3. Precautions in the use of the injections are suggested.
4. Observations without definite follow-up figures are made with regard to the intra-articular injection of gomenol.

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Clinical Page

GLANDULAR FEVER

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History.

Glandular fever (*Infectious mononucleosis*) belongs to the group of virus diseases. It is an acute infectious condition, characterised by fever, enlargement of the lymphatic glands, changes in the blood (especially a lymphocytosis), and by the presence of heterophile antibodies. The discovery of the blood changes and the heterophile antibodies has established the existence of glandular fever as an "entity." Outbreaks of the condition in the last few years have revealed its extraordinary protean nature. Bernstein says of the condition that it closely resembles syphilis by virtue of its ability to simulate so many other diseases.

The disease was first described by Emil Pfeiffer, 1889, under the title of "Drüsenfeiber," although Filatow, a Russian paediatrist, gave an account of it in 1885. In Britain, the first article about this condition, as seen in children, was published by Dawson Williams in the *Lancet* in 1897. In November 1930 Sprunt and Evans, in America, published an article in which the existence of an infectious lymphocytosis was clearly stated. They named it "Infectious mononucleosis," but made no reference to Pfeiffer's "Drüsenfeiber." For some time subsequently the identity of the two types was denied in America. In March 1921 Morley and Tidy published the first case of glandular fever, in which the presence of lymphocytosis was recognised. By 1925 the identity of the two conditions was accepted tacitly by Britain and America, but on the European continent for many years its dual existence was still doubted. The argument that monocytic angina was glandular fever was put forward by Glainzmann in 1930, and about the same time an epidemic appeared in England. This febrile type was proved by Tidy, *et al.*, to be another manifestation of glandular fever. More recently, epidemic hepatitis appears to be the latest guise of this disease, and Bernstein supports this view. One must wonder what clinical coat glandular fever will don when it next presents itself?

Aetiology.

Its distribution is universal, and no age appears to be immune. The glandular and hepatic types affect children and adolescents between 6 and 20 years; the anginose and febrile types are mostly seen in adults of 20 and 30 years. The incubation period is from 5-12 days, usually 11 days. The degree of infectivity is not high, and is limited to small localised outbreaks. It is very rarely sporadic, and the duration of infectivity is about one week.

Clinical Manifestations.

It is now established that the manifestations of glandular fever are protean. The essential features may be stated as fever, glandular enlargement, faucial affections, jaundice, blood

changes, and the characteristic heterophile antibodies. The predominance of any one of the first four features enables the separation of the condition into four clinical groups.

(i) Glandular or Pfeiffer's type.

This is seen between 6 and 20 years of age, more frequently in males than females. The prodromal period is 1-4 days. The mode of onset is acute, with headache and malaise. The faucial symptoms are those of sore throat, reddening of the fauces and tonsils, and follicular tonsillitis. Constitutional symptoms are slight. There is no anaemia or eruption, but vomiting, epistaxis, abdominal pain and cough are not infrequent. The enlargement of the lymphatic glands is the predominating feature. The cervicals are enlarged, especially those situated behind the upper half of the anterior border of the sternomastoids. They are discreet, moveable, and of firm consistency. Other glands to enlarge are the preauricular, sub-maxillary, axillary, inguinal, thoracic, salivary and mesenteric glands. In 50 per cent of the cases the spleen and liver are slightly enlarged. The glandular enlargement is obvious for 2-3 days, after which the temperature falls, the general symptoms subside, and convalescence sets in, but the glands may remain palpable for a considerable time. Relapses are not uncommon, but convalescence is usually immediate and rapid. The final prognosis is invariably good.

(ii) Anginose Type (Monocytic Angina).

This is rare. The age incidence is between 10-25 years, and more cases are met with in males than in females. The prodromal period is 1-3 weeks, and the mode of onset is insidious, with malaise and pyrexia. On examination the tonsils are red and swollen, and the membrane when formed is indistinguishable from diphtheria. It may be uni- or bilateral. Peritonsillar oedema is common. The cervical glands are always enlarged by the time the membrane is developed. Oedema of the lids and neck are not uncommon. The axillary glands may also be enlarged. The spleen may be palpable, but eruptions are not known. The faucial membrane may persist for several days; as it separates, so the temperature falls and the fauces becomes more comfortable. Convalescence sets in rapidly. Recurrences sometimes occur but are never serious.

(iii) Febrile type.

This occurs in the adult period of 20-30 years. It has a fairly characteristic course and clinical picture.

The stage of invasion is from 1 to 3 days. The onset is sudden with headache, malaise, a temperature of 102-103°, and one or more rigors. The face is flushed and moist, and photophobia, oedema of the lids, and conjunctivitis are common. In fact it may simulate an attack of meningitis. Its duration is from three to several days.

The stage of eruption is from 4 to 7 days. Two types of rash, (a) *maculo-papular*, (b) *roseolar*, are met with. The spots are 2 to 5 mm., pinkish brown in colour, disappearing on pressure, usually scanty, and distributed mostly on the front of the trunk, back and limbs. The rash is irritating and lasts from 4 to 6 days. During the eruption the constitutional symptoms get more marked. The temperature rises to 103-104°, but vomiting, epistaxis, gastro-intestinal symptoms and abdominal pains are rare. The spleen is not usually palpable. The Wasserman reaction is positive. The duration of this stage is 10 to 14 days.

The stage of glandular enlargement occurs between the 18th and 25th day. The palpable glands enlarge in the same fashion as in the glandular type, but are definitely smaller. The spleen is usually palpable, but the faucial symptoms are uncommon. The temperature rises with the glandular enlargement to 102-104°, receding to normal in a couple of weeks. The constitutional symptoms gradually lessen, leaving the patient exhausted and weak. The Wasserman reaction is positive in many cases. The duration of this stage is usually about 4 weeks.

(iv) Hepatic Type.

This occurs between 6 and 20 years, and is more common in males than in females. It has a prodromal period of 1 to 4 days. The mode of onset is acute, with vomiting, head-

ache, malaise, abdominal pain, and some constipation. Slight fever is always present. A sore throat is complained of and is attributed to the vomiting. Two or three days later the urine contains excess bile, and the stools have a clayey appearance. The patient by now develops jaundice, the clinical course of which is similar to acute catarrhal jaundice. It subsides in 7 to 10 days. The glandular enlargement, whose distribution and character is similar to that of the glandular type, makes its appearance as the jaundice begins to recede. The liver and spleen are also slightly enlarged. The glandular enlargement is followed by catarrhal bronchitis which gradually subsides in 1 to 2 weeks. Convalescence then sets in and recurrences are uncommon. The prognosis is always good. The onset of the jaundice is due to the pressure exerted by glandular swellings in the bile ducts. The Van den Bergh reaction is usually biphasic, i.e. direct and delayed.

Complications.

The complications met with in glandular fever are not of a serious nature. Sepsis is rare. Tidy states that he has never seen these glands suppurate. Epistaxis is not uncommon, and may occur at any time in the course of the illness. Hematuria is not a serious complication, and is not confined to the anginose type as one might expect. Purpura and other skin haemorrhages are extremely rare; on the other hand, oedema of the lids and conjunctivitis are not uncommon findings, occurring in one-third of the cases. Meningitis is a rare complication. The C.S.F. shows an increased pressure, an increase in protein and lymphocytosis. Bronchitis and broncho-pneumonia are not uncommon sequelae in the hepatic type: they are invariably of a mild character.

Morbid Anatomy.

The lymph glands at biopsy show two principal changes: (a) lymphoid hyperplasia in the early stages, (b) hyperplasia of the reticulo-endothelial tissues in all its stages. It has been suggested that the hyperplasia of the reticulo-endothelial cells is the cause of the appearance of plasma cells, or monocytes, in the blood.

The myeloid tissue at sternal puncture shows that it can react initially either by a polynucleosis or a neutropenia.

The blood picture shows no change in the red cells and no anaemia in the ordinary course of the illness, except perhaps in convalescence. The thrombocytes are not affected. The total leucocytes count rarely exceeds 40,000 per c.cms. A closer examination of these polynuclear leucocytes frequently shows a "shift to the left" due to the strain thrown on the bone marrow (myeloid tissue) by the virus. This polynucleosis is present in the initial stages, never develops during the course, and is always transient. Sometimes an outstanding feature, and the usual criterion, of this disease is the absolute lymphocytosis which appears in the prodromal stages, a little later than the polynucleosis, and lasts throughout the illness. The degree of lymphocytosis does not show any relation to the size of the glands involved. It has now been established that this lymphocytosis, or mononucleosis, consists of typical and atypical cells. These mononuclear cells have been divided into (a) normal lymphocytes, (b) primitive lymphocytes or monocytes (i.e. plasma cells not unlike "Turk" cells, and derived from the reticulo-endothelial cells). They are of two types—large cells, slightly basophilic, with pale nuclei but no nucleoli, and large cells distinctly basophilic but with definite nuclei and one or more nucleoli. (c) Abnormal cells (i.e. glandular fever cells). These are of varying types, but the commonest are to-day accepted as characteristic. They are larger than the small lymphocytes, distinctly basophilic, and show "fenestration of their nuclei."

The Liver Studies. (Dible: quoted by Kilham and Steigman, 1942.)

The Van den Bergh test usually gives a direct reaction. Sections from liver punch biopsy show well-marked focal acute hepatitis. The maximum change is seen in the portal tracts of the lobules where there is loss of liver cells and a well-developed histiocytic reaction with some early proliferation of bile ducts. There are also isolated foci of similar histiocytic reactions in other parts of certain of the lobules, and the sinusoids show an excess of cells, some of which are Kupffer cells, and others resemble monocytes. The glycogen content of the hepatic cells is well preserved, and the general appearances suggest that an earlier phase of necrosis has preceded the present histiocytic reaction. The reticular pattern of the lobules is disturbed in the affected portal zones, but there is no true fibrosis.

Pathogenesis.

Many attempts have been made to determine and isolate the virus. Bacteriological examinations of the blood, glands and throat swabs, and sternal punctures have proved nothing. Nyfeldt's bacterium *monocytogenes hominis*, spirochaetes, streptococci, and Vincent's organisms are not held to be the causative agents. By animal experimentation Blands' was able to identify a "Protozoon of the Genus *Toxoplasma*." He claimed this to be the causative factor. Paul Bunnell was able, by immunological studies, to demonstrate the presence of heterophile antibodies in the blood of these cases. Three types of heterophile antibodies are found in human sera which agglutinate sheep erythrocytes. One type found in normal sera is not absorbed by either ox erythrocytes or guinea pig kidney. Another type found in human sera, after horse serum injection or parenteral liver extracts, is absorbed by both. The type found in infectious mononucleosis is only absorbed by ox erythrocytes and not by guinea-pig kidney. By Barrett's test, a modification of the Paul Bunnell test, one is able to differentiate these three types of heterophile antibodies. One is tempted to speculate whether the Paul Bunnell test supports, by analogy, the view that infectious mononucleosis is of virus origin, and whether, in other virus diseases, the serum of the patient will be found to agglutinate the red cells of certain animal species. That it is virus infection has been proved by its transmission to the monkey and then propagated, as virus infections usually are, by air convection. Wising (1942) finds support for the assumption that a virus is the responsible agent and not *Listeria monocytogenes hominis* or a toxoplasm. He studied 27 cases, but unfortunately unfiltered blood was used for the one successful experiment in transmission. The changes seen in the lymph nodes could be explained by the presence of a virus. This was confirmed by Nettleship (1942) and Van den Bergh and Liessens (1939). The suggestion that *Listeria Monocytogenes* might be the cause has been made by Nyfeldt (1929), Pons and Julianelle (1939), and Webb (1941). Recently Webb (1943) describes the fourth case to be recorded in the world literature. He states that more cases will be isolated with care, it may be that this bacteraemia may be intermittent early and the blood picture transient.

Diagnosis.

If the characteristics of fever, glandular enlargement, lymphocytosis (with or without faucial changes), jaundice or eruption, are present and recognised, the diagnosis is easy. But if these characteristics are not developed or are atypical the diagnosis is made difficult. Recourse should then be made to haematological and immunological tests. The Barrett test, a modification of the Paul Bunnell test, normally becomes positive in 4-5 days of infection, in dilutions of 1 in 80 to 1 in 1,280. It remains so for several weeks. In diagnosis each type has its pitfalls.

The *glandular* type should be differentiated from:

1. *Acute leukaemia*.—The patient is seriously ill. There is gross anaemia. Typical and atypical mononuclear cells are seen, and the total and differential counts reach alarming figures.
2. *Sepsis and Mumps*.—A definite mass suggestive of the condition is noted. The parotid gland is chiefly involved.
3. *Tuberculosis, Hodgkin's Disease, and Syphilis*.—Here the distribution, the constitutional symptoms, Wasserman and biopsy examinations are the chief distinguishing features.
4. *Agranulocytosis*.—The history of drug therapy, together with the other toxic symptoms are essential points.

The *anginose* type should be differentiated from:—

1. *Diphtheria*.—There is a short prodromal period, typical membrane, marked constitutional symptoms and spinal complications.
2. *Vincent's Angina*.—There is a sloughing membranous condition, the demonstration of the spirilla and its response to nicotinic acid.
3. *Scarlet fever and sera reactions*.—The history, the clinical course, the typical rash, and the absence of lymphocytosis and the serological test are distinguishing features.

The *febrile* type should be differentiated from:—

Typhoid and other prolonged fevers by the history and the abdominal features, the pulse

temperature and respiration rate, the roseolar rash, and the special agglutination tests.

Rubella, Fourth disease, Pertussis, Measles, Mickulwicz's syndrome and Trichiniasis by a careful history, a methodical examination of signs and symptoms, a blood picture, and the Paul Bunnell test.

The *hepatic* type should be differentiated from:—

Other forms of jaundice, whether they be obstructive, toxic, or hemolytic. The blood picture, a positive Paul Bunnell, a liver punch biopsy, glandular enlargement, and catarrhal bronchitis, together with jaundice, are the distinguishing features.

Treatment.

Treatment at best is purely symptomatic. The patient should be put to bed until apyrexial and until the glands show a reduction in size. No specific treatment has so far been evolved; the latest drugs to be tried being the sulphanilamides, but the results have not been convincing. Sears has suggested that sulphonamides may be hazardous in infectious mononucleosis because of the present co-existence of granulocytopenia. For this reason sulphadiazine or sulphathiazole are indicated in the anginose type, where granulocytopenia is not an uncommon feature.

Berkeley (1942) has put forward the therapeutic value of anti-scarlatinal serum in the treatment of infectious mononucleosis.

In convalescence, tonics and iron together with a quiet country or sea-side holiday of 4-6 weeks is beneficial.

Preventative measures are particularly indicated in boarding schools. Notification, isolation, and enforcement of the preventative measures laid down in the Ministry of Health Infectious Disease Order are all that are required.

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CORRESPONDENCE

Wellcome Museum of Medical Science Wellcome Historical Medical Museum

SIR,

Frequent enquiries are being received, both from this country and abroad, with regard to the two Wellcome Museums. They are, and will continue to be, housed in the Wellcome Research Institution, 183-193, Euston Road, N.W. 1. Although the Wellcome Research Institution building suffered considerable damage by enemy action, its structure was unharmed and the Museums can quickly be put into shape again as soon as labour and materials become available after the war.

While some of the objects in the Wellcome Historical Medical Museum were damaged, it has been possible to replace or repair most of them. Fortunately the specimens and other valuable material in the Wellcome Museum of Medical Science remained comparatively intact.

Both Museums are now under the Directorship of Dr. S. H. Daukes. A comprehensive scheme for the Wellcome Historical Medical Museum has been prepared and will be brought to completion as speedily as possible after the cessation of hostilities.

The Wellcome Medical Library, comprising over 150,000 volumes, will also be in the same building and suitable accommodation will be provided for research workers so that both the Library and Collections may be readily available.

The Wellcome Museum of Medical Science—which in the past has been much used by teachers, students and those engaged in post-graduate studies—will be re-established in its entirety at the end of the war with the utmost possible speed. The large Lecture Hall will be fully re-equipped, including film projection apparatus, and will then be available for scientific lectures and meetings.

Yours faithfully,
 L. G. MATTHEWS,
Secretary.