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Tests for infectious mononucleosis

Infectious mononucleosis is an acute infection by Epstein-Barr virus,[1] a herpesvirus that has also been implicated in Burkitt's lymphoma and nasopharyngeal carcinoma. A few cases of infectious mononucleosis are caused by another herpesvirus, cytomegalovirus.[2]

It was in 1888 that a German physician, Emil Pfeiffer of Wiesbaden, described the clinical picture of what he somewhat coyly termed *Drüsenfieber* ("glandular fever"): fever, lymphadenopathy, and sore throat with, in some cases, enlargement of the liver and spleen.[3] Over 30 years later Sprunt and Evans[4] described the association with characteristic abnormalities of the white blood cells. Next came the discovery by Paul and Bunnell in 1932 that the serum of patients with infectious mononucleosis contains antibody to the erythrocytes of non-human species such as the horse, sheep, or guinea-pig.[5] They showed that the production of antibodies to a wide variety of antigens is characteristic of infectious mononucleosis but by no means confined to it.

The detection of these heterophil antibodies, as they are called, may be a trumpet which gives an uncertain sound. Their variety, their comparative transience, and the inevitable overlap with the production of heterophil antibodies in other diseases mean that the findings must be interpreted with caution. The explanation of their formation may be that Epstein-Barr virus, which is known to infect B lymphocytes, may stimulate those already committed to the production of certain antibodies. In practical terms, the production of heterophil antibodies is of great diagnostic value in infectious mononucleosis, with the antibodies to erythrocytes in particular being usually chosen as the basis for laboratory tests.

There are, therefore, three hallmarks of infectious mononucleosis—the clinical picture, the blood picture, and the serological findings. The discovery of Epstein-Barr virus[6] has now made it possible to corroborate the diagnosis by finding antibodies to the virus itself. These may be detected by fluorescent antibody staining of transformed lymphocytes infected with the virus. This investigation is not, however, generally performed in routine virus laboratories, and furthermore the antibody may appear very early and its titre rise rapidly, so that this rise may be missed. Nevertheless, it is useful as a confirmatory test, since in some cases of infection with Epstein-Barr virus the results of tests for heterophil antibody are negative, particularly in children with an atypical illness. Even if a serum sample has not been taken early enough for a rise in titre to be detected, a single titre of antibody against Epstein-Barr virus of 1:80 or higher, or the presence of specific IgM, may be accepted as diagnostic. Hence, even in the absence of a positive heterophil antibody test, Epstein-Barr virus may be implicated with certainty as the cause of the illness.

The technique of testing for the heterophil antibodies specific for infectious mononucleosis has not stood still. The Paul-Bunnell test was first refined with the discovery by Davidsohn and Walker[7] that absorption of the patient's serum with guinea-pig kidney (containing Forssman antigen) increased the specificity of the test, and soon afterwards horse erythrocytes were reported to be more sensitive than sheep. The horse cell agglutination tube test[8] of Lee and Davidsohn has a greater sensitivity than the conventional Paul-Bunnell test, but is of comparable specificity. The advent of commercial kits (such as the Monospot test) has rendered confirmation (or otherwise) of a clinical diagnosis even easier and quicker.[9] These tests are usually performed on a slide at a single serum dilution and depend on agglutination of formalin-treated horse erythrocytes with or without prior absorption with guinea-pig kidney. Not surprisingly, there are sometimes false-positives. A series of five patients in whom the Monospot slide agglutination test was positive in the absence of other evidence of glandular fever, including specific serological evidence, was studied by Horwitz and others[10] (the latter, by the way, including the Henles, who originally brought to light the connection between infectious mononucleosis and Epstein-Barr virus).[11] The five patients continued to react positively to the Monospot test over periods from four to six years but had negative results to conventional testing by the horse cell agglutination test. Heterophil antibodies may persist for months or years after infectious mononucleosis, so that their presence may signify a past infection. For example, the use of the horse cell test showed that three-quarters of army cadets with infectious mononucleosis still gave positive test results 12 months later.[12] Investigation of the five patients with persistent Monospot responses for antibodies to Epstein-Barr virus-capsid antigens and to Epstein-Barr virus associated nuclear antigen showed that two of them had, in fact, had an Epstein-Barr virus infection at some time in the (distant) past. Two of the other three had no evidence of Epstein-Barr virus infection at any time. The fifth patient underwent seroconversion during the three-year period of observation but the positive response to the Monospot test remained unaltered.

Horwitz *et al*[10] mention six other patients with persistently

positive Monospot tests. Three had specific serological evidence of Epstein-Barr virus infection at some time in the past, but the other three did not. Clearly, in some individuals, the Monospot test may give an anomalous and at present inexplicable false-positive result. Nevertheless, these findings are uncommon, and their occasional appearance should not detract from the value of the Monospot test as a rapid and easily available test for mononucleosis to Epstein-Barr virus—though it should remind us that no one test is infallible. Fortunately, recourse to one of the conventional—if more laborious—tests, and the increasing availability and use of tests for antibodies to Epstein-Barr virus, should resolve most difficulties.

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Pregnancy in the underweight woman

A woman who is underweight before becoming pregnant runs an above-average risk of giving birth to an underweight infant.[1 2] A recent paper by Edwards and his colleagues deals in more depth with the maternal and fetal outcome in such cases.[3]

The results of this study show that in women who are 10% or more below the standard weight for height before pregnancy both mother and baby have an increased risk of complications. The infants tend to be premature and to have low apgar scores, and at 1 year to show inadequate growth with evidence of delayed neurological development. The mothers have a higher incidence of anaemia and premature rupture of membranes; underweight women, on the other hand, are less prone to develop pre-eclampsia. Although we need to know much more about the determinants of fetal growth, undernutrition before pregnancy clearly has both immediate and long-term implications for the health of the infant—whose optimum growth and development are related to the nutritional state of the mother not only during but for many years before pregnancy.[4] Nevertheless, underweight was not included in the otherwise comprehensive list of risk factors formulated by Wigglesworth.[5]

Obstetricians must therefore identify the underweight woman as at increased risk and ensure that she has intensive antenatal supervision and hospital confinement. With the increasing opportunities for counselling women before they embark on pregnancy doctors should encourage those who are underweight to improve their nutrition before becoming pregnant. At the same time they should identify and attend to factors such as smoking and chronic infection that may be associated with the poor nutritional state. Vitamin supplementation may also be extremely valuable in underweight patients with associated iron-deficiency anaemia reflecting long-term suboptimal nutrition; and it could possibly have a beneficial influence on the incidence of neural tube defects, particularly in high-risk areas,[6] though we need the results of a controlled trial before we can be sure. The neonatal paediatrician also should be alerted to the delivery of such women so that the babies are followed up carefully, with proper attention given to their nutritional requirements during the first year of life.

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Contraception by female sterilisation

Sterilisation is being used increasingly often as a routine method of contraception in women and especially in those who have only ever used the contraceptive pill as an alternative. Many different techniques are effective, but the surgical complications will be least when experienced surgeons use laparoscopy or a mini-laparotomy approach.

Laparoscopy has a small advantage over mini-laparotomy: it is quicker and less painful, has fewer complications, and offers a better view of the pelvis.[1 2] If the necessary equipment or experience is lacking, however, mini-laparotomy is a satisfactory second choice.[2 3]

Techniques of occlusion that require complex reorganisation of the tubes are difficult unless a full laparotomy incision is made—and a full laparotomy implies a longer hospital stay and higher incidence of complications. A bewildering choice of clips, rings, suture, cutting, and coagulation is available to surgeons using the limited approaches. Mini-laparotomy allows the fallopian tubes to be cut, cut and tied, tied, or clipped, while laparoscopy allows them to be coagulated, coagulated and cut, clipped, or ringed. Though many surgeons still use electric diathermy, this carries an extra risk of visceral burns and also destroys relatively much of the tube. If the tubes are coagulated and cut there is an additional risk of bleeding from vessels in the mesosalpinx, and further diathermy may then lead to serious damage to the tissues. Tubal rings are relatively difficult to apply; they also cause more postoperative pain and damage much of the tube.[4-6] Furthermore, all these techniques that damage relatively much of the tube