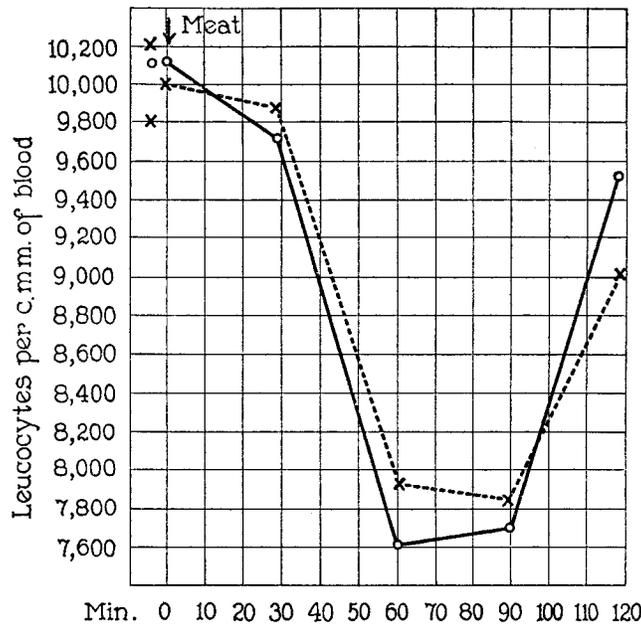
Taken for granted that certain symptoms of hypersensitiveness (attacks of asthma) in an individual are caused by the ingestion of a definite, but unknown, protein, how was this protein to be identified? Obviously the most exact way would be to feed the patient for a couple

of days on one protein only, changing after some days to another protein and going on in this way till the protein causing the attacks of asthma was found. This procedure, apart from offering considerable technical difficulties, would take a long time and, moreover, would suffer from the psychic factors which are of great influence in many cases of asthma.

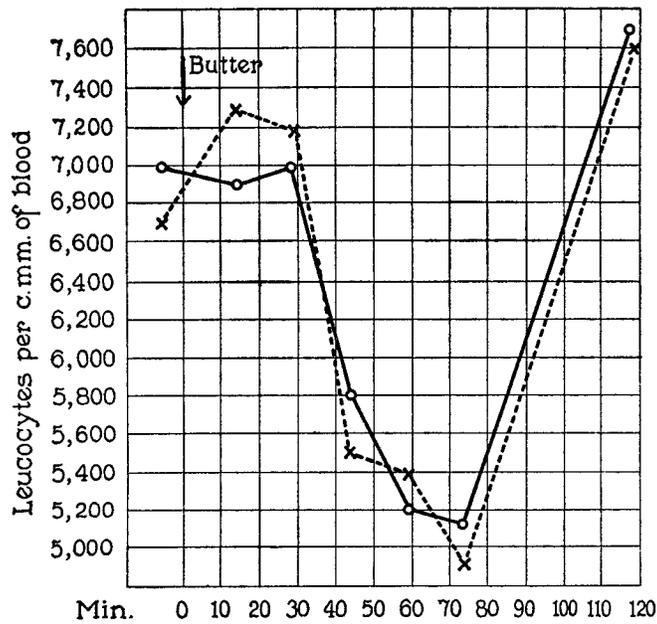
After having studied the work of Widal and his coworkers it seemed possible that the simple method indicated by him for the determination of the occurrence of a *crise colloïdo-clasique*, i.e. counting of leucocytes in the peripheral blood stream, might be adopted for our cases. Consequently a study was undertaken of the influence of ingestion of various proteins on the leucocyte counts in a number of asthma patients. After the first investigations it proved to be necessary to include a study of other foodstuffs, viz. fat and carbohydrates, and to extend our investigations to the behavior of normal men. The result of this work which includes 150 observations on 50 individuals is given below.

In our first tests we followed exactly the instructions given by Widal. Leucocyte counts were made in the morning before any food had been taken, then the patient took the food to be tested, and during the next 2 hours counts were made at intervals of 20 minutes. At first three kinds of test meals were used; viz., 300 cc. of milk, or three eggs, or 150 gm. of meat. Since, however, clinical observations had shown that in some of our asthma patients attacks of asthma were produced also by the ingestion of non-protein food, the investigation was extended to butter (100 gm.) and rice (150 gm.).

About the technique employed only a few words need be said. Blood was taken from the finger-tip and counts were made in a Bürker counting chamber (so that we used about the same method as Widal). In all observations to be reported here double counts were made; that is to say, either one investigator took blood in two pipettes and used two counting chambers and afterwards plotted the results obtained in each counting chamber separately, or blood was taken in two pipettes by two investigators each of whom made counts in one chamber. We wish to emphasize that the curves obtained in this way run almost entirely parallel; the technical error is certainly not higher than 5 per cent (Text-figs. 1 and 2), whereas those changes



TEXT-FIG. 1. Leucocytic counts made at the same time by two different observers. The arrow indicates the ingestion of 150 gm. of meat.



TEXT-FIG. 2. Leucocytic counts made in one experiment by one observer working with two pipettes and two counting chambers. The arrow indicates the ingestion of 100 gm. of butter.

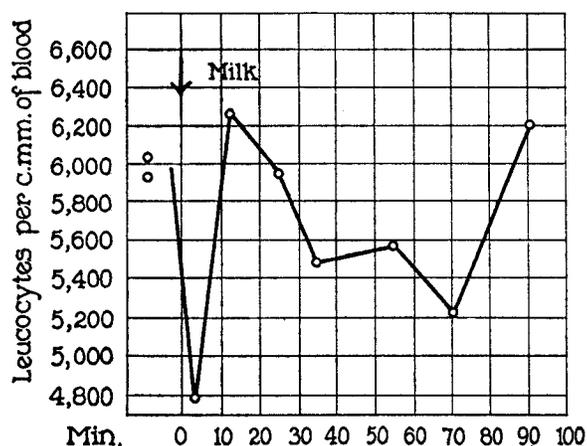
in leucocyte counts which are to be considered of clinical significance are about 20 per cent and higher, so that the method used, although not absolutely accurate, was sufficient for our purpose.

In nearly every case of asthma we found a *crise hémoclasique* after ingestion of some test meal but every case gave different results. Some reacted to milk only, others to meat, or butter, eggs, or rice only, still others reacted to butter and rice or to meat and eggs; in fact nearly every possible combination was found. Text-fig. 1 gives an instance of a definite fall in leucocytic counts after ingestion of meat, Text-fig. 2 after butter in another patient.

The fact that a fall in leucocytic count was found after ingestion of butter as well as after ingestion of protein showed that Widal's explanation as to the origin of the *crise* certainly could not hold good in our cases, since it is not very likely that ingestion of butter would cause after 20 minutes an increase in the albumose content of the portal blood stream. It is fair to state here that we are not the first to show that a fall in the number of leucocytes in the peripheral blood may occur after the ingestion of non-protein matter, as Widal has already found the same phenomenon after the ingestion of small amounts of glucose in diabetics (1).

Apart from this consideration, another observation was made which opened the question whether a leucopenia found in many of the cases in which the test meal consisted of protein could be explained on the same basis as in Widal's cases. Thus a considerable fall in the number of white blood cells (to more than 20 per cent below the original number) ensued within much less than 20 minutes after the ingestion of the food, so that it seemed hardly possible that in so short a time protein matter would be decomposed to albumoses and absorbed so as to produce a *crise*. This led us to decrease gradually the interval between the ingestion of the food and the first counting following it, so that in the end this interval was only 2 minutes. It was surprising to find that even in this last case a fall in the number of leucocytes occurred in some individuals. Text-fig. 3 gives an instance of such an incident. Before the ingestion of food the number of leucocytes was 6,000 per c.mm. The patient drank 200 cc. of milk, and 2 minutes afterwards blood was taken from a finger-tip; the number of white cells fell to 4,800; *i.e.*, a fall of about 20 per cent.

The end of this curve is equally interesting; it shows that 10 minutes after the ingestion of milk the number of leucocytes was about normal again; 10 minutes later, *i.e.* 20 minutes after the taking of milk, the curve shows a tendency to go down again, and gradually the number of leucocytes decreases and seems to reach a (second) minimum about 70 minutes after the drinking of the milk. Text-fig. 4 gives a similar curve after a test meal of rice. The original count of white cells was 9,000 in this case; 2 minutes after the eating of rice the leucocytes fell to 6,800, *i.e.* a drop of about 25 per cent; during the next three counts, made at intervals of 3 minutes, they increased to about 8,200,

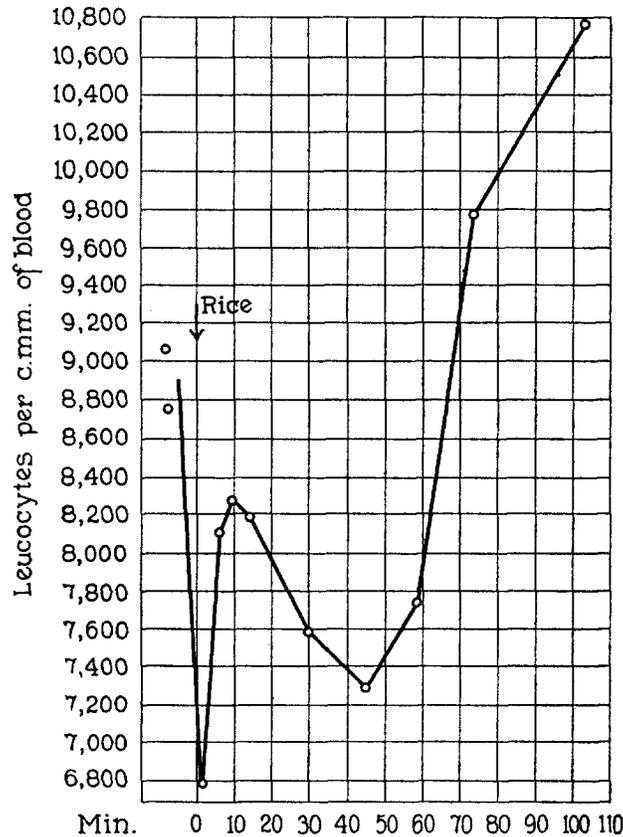


TEXT-FIG. 3. Decrease in the number of leucocytes within 2 minutes after the ingestion of milk. The arrow indicates the ingestion of 200 cc. of milk.

then followed a second drop, and subsequently a rise, far above the original number. This rise in leucocytes, which often occurs if counts are made during a sufficiently long time, is nothing else than the so called physiological leucocytosis after ingestion of food and will be left out of consideration, since the phenomena which are of interest here all occur before this physiological leucocytosis sets in.

The fact that a fall in number of white cells often occurs within 2 minutes after the ingestion of food excludes any possibility that *this* fall has a connection with absorption of cleavage products of the food administered; very likely it is caused by some reflex action from the alimentary canal, and we consider it highly probable that the phenom-

enon is only an expression of a change in the distribution of the white cells in the different regions of the blood stream. This opinion is strengthened by two observations; first, it was found that during this initial fall no characteristic change in the leucocyte formula



TEXT-FIG. 4. Decrease in the number of leucocytes within 2 minutes after the ingestion of rice. The arrow indicates the ingestion of 150 gm. of cooked rice.

occurs, and secondly, it was shown that the red cells show a decrease in number nearly parallel with that of the white cells.

The considerations mentioned made it probable that the fall in the number of leucocytes observed in the asthmatics was not to be considered as an expression of a pathological state in the individual

tested, but merely as a physiological occurrence. The correctness of this surmise was proved by finding exactly the same decrease in the number of leucocytes in normal individuals after a test meal of milk, meat, rice, and other foodstuffs. From this investigation on normal individuals it was found that in many cases a curve obtained by plotting the number of leucocytes of the peripheral blood counted at very short intervals after the ingestion of food will show the characteristics found in Text-fig. 3; *i.e.*, shortly after the test meal a sharp fall in white cells occurs. As this fall may last a few minutes or even a little longer, it is uncertain whether it will be detected if counts at intervals of 20 minutes are made. After the first fall comes a rise to about the original level, and subsequently there is a gradual fall followed by a final rise (physiological leucocytosis).

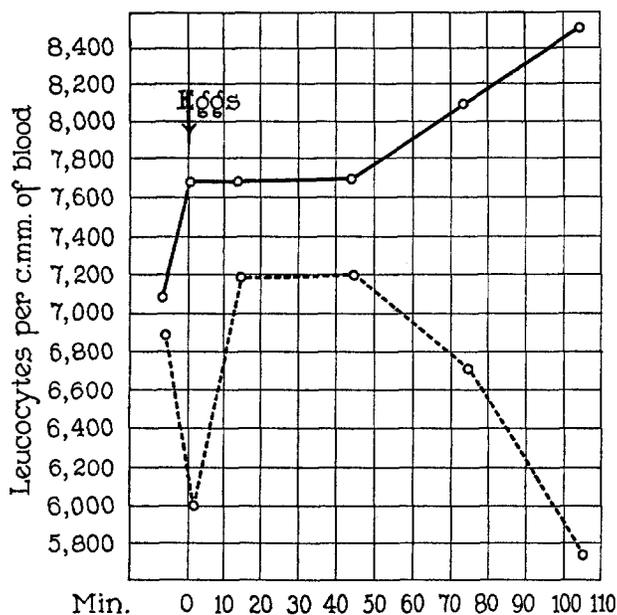
It must be stated, however, that although this type of curve frequently occurs, in other instances the curve may show a different shape. There may occur a sharp rise after some minutes, instead of a fall, or the second minimum may be absent and even replaced by a rise, and so forth.

The facts described above are in agreement with the findings of Dorlencourt and Banu (4) who studied digestive leucocytosis in normal infants. They found a decrease in leucocytes immediately after the ingestion of milk; this was followed by an increase and subsequently by a second decrease. Only after this period had passed, did the real digestive leucocytosis set in.

Adelsberger (5) and Schiff and Stransky (6) also found in normal infants and children a decrease in the number of leucocytes of short duration following shortly after the ingestion of milk and other proteins, fats, and carbohydrates.

After it was found that in many cases ingestion of food, either of protein or of non-protein nature, may cause an initial fall in the number of white cells, which may last for 5 to 20 minutes, and which may be followed first by a rise and afterwards by a second fall eventually followed by a second rise, and since it was also found that the time during which these falls and rises are demonstrable may vary from case to case, the question arose whether curves obtained by plotting the results of blood counts made at intervals of 20 or 30 minutes gave a true picture of the change in the number of leucocytes occurring in

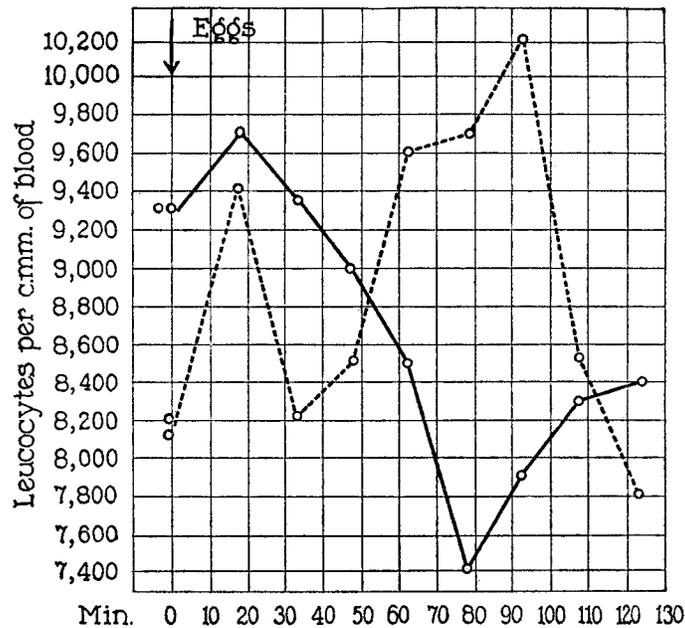
the blood. In fact it seemed very likely that results obtained in this way might be to a large degree dependent on mere chance, and the finding of a decrease of the number of white cells after the ingestion of some foodstuff could not be considered as an indication of the presence of a *crise hémoclasique* nor be an indication that this particular foodstuff was in any way related to pathological phenomena occurring in the body. To test this supposition control estimations



TEXT-FIG. 5. Leucocytic counts made by the same observer with the same food on the same patient but on 2 different days. The arrow indicates the ingestion of three eggs.

were carried out on a number of patients and normal individuals. In these cases blood counts were made at intervals of 20 minutes after the ingestion of eggs or other foodstuffs, and 2 or 3 days later the tests were repeated on the same individual, with the same foodstuffs. The curves obtained on 2 different days sometimes agreed with each other, but often there was a considerable disagreement (Text-figs. 5 and 6). In Text-fig. 5 the first observation revealed an initial fall of leucocytes of about 13 per cent followed by a second fall of

about 20 per cent. In the second observation on the same person with the same food, only a rise in leucocytes was found. Text-fig. 6 shows a marked discrepancy between the findings on 2 different days. Attention should be called to the fact that these discrepancies cannot be ascribed to technical errors since two estimations on the same patient on the same day, even if the countings were made by different investigators, showed a nearly complete agreement (see Text-fig. 1).



TEXT-FIG. 6. The same experiments as in Text-fig. 5 but on another patient.

DISCUSSION.

Before entering into a discussion of the results we want to state that our work does not enable us to criticize Widal's conception of an interrelation of symptoms of hypersensitiveness, or anaphylactic shock, with the occurrence of a *crise hémoclasique* (*colloïdoclasique*). In all their former work and in the main part of their later work Widal and his coworkers founded their diagnosis of *crise hémoclasique* not on *one* symptom but on a complex of four or more symptoms. Later

Widal stated that since the occurrence of a fall in the number of white cells in the peripheral blood was the most prominent part of the *crise*, it was sufficient for the diagnosis of the same; we believe that our investigations have proved this last statement to be incorrect. We found a fall of white cells at various periods—from 2 to 50 minutes—after the ingestion of a meal in normal individuals and asthmatics. Moreover, a study of the blood pressure in some of these cases at short intervals showed an absence of a fall in pressure, so that there is no doubt that in our cases the fall of leucocytes in the peripheral blood was not an indication of the existence of a *crise colloïdoclasique*.

Soon after the appearance of Widal's papers on the *crise colloïdoclasique* a number of other workers started investigations as to the occurrence of *crises* in various conditions. Often the only criterion used for the diagnosis of a *crise* was the counting of the white blood cells. It is clear that as a consequence of our studies related above, those results can no longer be considered as conclusive. The fundamental observations of Widal and his coworkers, however, remain untouched by our work.

CONCLUSIONS.

Counts of the number of white blood cells at short intervals after the ingestion of a meal (meat, eggs, milk, rice, or butter) in normal individuals and in a number of asthmatics reveal the following facts.

As a rule, a sharp fall in the leucocytic curve occurs within 1 or 2 minutes after the meal; generally the curve rises within 10 to 20 minutes, but often a second fall follows 30 to 50 minutes after the meal. This may be followed by a slow rise in the curve (physiological leucocytosis). The first sharp fall is often accompanied by a similar decrease in red cells, the leucocytic formula is not changed, the blood pressure also remains unchanged, and this makes it probable that the leucopenia observed is only a manifestation of a change in distribution of the blood in different regions of the body.

Not infrequently the leucocyte curve after ingestion of food shows a form differing considerably from that described above. Counts of white cells made at intervals of 20 minutes in the same patient at different times but after ingestion of the same food show very differ-

ent leucocytic curves. Such counts do not give evidence of the existence of a *crise hémoclasique* and consequently cannot be used to identify the causative agent of cases of hypersensitiveness to foodstuffs or drugs. Whether such an identification can be obtained if instead of simply counting white cells the whole complex of symptoms originally described by Widal as characteristic for a *crise hémoclasique* is used, remains undetermined by our work.

BIBLIOGRAPHY.

1. Widal, F., Abrami, P., and Iancovesco, N., L'épreuve de l'hémoclasie digestive dans l'étude de l'insuffisance hépatique, *Presse méd.*, 1920, xxviii, 893.
2. Widal, F., Abrami, P., Brissaud, E., and Joltrain, E., Réactions d'ordre anaphylactique dans l'urticaire. La crise hémoclasique initiale, *Bull. et mém. Soc. méd. hôp. Paris*, 1914, xxxvii, 256. Widal, F., Abrami, P., Brissaud, E., Bénard, R., and Joltrain, Les modifications de l'indice réfractométrique des sérums, au cours des crises hémoclasiques, *Compt. rend. Soc. biol.*, 1914, lxxvii, 280. Widal, F., Lermoyez, Abrami, P., Brissaud, E., and Joltrain, E., Les phénomènes d'ordre anaphylactique dans l'asthme. La crise hémoclasique initiale, *Presse méd.*, 1914, xxii, 525. Widal, F., Abrami, P., and Brissaud, E., Étude sur certains phénomènes de choc observés en clinique. Signification de l'hémoclasie, *Presse méd.*, 1920, xxviii, 181.
3. Storm van Leeuwen, W., and Varekamp, H., On the tuberculin treatment of bronchial asthma and hay fever, *Lancet*, 1921, ii, 1366.
4. Dorlencourt, H., and Banu, G., La leucocytose digestive chez le nourrisson normal, *Presse méd.*, 1920, xxviii, 429.
5. Adelsberger, L., Die Verdauungsleukocytose beim Säugling, *Z. Kinderheilk.*, 1921, xxix, 156.
6. Schiff, E., and Stransky, E., *Jahrb. Kinderheilk.*, 1921, xcv, 286.