REFRESHER COURSE FOR GENERAL PRACTITIONERS

GLANDULAR FEVER

BY

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Glandular fever is an acute infectious disease characterized by fever, enlargement of the lymphatic glands, and changes in the blood, especially lymphocytosis and the presence of heterophil agglutinins, and with a uniformly favourable course. The causal agent has not been identified.

The degree of infectivity is only moderate. Susceptibility, however, seems to be almost universal: if two or three cases develop in a school or closed community a high proportion of the occupants tend to become infected. The duration of infectivity is uncertain. The incubation period is between 5 and 15 days, in most cases between 7 and 10 days. In spite of many studies it is impossible to fix an upper limit.

Glandular fever was first identified as an entity in 1889. It was described as a simple harmless cervical adenitis occurring in children. No pathological changes were known and the diagnosis rested on rather indefinite clinical features which scarcely differentiated it from some bacterial infections. Its existence as an entity became doubted, and by 1900 it was almost forgotten and remained so for 20 years. In 1920 mononucleosis was discovered in the blood and the disease was resuscitated. Paul and Bunnell in 1932 made by chance the curious discovery that heterophil antibodies to sheep's red cells are present in high titre in the blood in glandular fever and, for practical purposes, in no other known disease. Laboratory methods thus became available by which the diagnosis could be firmly established.

Glandular fever is remarkable for the numerous clinical forms in which it appears. They are, of course, all due to the same infection, and intermediate and overlapping types are not uncommon. Some of the forms are confusing and the diagnosis is difficult, especially in sporadic cases. The differences between the chief types are great enough for several of them to have been initially regarded as new entities before being recognized as variants of glandular fever. Hence for the purpose of diagnosis it is important to be aware of their principal features. The following six clinical groups are separately described: (1) juvenile glandular type—occurring mainly in children and characterized by the rapid formation of a visible mass of glands; (2) adolescent type—more insidious and commoner in young adults, represents "infective mononucleosis" as frequently seen in America; (3) prolonged febrile types; (4) anginose type (monocytic angina); (5) with neurological manifestations; and (6) onset with jaundice.

Juvenile Glandular Type

This is the form commonly seen in children, but it may occur at any age. The onset is usually acute. There may be a short prodromal period of malaise, but this is commonly overlooked, and the glandular enlargement often first attracts attention.

The cervical glands are most often involved. They tend to enlarge rapidly, and may form a visible tumour within 24 hours. The mass is normally painless and only slightly tender, though young children may object to palpation.

The gland which is most characteristically enlarged is deep to the sternomastoid muscle, about the middle of its length, and somewhat below the angle of the jaw; it lies transversely and can be felt on both sides of the muscle. It is striking how often this gland can be recognized. There is usually some enlargement of axillary glands, and they may be present without any involvement of the cervical groups. Other superficial glands may enlarge, including the preauricular, submaxillary, submental, supratrochlear, and occipital. The deep glands may also be involved. Enlarged mediastinal glands may press on the bronchi, and the transient obstruction in rare instances produces very confusing and rapidly changing physical signs.

In the fauces there is little change, though some complaint of sore throat is common. Eruptions are unusual. Torticollis is an occasional complication.

The temperature is raised to about 101° F. (38.3° C.). Constitutional symptoms are slight and the patient does not appear ill. The spleen becomes palpable in about 50% of the cases, but only by one or two fingerbreadths. The main mass of the glands and the constitutional disturbances generally subside in the course of a few days, and the patient recovers in one to two weeks. The glands may remain just palpable for many weeks or even several months. Suppuration of the glands is no part of the ordinary course of glandular fever, but in very rare cases it has followed a pre-existing tonsillitis.

Mononucleosis is usually present when the glands appear, otherwise it develops within a few days. The total number of leucocytes in most cases lies between 10,000 and 20,000 per c.mm., with 60 to 80% of mononuclear cells. Both monocytes and lymphocytes contribute to the excess, but the monocytes subside rapidly and leave the lymphocytes to predominate. Some degree of lymphocytosis may linger for several months.

Recrudescences or relapses are by no means rare. The course may be similar to the original attack but tends to be milder. Recrudescences may take place after considerable periods of freedom; there may be several over a period of some months, gradually decreasing in severity. If recurrences extend over a longer period the diagnosis should be carefully reviewed.

In children under the age of 5 years the picture is less characteristic: the constitutional symptoms are often more severe, the glandular enlargement is slighter, and the diagnosis may be difficult.

Adolescent Type

Among adolescents and young adults the onset is insidious, the course longer, and the glandular enlargement less pronounced than in the juvenile form. The onset is slow, with fatigue and depressed health gradually becoming severe enough to cause the subject to report to a medical officer. The glands may be found then or subsequently, often on routine examination. This is the form—the so-called infective mononucleosis—in which glandular fever is commonly seen in America, among college students, and American descriptions of the disease are essentially based on this age group.

Prolonged Febrile Type

This type apparently represents the full development of glandular fever. It occurs rarely in epidemics, but sporadic cases and milder grades are fairly common. In these severe forms the characteristic features of glandular enlargement

and mononucleosis develop late and the glands seldom attain any great size. In many cases the severe constitutional disturbances are already subsiding before the glands become palpable, and cases have often been mistaken for anomalous forms of enteric fever.

The initial febrile period is of variable duration, and recrudescences may lengthen it to many weeks. During this stage there may be no diagnostic features on either clinical or laboratory investigation. Headache is often severe. There may be a few rigors. Sweats are nearly always profuse; they are greatly increased by the administration of antipyretics and then become associated with extreme exhaustion. The Wassermann reaction and Kahn test may become temporarily positive.

An eruption is common. It usually appears about the end of the first week, and the temperature, which may have been falling, rises again. The temperature has no regular course, but it generally falls to normal or nearly normal before the glands enlarge, when it rises again. The glands are often discovered by chance or by a routine examination when the temperature rises. The spleen may become palpable at this stage. Rapid improvement often follows and convalescence sets in, but recurrences are not uncommon.

The course of the blood changes is important. At the onset there may be a definite polynucleosis. The polynuclear cells always fall rapidly, and for a period the blood count may be within normal limits. In some cases there is a leucopenia at the onset. Leucopenia is also often present about the time the glands begin to enlarge, but mononucleosis always develops.

Anginose Type

The importance of this type is its ready confusion with diphtheria. It was first discovered, in hospitals for infectious diseases, that a condition existed which was non-bacterial but characterized by the formation of a membrane indistinguishable from that of diphtheria and with an absolute lymphocytosis. Its relationship with glandular fever was not recognized for some time. It is probably a complication following two to three weeks after a mild attack of glandular fever and may be the result of leucopenia. The angina never occurs as an epidemic, but several cases may appear almost simultaneously in a closed community.

This type 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. It rarely involves the larynx. Oedema of the neck and tenderness of the enlarged cervical glands are common, but not to the extreme degree of diphtheritic bull-neck, and suppuration is very rare. Oedema of the fauces causes great discomfort and anxiety, but in spite of this and the high temperature, often about 104° F. (40° C.), the patient does not appear to be toxic and does not 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. Mononucleosis is generally present at the time of appearance of the membrane and is always present and absolute within a day or two, but at the onset it is often only relative, since an initial leucopenia is common. There are no cardiac or nervous complications and recovery is uneventful.

Neurological Manifestations

The neurological manifestations of glandular fever attracted little attention until recently, but a number of cases have been recorded in the past few years. 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. The commonest types are probably polyneuritis (Guillain-Barré's syndrome) and benign lymphocytic meningitis. There is no constant order in which the ordinary

manifestations of glandular fever and the neurological symptoms respectively develop, or in their comparative severity. Thus the glandular enlargement, lymphocytosis in the blood and in the cerebrospinal fluid, and meningeal or other neurological symptoms may develop and subside simultaneously. In other cases the glandular fever may run its course and subside, to be followed by the development of nervous symptoms and lymphocytosis in the cerebrospinal fluid, but with a normal blood picture and agglutination titre which may be either raised or not. Or again the symptoms of a benign lymphocytic meningitis may be subsiding before the features of glandular fever appear. In this last group the blood count may show an initial polynucleosis even with a high mononucleosis in the cerebrospinal fluid. In the more severe neurological forms the glandular swelling tends to be slight, as with other severe types of glandular fever, and may be overlooked during convalescence from the nervous features, unless specifically sought.

Recovery from neurological manifestations can take place with extraordinary rapidity. A comatose and paralysed patient with an extensor plantar response may be apparently normal mentally and physically in three days.

The interpretation of the Paul-Bunnell reaction in neurological cases needs careful consideration. In assessing the value of a negative reaction the time relations described below must be taken into account. Cases of benign lymphocytic meningitis have been recorded in the neurological literature in which glandular fever is held to be finally excluded by a negative agglutination, although the reaction has been performed at a point during the course when it would not be expected to be positive.

Onset 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 past 15 years. 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 glandular fever often follows the discovery of lymphocytosis in a routine blood count or the observation of some glandular swelling.

Jaundice adds the symptoms of infective hepatitis to those of glandular fever but does not appear otherwise to affect the immediate course. Jaundice is rarely severe when developing later in the illness. It is not known if cirrhosis of the liver may follow.

Eruptions

The rash in glandular fever may cause much difficulty owing to its close simulation of many of the exanthems. During the course of glandular and anginose types well-defined eruptions are rare and tend to be transient. In the febrile forms eruptions are common, though the incidence has varied greatly in different epidemics; the rash usually appears within a few days of the onset but may develop at any point in the course. There are two common types: macular, or maculo-papular, and rubelliform. The macular or maculo-papular type is the eruption most often seen in the febrile forms and may closely resemble the rash of typhoid fever. The rubelliform eruption is the usual type in the glandular forms, and may be indistinguishable from rubella. It may appear and fade two to three weeks before the glands enlarge.

Blood Changes

It is probable that mononucleosis develops in every case of glandular fever. It is by the presence of this mononucleosis, or, as it is usually expressed, "lymphocytosis," that the diagnosis is usually determined. Nevertheless the blood changes are not as simple as may appear at first sight even in the common mild glandular types.

Both the monocytic and lymphoid blood-forming tissues are affected and cells of both series are increased in the circulating blood. When a first examination of the blood is made early in the attack both types of cells are prominent. The monocyte excess, however, tends to fall rapidly, often with striking rapidity in the course of 24 or 48 hours, while at the same time the lymphocytes are usually increasing.

These factors produce the characteristics of the blood in the acute stages, various types of mononuclear cells being present simultaneously, the relative proportion changing with great rapidity. Blood pictures taken within a few hours of each other may show marked differences both in the differential count and in the total number of cells. It is often difficult to distinguish slightly primitive monocytes from lymphocytes, and cells may be variously interpreted by different observers. These results may cause doubt to be thrown on the accuracy of records. Differences of this nature in differential counts, however, are of little practical importance and rarely would influence a diagnosis.

The myeloid system may also be affected, producing polynucleosis, though this is rarely obvious except in severe febrile types. In these cases there may be at the onset 15,000 to 20,000 leucocytes per c.mm., with 75 to 80% polynuclear cells. Such polynucleosis is only initial and transient and never develops during the subsequent course. Its possibility is not generally realized, and it frequently causes an error in diagnosis. The polynucleosis may overlap the monocytic and lymphocytic reactions, introducing a further changing factor.

It should be realized that no single blood picture is exclusively typical of glandular fever. Most characteristic during the active stages are the presence simultaneously of various types of mononuclear cells and the rapidity with which their relative proportions change. As the attack subsides the surviving cell is undoubtedly a lymphocyte.

The existence of a specific "infective mononucleosis cell" is doubtful. It is probable that they are primitive monocytes. Similar cells are present in the circulating blood in many other infections. It would be unsafe to base a diagnosis on the presence of such cells, and certainly unsafe to exclude glandular fever in their absence.

Paul-Bunnell Reaction : Heterophil Agglutinins

The term "heterophil antibodies" is applied to antibodies which can react with antigens which are unrelated to the cause of their development. In glandular fever, and in no other entity, the serum contains antibodies which can agglutinate sheep's red cells. Hence a positive Paul-Bunnell reaction is for practical purposes proof of glandular fever. It is consequently important to know if a negative reaction excludes glandular fever and to be familiar with the stage in the disease at which the reaction becomes positive.

In the ordinary mild glandular types of short duration the reaction is often positive at the first examination, which may be four or five days after the onset. If the examination is earlier the test may be negative or indefinite, the titre rising in the next few days. The titre is positive in nearly 90% of such cases. But in the severer febrile forms the reaction may and generally does remain negative during the weeks of pyrexia and constitutional disturbances, and becomes positive at about the same time as the mononucleosis and glandular swelling develop.

The development of agglutinins seems to be associated with the glandular enlargement and with the mononucleosis. Hence in severe and prolonged febrile forms a positive reaction is related to the end of the attack rather than to the beginning and may be connected with the development of immunity, as Himsworth suggests. It is striking how often the constitutional symptoms rapidly abate within a few days of the rise in titre.

It is very important that this time-relationship should be borne in mind. A negative reaction during the stage of constitutional or nervous symptoms must not be lightly

interpreted as excluding the possibility of glandular fever. The agglutination reaction is of most value in confirming that enlarged glands and mononucleosis are due to glandular fever.

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

Diagnosis

Diagnosis depends on the clinical features, the mononucleosis, and, when necessary, on the result of the agglutination reaction. In simple glandular types diagnosis is often easy and sufficiently confirmed by the blood changes. Special difficulties in each type are discussed.

Simple Glandular Types

Mumps.—In glandular fever the parotid gland is never affected.

Sepsis.—Differentiation is occasionally difficult. Definite oedema in the neck and over the gland is present only in the anginose type. The glands are rarely more than slightly tender, but a small child often strongly resents palpation. Doubtful cases usually prove to be sepsis, and it is advisable to treat them as such.

Acute Leukaemia.—The diagnosis is rarely difficult. In glandular fever the patient is not seriously ill and there is no anaemia; many types of mononuclear cells are present simultaneously and their proportions vary rapidly, and the total and differential counts do not reach the figures usually present in leukaemia. An extremely difficult diagnosis may be caused by the rare, slowly progressive lymphoid leukaemia which may begin even in childhood. In the earliest 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, and they gradually creep up until the diagnosis becomes clear.

Acute Infective Lymphocytosis.—In this syndrome there is moderate general enlargement, especially of the cervical glands. The white-cell count tends to be higher than in glandular fever, and may reach 100,000 per c.mm. The mononuclear cells are all lymphocytes, and the type remains unchanged throughout the course. The Paul-Bunnell reaction is negative. As recovery is invariable and uneventful confusion with glandular fever is not a serious matter.

Infective Non-bacterial Adenitis.—There is a further entity of infective non-bacterial adenitis which occurs in epidemics and in which there are neither blood changes nor agglutinin formation. A rubelliform eruption may be present. Little is known of this disease, but recovery is uneventful.

Anginose Type

The important distinction is from diphtheria; the clinical differences have been described above. The mild constitutional effects, in spite of the discomfort, and the entire absence of toxæmia are rapid guides to the diagnosis. In diphtheria there is an absolute polynucleosis increasing with the severity of the infection and never changing to mononucleosis. Cases of Vincent's angina never develop mononucleosis.

Prolonged Febrile Type

In this form there may be no means of establishing the diagnosis until the glands enlarge and the pathological tests become positive. The eruption when present may closely simulate enteric fever, but cultures are negative and T.A.B. agglutinins do not develop.

Neurological Manifestations

The difficulties of diagnosis are most apparent when there are neurological manifestations. The mononucleosis in the blood and the formation of agglutinins are associated with the development of the glandular enlargement and not with the neurological features. If the glandular changes precede the neurological symptoms both these pathological tests may have become negative before the period of nervous manifestations: this may be so even in the presence of lymphocytosis in the cerebrospinal fluid. If the nervous symptoms come first the reactions may not have developed. This sequence is often overlooked when the Paul-Bunnell test is applied to cases of benign lymphocytic choriomeningitis. The timing of the Paul-Bunnell test is thus of great importance in interpreting the value of a negative reaction in these cases. In a recent well-authenticated case the agglutinin reaction was positive in the cerebrospinal fluid: in all previous instances it has been negative. With regard to the clinical signs, the most striking features are their bizarre nature and the rapidity with which a structure that appears to be seriously affected recovers.

Prognosis and Treatment

Recovery from glandular fever is, with very rare exceptions, always complete. Occasionally there is a long convalescent period of debility and headache which is suggestive of encephalitis. A few deaths have occurred in debilitated children. One or two deaths have taken place during comatose stages of nervous complications, but no permanent paralyses or sequelae have yet been recorded. There is no authentic instance of the subsequent development of leukaemia; reported cases are errors in diagnosis or confusion with the type of chronic leukaemia described above.

No drug has yet been found to influence the course. All the antibiotics have been tried, with negative results when properly controlled.

Next Refresher Course Article.—"Irregular Vaginal Bleeding," by Mr. Malcolm Donaldson, will be published on September 6.

CENTENARY OF THE UNIVERSITY OF SYDNEY

BY

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A community which feels the need of a university has the higher outlook, for it has been truly said that a university is the soul of a people. The people of Sydney realized this a century ago, and the University of Sydney was founded in 1850, though the real teaching work did not begin until 1852.

The main building (Fig. 1) is of perpendicular Gothic architecture and was built of sandstone from the Pyrmont quarries; it was begun in 1854 and finished about 1860, the architect being T. Blacket. A special feature is the Great Hall, in which are held official functions of all faculties. Outstanding among the attractions of the Great Hall are the stained-glass windows, which, before being sent to Australia, aroused the interest of Queen Victoria and the Prince Consort, and were set up in the Waterloo Gallery in Windsor Castle for inspection. The windows show representations of the founders of the colleges of the Universities of Oxford and of Cambridge, portraits of the kings and queens of

FIG. 1.—The main University building.

England since the Norman Conquest, and portraits of persons celebrated in British history, literature, science, and art. Projecting into the Hall from the Senate Room is an oriel window. The stone used in making this window is carved with armorial bearings, and came from Caen, in Normandy.

The Medical School

The medical school was established in 1883. P. T. Anderson Stuart came from Edinburgh to Sydney as Professor of Anatomy and Physiology, and A. MacCormick was his first demonstrator. There were four students, and classes were held in a small cottage of four rooms. A model of this cottage is now in the historical section of the museum in the New Medical School.

It was largely due to the initiative and enthusiasm of Anderson Stuart that funds were forthcoming for the construction of what is now known as the Old Medical School (Fig. 2). A document signed by representative citizens of Sydney appealing to the Government of New South Wales for funds to establish a medical school is to be seen in the historical section of the museum. Many thought Anderson Stuart's plans too ambitious, and when the first half of the Old Medical School was completed the building was referred to by some as "Stuart's folly." Not many years passed, however, before the other half of the Old Medical School had to be added.

In 1887 J. T. Wilson came to Sydney from Edinburgh, and he was appointed Professor of Anatomy in Sydney when Anderson Stuart's department was subdivided in 1890. Wilson filled this chair until 1920, when he went to Cambridge as Professor of Anatomy, retiring from this appointment in 1934.

Wilson's influence spread far, especially in British countries, for among his pupils were Grafton Elliot Smith, J. L. Shellshear, A. N. Burkitt, R. A. Dart, and John Irvine Hunter, who held Chairs of Anatomy in London, Manchester, China, South Africa, and Sydney. Hunter was appointed Challis Professor of Anatomy at Sydney when

FIG. 2.—The Old Medical School.