

# BLOOD

## *The Journal of Hematology*

VOL. III, NO. 8

AUGUST, 1948

*This issue is the fourth part of the George Richards Minor Anniversary Volume.*

### INFECTIOUS MONONUCLEOSIS

By SIR HENRY TIDY

**E** PFEIFFER, a pediatrician of Vienna, gave in 1889 the first clear description of the disease which we are here discussing, under the title Drüsenfieber or glandular fever. He recognized that it was infectious and occurred in epidemics, described accurately the course of the enlargement of the cervical glands in young children, though he denied that other glands were involved, and stated that the glands never suppurated and that the prognosis was uniformly favorable.

Other observers in Germany quickly reported epidemics. Spread of its knowledge was somewhat slow but Park West (1896) reported an epidemic in America and Dawson Williams (1897) in England. The disease appeared to be successfully launched, but the diagnosis in sporadic cases rested on rather indefinite clinical features. It soon became confused with septic infections, and rapidly fell into disfavor. By 1900, it was practically dead. No mention of it appears in the Medical History of World War I, although information subsequently collected proves that it was not uncommon. It remained in suspended animation until 1920.

It is remarkable that during a period of thirty years, covering rapid developments in the knowledge of hematology, there should have been no systematic examination of the blood in a condition characterized by enlargement of lymphatic glands and often by enlargement of the spleen. To this lack of observation there is one exception. J. E. Burns, in 1908, fully described the lymphocytosis in two epidemics which he diagnosed as glandular fever, and published a well-documented report. The communication was completely overlooked and I was unaware of its existence until it was quoted by Bernstein (1940) in his monograph. Priority for the recognition of infectious mononucleosis clearly belongs to Burns.

Nevertheless, the establishment of the hematologic features of the disease did not come for practical purposes until 1920. Sprunt and Evans, in November 1920, published their observations on transient mononucleosis recorded in a series of six young adults during the previous six years. They recognized that the condition was infectious, observed the general glandular enlargement and gave an accurate though brief description of the various types of cells in the blood. They were clearly unaware of the existence of Pfeiffer's glandular fever, and thought they had discovered a new disease—a very venial mistake—and named it "infectious mononucleosis."

Authoritative articles soon followed. Longcope, in 1922, described fully the clinical aspects. He noted the long febrile period which might occur, and suggested the possibility of encephalitis in one case. Downey and McKinlay, in 1923, gave a complete description of the cells, beautifully illustrated, to which nothing effective has been subsequently added.

This One



N7W5-01G-SJCN

Meanwhile, Morley and I, in June 1920, recognized the existence of a transient lymphocytosis in the case of a boy whom we diagnosed as suffering from glandular fever, and we reported it with other evidence at a meeting of the Royal Society of Medicine in December 1920. At that time we were unaware of the article by Sprunt and Evans, but our attention was called to it when our article was in type and we formed the opinion that it was the same entity. In the course of the next few years, I saw a number of epidemics in boys' schools in England, and also cases in adults.

The recognition of the identity of infectious mononucleosis and glandular fever was not immediate in America, though Longcope used both terms in 1922, but it was probably general by 1925. The material on which the observations were based in America was predominantly from college students about the ages of 18 to 24 years, while in England it was supplied by resident preparatory school boys of 8 to 14 years. Although any type of the disease may occur at any age, there are considerable differences, when numbers of individuals are involved, between the clinical manifestations in the two age groups, the glandular enlargement being more marked at the younger ages. These factors no doubt account for the difference in nomenclature, for the disease is invariably known as infectious mononucleosis in America while in Britain it is generally named glandular fever. On the continent of Europe, the disease in young boys is now frequently described as "Pfeiffer's glandular fever" and that in adults as infectious mononucleosis, the identity of its infection in the two groups being accepted.

Neither resident college life nor resident preparatory schools are a part of the educational system in Europe outside Britain, and the recognition on the continent of a recoverable mononucleosis (other than that of whooping cough) was based on a different type of material, garbed in entirely other guise from that presenting in America and England. Deussing, in 1918, reported a series of cases with transient absolute lymphocytosis under the title "Über diphtherieähnlicher Anginen mit lymphatischer Reaction" (Angina resembling diphtheria with a lymphatic reaction). But it was a communication by Schultz in 1922, to the Congress for Internal Medicine on "Monozytenangina" which first attracted attention to the subject. Both communications were based on the same type of material, being in regard to patients admitted to a hospital for communicable diseases who had membranous tonsillitis in which no diphtheria bacilli were found and in whom recovery followed without the injection of antitoxin.

The continental authorities went astray from the start. They were obsessed with the idea that the development of the lymphocytosis was due to a constitutional peculiarity of the patient resulting in a "lymphatic reaction" and that the same angina in other individuals would result in a polynucleosis. The possibility of infection was scarcely considered. Secondly, they embarked on a tedious and sterile dispute amongst themselves covering many years as to whether the cells were monocytes or lymphocytes. They failed to recognize that both types of cells were often present at the same time and that either type might predominate at different periods in the same patient. Not until Glanzmann's monograph in 1930 did they admit that monocytic angina was a manifestation of infectious mononucleosis and recognize the influence of an infective factor as opposed to a constitutional diathesis.

The definite differentiation of monocytic angina from diphtheria was a clinical advance of importance, and it is somewhat surprising that so little notice was taken of it in American and British literature. The identity of monocytic angina with infectious mononucleosis was accepted without discussion by the specialists on communicable diseases, but its existence was certainly not generally known to the profession in Britain, even to the commencement of World War II. A brief clinical description of this type follows.

Monocytic angina or the anginose type of infectious mononucleosis is characterized by the development of a tonsillar membrane or of ulceration. The membrane in typical cases is indistinguishable in appearance from that of diphtheria, although it is a true membrane, and it often forms very rapidly. Edema of the neck and tenderness of the enlarged cervical glands is common but suppuration is very rare. Edema of the fauces causes great discomfort and anxiety, but in spite of this and the high temperature, the patient does not appear to be severely toxic nor does he become so, although the membrane may persist for several days or more than a week before separating, after which the symptoms improve with surprising rapidity. There is a previous period of slight malaise for two or three weeks with increasing sore throat, and some glandular enlargement may or may not have been observed.

There is no proof that the disease is infectious at this stage or that it spreads in this form, although a number of cases may occur in a unit of young adults. It is possible that the angina is a complication connected with the leukopenia which is often present initially, before the mononucleosis develops.

An extensive epidemic in England in 1930 was characterized by the severity and long duration of the attacks and by the high proportion of adults involved. During an initial febrile period which might last several weeks, the constitutional symptoms in this type are often suggestive of typhoid, and the characteristic features of infectious mononucleosis absent. Glandular enlargement develops late and is rarely of any great extent. The blood at the onset may show a definite polynucleosis. In prolonged cases, this may be observed to subside and for a period the blood count may be strictly within normal limits or passing to a leukopenia. The mononucleosis tends to develop about the time of the glandular enlargement and with their appearance the constitutional symptoms improve, often very rapidly, and the patient becomes convalescent.

Sporadic cases of this type are not uncommon and one instance was included in Longcope's article in 1922.

Four groups of clinical manifestations have so far here been indicated: (1) Pfeiffer's glandular fever in children, characterized by rapid and visible swelling of the cervical glands and a short duration, (2) infectious mononucleosis in young males with a longer but milder febrile stage and comparatively slight glandular swelling (3) "monocytic angina" and (4) long febrile types with late and slight enlargement of glands.

This grouping was useful while the clinical features of the disease were being carefully studied, but the disease is apparently a single entity and every permutation and combination of the four groups occur. Milder cases often fall fairly clearly into one group, but this is rarely so for the severer forms.

## THE BLOOD PICTURE

It is probable that mononucleosis develops in every case of infectious mononucleosis.

All the blood-forming tissues are affected, myeloid, monocytic (or reticulo-endothelial) and lymphoid, but at different times and to different degrees and varying in different cases and indeed in the same case at different stages. The effect on one system may be decreasing while on another it is increasing, thus producing the rapid changes in the blood picture which is so characteristic of the disease. The sequence of the changes is best observed in the long severe febrile cases, but unfortunately the diagnosis is rarely made in the early stages.

The myeloid system is earliest involved, but less constantly or severely and for a shorter time than the other systems. In mild cases, there may be no change in the circulating myeloid cells, but in severer forms an initial polynucleosis, such as 15-20,000 leukocytes with 75 per cent polynuclears, is not infrequent. This initial polynucleosis is a common cause for the diagnosis being overlooked. Polynucleosis is always transient and initial and never develops during the course of the attack. The rise of the mononuclear reaction may overlap the fall of the polynuclear cells, but in the more severe forms this reaction is delayed and the blood count becomes within normal limits and may remain so for two or three weeks or more, or may fall further to a leukopenia before the mononucleosis appears. Leukopenia is fairly common at the onset or during the course of severe cases before the mononucleosis develops. It is mainly due to granulopenia but even the lymphocytes may fall. In milder clinical types a mononuclear reaction may be present at the first examination or within a few days of onset.

The monocytic and lymphocytic reactions overlap, but the monocytic system subsides first and a pure lymphocytosis is finally left. So rapidly may alterations take place in the types of white cells and their number and so great are the differences in different cases that no single blood picture is exclusively typical of the disease. But most characteristic during the active stages is the presence simultaneously of various types of mononuclear cells, particularly with a high incidence of monocytes, an appearance rarely seen in any other disorder of the blood.

## HETEROPHIL ANTIBODIES

Paul and Bunnell (1932) made the curious discovery that heterophil agglutinins develop in high titer in human serum in infectious mononucleosis and in no other disease, with some unimportant exceptions. The development of heterophil antibodies and the technic of estimation will not be discussed.

Important questions which arise are at what stage does the reaction become positive, and in what proportion of cases is it positive, and does a negative reaction exclude infectious mononucleosis.

In the common mild types the reaction is frequently positive at the first examination, which is usually four or five days after the onset. If the examination is earlier, the test may be negative or indefinite, the titer rising in the next few days. Owing to the certainty with which the diagnosis can be made on clinical and hematologic grounds, the test is not always repeated. Nevertheless, in these circumstances the reaction is positive in nearly 90 per cent.

But in the severer febrile forms the reaction may remain negative during several weeks of pyrexia and constitutional disturbances, and become positive about the same time as the mononucleosis and glandular swelling develop. It is striking how often the constitutional symptoms rapidly ameliorate within a few days of the rise in titer. Thus, the development of a positive reaction is related to the end of an attack rather than to the onset, and it may well be connected with the development of immunity, as Himsworth (1940) suggested. On more than one occasion, I have known the reaction to become positive for the first time during a relapse.

The titer has no constant relationship to the severity of the disease, the extent of the glandular swelling or to the degree of lymphocytosis. The time during which a reaction remains positive is very variable, but little more is known. The titer may fall from a very high dilution to negative in the course of a few days. In ordinary mild cases, it may become negative within two weeks of recognition, but it often persists for several weeks and has been found still positive after several months.

The significance of a negative test especially arises in epidemics in which all results are reported as negative, and in individual cases in which the test is repeatedly negative. The question arises whether or not there are two types of infectious mononucleosis, giving respectively positive and negative reactions. There is nothing inherently improbable in the existence of two viruses, but until we know more about heterophil agglutination, the evidence must be regarded as inconclusive.

I agree with the opinion of Paul and others that a positive reaction is proof of infectious mononucleosis and a negative reaction does not exclude it.

#### NEUROLOGIC MANIFESTATIONS

The neurologic manifestations of infectious mononucleosis have attracted attention recently and quite a number of cases have been recorded in the last few years. It is obvious that the presence of infectious mononucleosis in similar cases must previously have been overlooked. The existence of encephalitis was suspected by Longcope (1922) and by Glanzmann (1930) but the first clear descriptions of neurologic features were given by Epstein and Dameshek (1931) and by Johannsen (1931). The clinical pictures are extraordinarily varied and bizarre, and no two cases appear to be quite similar. The brain (encephalitis), meninges, cord, cranial nerves and peripheral nerves may be affected, either separately or in combinations or sequences. There is no constant order in which the ordinary manifestations of infectious mononucleosis and the neurologic symptoms respectively develop, or in their comparative severity. The glandular enlargement, lymphocytosis in the blood and in the cerebrospinal fluid, and meningeal or other neurologic symptoms may develop and subside simultaneously, as in Epstein and Dameshek's case. In other cases, the infectious mononucleosis may run its course and subside to be followed by nervous symptoms, lymphocytosis in the cerebrospinal fluid and a normal blood picture. Or again the symptoms of a benign lymphocytic meningitis may be subsiding before the features of infectious mononucleosis appear. In this last group the blood count may show an initial polynucleosis even with a high mononucleosis in the cerebrospinal fluid.

The symptoms of benign lymphocytic meningitis are exactly reproduced in certain of the cases. It is also noteworthy that in the more severe neurologic forms, the blood changes tend to be late and the glandular swelling slight as with other severe types of infectious mononucleosis.

The heterophil agglutinins have been estimated in all recorded cases since 1938 and the test always has been positive in the blood at some stage with the exception of two cases in sisters (Thelander and Shaw 1941), but it has never been positive in the cerebrospinal fluid. Observers might naturally hesitate to attribute to infectious mononucleosis neurologic symptoms with negative agglutination.

Recovery from neurologic manifestations takes place with extraordinary rapidity. A comatose and paralyzed patient with an extensor-plantar response may be apparently normal mentally and physically in three days. The question of encephalitis requires further observation. Severe headache is the commonest symptom in neurologic cases and is also an occasional complaint in ordinary types. Children and adolescents may take a surprisingly long time, six to twelve months, to recover their usual powers of concentration and application after a simple attack although apparently physically normal. It is possible that this is a sequel of encephalitis.

#### ASSOCIATION WITH JAUNDICE

Jaundice is now not uncommon at the onset or during the course of the severer forms but the association has become frequent only in the last ten or twelve years. It was not recorded in the epidemic in England in 1930, but in 1935 and 1936 many cases were observed in St. Thomas's Hospital (Tidy 1937) and it is now a recognized complication. When occurring at the onset, the jaundice is often of considerable severity and there is nothing to distinguish the clinical condition from an ordinary infective hepatitis. As the jaundice subsides, the pyrexia persists and the diagnosis of infectious mononucleosis often follows the discovery of lymphocytosis in a routine blood count or the observation of some glandular swelling, which occasionally is present at the onset.

Jaundice adds the symptoms of infective hepatitis to the symptoms of infectious mononucleosis but does not appear otherwise to affect the course. Jaundice is rarely severe when developing later in the illness. Whether the jaundice is due to a separate virus cannot at present be determined.

#### DIAGNOSIS

Possible errors in diagnosis are numerous and mistakes in practice are not uncommon, but with the transitory nature of ordinary attacks they usually settle themselves without important consequences. They will not be considered seriatim.

In the severer febrile forms, there may be no means of establishing the diagnosis for several weeks. This may also apply to onset with jaundice or with neurologic symptoms. The possibility of infectious mononucleosis as the essential factor in some cases of benign lymphocytic chorio-meningitis should be borne in mind. The blood changes should not cause difficulty in differentiation from leukemia when the patient is seen in the acute stage. In acute leukemia, the toxic symptoms are always severe.

An occasional but extremely difficult diagnosis may be caused by the rare slowly-progressive chronic lymphoid leukemia. In the earlier stages, there are periods of exacerbation with pyrexia and moderate glandular swelling. The lymphocytes for several years may be only at the upper limits of normal. They gradually creep up and the diagnosis, long suspected, slowly becomes confirmed. Diagnosis is especially difficult when it is asked for on a patient some months after a pyrexial attack with lymphocytosis considered to be infectious mononucleosis. Either lymphocytosis or glandular swelling may persist for several months after infectious mononucleosis, but if both features are present for six months the diagnosis must be considered to be in doubt, unless it has been fully established. I have watched three such cases, originally diagnosed doubtfully as infectious mononucleosis, gradually develop into fatal lymphoid leukemia or lymphosarcoma over periods of three to ten years.

## REFERENCES

- BERNSTEIN, A.: *Medicine* 19: 85, 1940.  
BURNS, J. E.: *Arch. Int. Med.* 4: 118, 1909.  
DEUSSING, R.: *Jahrb. f. Kinderheilk.* 88: 421, 1918.  
DOWNEY, H., AND MCKINLAY, C. A.: *Arch. Int. Med.* 32: 82, 1923.  
EPSTEIN, S. H., AND DAMESHEK, W.: *New England J. Med.* 205: 1238, 1931.  
GLANZMANN, E.: "Das lymphoemoide Drusenfieber." Berlin, 1930.  
JOHANSEN, A. H.: *Acta med. scand.* 76: 269, 1931.  
LONGCOPE, W. T.: *Am. J. M. Sc.* 164: 781, 1922.  
PAUL, J. R., AND BUNNELL, W. W.: *Am. J. M. Sc.* 183: 90, 1932.  
PFEIFFER, E.: *Jahrb. f. Kinderheilk.* 29: 257, 1889.  
SCHULTZ, W.: *Deutsch. med. Wchschr.* 48: 1491, 1922.  
SPRUNT, T. P., AND EVANS, F. A.: *Bull. Johns Hopkins Hosp.* 31: 410, 1920.  
TIDY, H. L., AND MORLEY, E. B.: *Brit. M. J.* 1: 100, 1921.  
—: *St. Thomas's Hosp. Rep.* 2: 104, 1937.  
WEST, J. P.: *Arch. Pediat.* 13: 889, 1896.  
WILLIAMS, D.: *Lancet* 1: 160, 1897.