EDITORIAL

Diagnosis of Infectious Mononucleosis

CLINICIANS, serologists and hematologists have all written on infectious mononucleosis; therefore prerequisites for diagnosis have varied considerably, and reports of cases with "protean" manifestations and of epidemics, probably involving other diseases, have appeared.

When Pfeiffer\(^1\) described "Drüsenfieber" in 1889, examinations of stained blood smears were unknown.\(^2\) Beginning about 1908, relative lymphocytosis became a prerequisite for diagnosis. In 1932, the discovery\(^3\) of heterophil antibodies in the sera of patients with mononucleosis raised the question of the diagnostic significance of this phenomenon. Paul himself did not consider it a *sine qua non* for diagnosis.\(^4\) Until about 1952 this belief prevailed, although as early as 1939 Schultz,\(^5\) in Germany, had suggested using the heterophil antibody reaction to separate mononucleosis from clinically and hematologically similar diseases. His idea was ignored in his own country and apparently elsewhere.

In 1952 Hoagland\(^6\) and Bender,\(^7\) independently and without knowledge of Schultz' prior publication, recommended that mononucleosis be diagnosed only when both characteristic blood smears and heterophil antibody reactions were observed. Until recently the chief disagreement centered around the requirement of a positive heterophil reaction for diagnosis. Sturgis, in his well known textbook,\(^8\) stated: "It should be emphasized that in the presence of other convincing evidence of the disease, a negative Paul-Bunnell test should not by any means eliminate the diagnosis of infectious mononucleosis."

Only one relatively recent article will be mentioned—that of Cronk and Naumann, who reported on 1500 cases of mononucleosis.\(^9\) The heterophil antibody reaction was not a prerequisite for diagnosis; and, as usual under such circumstances, the authors termed mononucleosis "protean," and stated that "any bizarre group of symptoms and signs should arouse one's suspicions that the patient had mononucleosis."

Since 1956 there has been a new development. Articles have appeared in which the diagnosis of infectious mononucleosis was based chiefly, and even solely, on the heterophil test—in the absence of either characteristic clinical manifestations or of characteristic hematologic findings—i.e., infectious mononucleosis without mononucleosis! Durfey and Allen\(^10\) reported a case of "mononucleosis" in a 4 year old girl with the Guillain-Barré syndrome. The diagnosis rested solely on the detection of heterophil antibodies in the blood in a titer of 1:448 after guinea pig kidney absorption and an "associated" positive heterophil antibody reaction of spinal fluid. Hollister\(^10b\) reported on a 40 year old man who had no clinical manifestations of mononucleosis (except for fever); the diagnosis rested solely on heterophil antibodies in blood, in a titer of 1:224 after guinea pig kidney absorption and 1:28 after absorption with ox erythrocytes, and in spinal fluid, in a titer of 1:56, after guinea pig kidney absorption (1:14 after ox erythrocyte absorption). Neither patient had enlarged lymph nodes or other commonly observed clinical mani-
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festations. Neither patient had a characteristic blood smear; on the contrary, both had leukocytosis and marked polymorphonuclear leukocytosis.

Fish and Barton diagnosed infectious mononucleosis in a patient who died of acute myocardial disease. The initial clinical manifestations were those of pneumonia. The authors stated that the positive heterophil test was a surprise finding because lymph node enlargement and other common manifestations of mononucleosis were absent. Blood smears failed to disclose relative lymphocytosis. The diagnosis rested on a positive heterophil antibody reaction and on the result of autopsy. Histologic examination revealed numerous focal microscopic areas of necrosis of heart muscle fibers with partial to complete fragmentation of two to three fibers in each focus, with loss of nuclei and with some muscle fibers broken down almost completely. (The histopathology of mononucleosis is not pathognomonic; furthermore, the cardiac lesions described in this case have never been reported in mononucleosis and militate against the diagnosis.)

It is always unsound to base the diagnosis of any disease chiefly, or solely, on a nonspecific test; and the heterophil antibody reaction should be considered as such. Since positive heterophil reactions usually persist one to two months, a disease occurring weeks after a patient has had mononucleosis may be misdiagnosed by reliance on this test alone. Furthermore, Bender has recently reported on the anamnestic resurgence of the heterophil reaction in a patient who had pneumonia about three months after having mononucleosis.

It is indeed remarkable that a single criterion for diagnosis (the heterophil reaction) which has been regarded as unessential by some authors is now regarded as a sole and sufficient touchstone for diagnosis by others. Now that the persisting, and in my opinion erroneous, belief that the diagnosis of infectious mononucleosis can be made regardless of the heterophil antibody test has been joined by another fallacy (basing diagnoses chiefly or solely on serology), the need for sound criteria for diagnosis must be emphasized.

If diagnosis of mononucleosis is restricted to cases in which there are both a positive heterophil antibody reaction and a characteristic blood picture, there will emerge a clear (not "protean") clinical picture composed of cases which are unquestionably mononucleosis. The results of disregarding either the heterophil agglutination test or the characteristic blood picture as prerequisites for diagnosis will help to perpetuate considerable error and confusion in the further knowledge of this interesting disorder.

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REFERENCES

2. Schilling, V.: Personal communication to the author.
DIAGNOSIS OF INFECTIOUS MONONUCLEOSIS


LEUKEMOID REACTION AND LYMPHADENOPATHY IN BUTADION TREATMENT.

A patient suffering from acute rheumatism complicated by mitral valve disease was treated with 150 mg. of Butadion (sodium salt of Butazolidin) t.i.d. After 10 days she developed a marked leukopenia with the appearance of lymphoblasts in the peripheral smear and a differential count of 74 per cent cells of the lymphocytic series and 9 per cent monocytes. She also presented a generalized lymphadenopathy and an enlarged spleen. Three days after discontinuation of the drug the blood picture returned to normal, the spleen was no longer palpable and the lymph nodes disappeared. The leukemoid reaction and the lymphadenopathy were attributed to Butadion.—J. J. B.

A METHOD FOR THE CYTOCHEMICAL DEMONSTRATION OF SUCCINIC DEHYDROGENASE IN HUMAN LEUCOCYTES. E. J. de Souza and S. N. Kothare. From Topiwala National Medical College, Bombay, India. J.Histochem.& Cytochem. 7:77, 1959.

A method for demonstrating succinic dehydrogenase in human leukocytes with the use of p-nitrophenyl ditetrazole is described. In some of the leukocytes the formazan appeared as fine blue discrete granules or rods. It is proposed to extend this study to leukocytes in disease, with emphasis on the leukemias.—O. P. J.
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