INFECTION MONONUCLEOSIS

The current working concept of infectious mononucleosis is that it is a self-limited, lymphoma-like illness caused by a virus which, however, in some people, may produce a malignant lymphoma.

William Dameshek described infectious mononucleosis as a self-limited neoplasm. Summarizing evidence before 1967, he remarked that the only distinction between infectious mononucleosis and lymphoma was that infectious mononucleosis regressed spontaneously, (Dameshek & Gunz, 1964). The evidence for this statement is of three types: histological, cytological and virological.

A. Histology

Patients with infectious mononucleosis have lymph node pathology which is easily confused with lymphoma. In one series, five of 11 lymph node biopsies were initially read as lymphoma (Salvador et al, 1971). The architecture is often distorted by large dark lymphoid cells and the capsule may be infiltrated (Custer & Smith, 1948). Reed-Sternberg cells have been reported on at least three occasions (Lukes et al, 1969; McMahon et al, 1970; Agliozzo & Reingold, 1971). Moreover, involvement is not limited to lymphoid tissue; perivascular cuffing of brain, inflammation of liver, and infiltration of kidney and bone marrow have been repeatedly observed (Custer & Smith, 1948). LDH and alkaline phosphatase values may be as high as in infectious hepatitis (Gelb et al, 1962).

As one might predict from the pathology, infectious mononucleosis is a multisystem disease and may present with a variety of clinical syndromes: meningoencephalitis, Guillain-Barre syndrome, respiratory distress associated with swelling of the tracheal and pharyngeal tissues, purpura, haemolytic anaemia, hepatitis, splenic rupture, and nephrotic syndrome (Carter & Penman, 1969).

B. Cytology

Cytologic studies in infectious mononucleosis were given a great impetus by the discovery that 5% of the peripheral blood cells may be in DNA synthesis (Bond et al, 1959); similar proportions of cells in acute leukaemia and chronic granulocytic leukaemia are in DNA synthesis. Mitoses accumulate when peripheral blood cells are incubated for 1–6 hr with colchicine (MacKinney, 1967). Rare mitoses have been reported in peripheral blood smears of patients with infectious mononucleosis (Moeschlin, 1941). These findings give credence to the idea of an actively proliferating, possibly invasive cell population.

C. Virology

The close kinship between Burkitt’s lymphoma and infectious mononucleosis provided further evidence of the pseudo-lymphomatous character of infectious mononucleosis: (1) Both Burkitt’s lymphoma cells and infectious mononucleosis cells can be easily adapted to long-term tissue culture (Epstein & Barr, 1964, 1965; Zurhausen et al, 1967; Pope, 1967;
Glade et al, 1968). After cultivation both have been shown to have herpes-type virus particles (Epstein-Barr virus, EBV) which are serologically (Henle et al, 1968; Henle & Henle, 1968; Klein et al, 1968; Gerber et al, 1968) and electron micrographically indistinguishable (Epstein et al, 1964, 1965; Moses et al, 1968). (2) High titres of antibody to this virus are found in the patients with infectious mononucleosis as well as patients with Burkitt's lymphoma (Henle et al, 1968). (3) A chromosome abnormality has been found in both Burkitt's lymphoma and infectious mononucleosis cultured cells. (This abnormality does not correlate well with the presence of the virus and is of uncertain significance (Kohn et al, 1968.)) (4) Cell lines from infectious mononucleosis patients have been shown to have malignant properties by transplantation into animal hosts (Adams et al, 1971). (5) Serum from patients with infectious mononucleosis stimulates the growth of bone marrow colonies in agar as does the serum from some patients with acute leukaemia and leukaemic mice of the AKR strain (Metcalf & Wahren, 1968).

D. Serology

Serologic studies of antibodies to the Epstein-Barr virus show that the age distribution among American children parallels antibodies to other common viruses, such as measles and mumps (Henle & Henle, 1967). In poor socio-economic groups, the antibody is acquired in about 80% of children, often without evidence of disease (Lehane, 1970; Henle et al, 1968). In higher socio-economic groups, however, only 25% have significant titres of antibody on entrance to college. Of those patients with antibody, none developed classical infectious mononucleosis. More than 90% of patients who develop infectious mononucleosis will develop antibody titres to the Epstein-Barr virus as well as heterophile antibodies (Evans et al, 1968). Titres rise during the acute illness and the antibody has been shown to be IgM antibody early with IgG antibody emerging later as in other classic immunologic reactions (Sutton et al, 1973; Hampar et al, 1971). High titres against the virus practically preclude the development of infectious mononucleosis (Saywer et al, 1971; Niederman et al, 1970). Antibodies to the virus persist for years: the original heterophile positive patient still has an EBV titre of 1:30 37 yr after diagnosis (Niederman et al, 1968). The virus has not been proven to cause infectious mononucleosis, in spite of rumours that the virus has been given to normal volunteers with development of disease. However, virus can be recovered from the pharynx after infection (Miller et al, 1973).

The serology of infectious mononucleosis is otherwise quite unusual. Antibodies against i, an antigen found on cord erythrocytes (Marsh & Jenkins, 1960), have been found in 20–80% of patients (Hossaini, 1970; Jenkins et al, 1965). This antigen normally disappears during postnatal life and is replaced by I (Marsh, 1961). In infectious mononucleosis, i antigen appears to be unmasked on the red cell. Acquired haemolytic anaemia is occasionally associated with i antibody (Troxel et al, 1966). The role of antibody in the production of neutropenia and thrombopenia is less well understood (Penman, 1968). Other unusual antibodies include false positive Wasserman reactions, antinuclear antibodies, cold reacting rheumatoid factor, and antibodies against Newcastle disease virus (Carter, 1966a; Kaplan & Tan, 1968; Copra et al, 1969; Barron et al, 1967).

Heterophile antibody, like anti i, is a macroglobulin (Carter, 1966b). It agglutinates sheep red cells, and can be removed completely from serum by pre-incubation with beef red cells,
but not by guinea-pig kidney (Davidsohn & Henry, 1969). Heterophile antibody titres usually rise after the third day of illness, peak at 2 weeks, and remain positive to 6 weeks (Hoagland, 1952). The Paul-Bunnell serologic agglutination method is being largely replaced for screening by a spot test: finely ground guinea-pig kidney or beef red cell stroma is added to serum on a slide followed by a drop of horse cells. The test is considered positive if agglutination occurs in the presence of guinea-pig kidney (which absorbs out Forssman antibody but not heterophile antibody) but is negative with beef red cell stroma (Lee et al, 1968).

E. Infectious Mononucleosis and Other Diseases

The association between infectious mononucleosis and other disease is instructive. One case of Burkitt's lymphoma has been reported following infectious mononucleosis. The finding has suggested the possibility that antibody does not protect against malignant transformation by the virus or that the diseases have different etiologies (Cohen et al, 1970). Intercurrent development of infectious mononucleosis during acute lymphocytic leukaemia in children has been reported at least 15 times, suggesting that these diseases have independent etiologies (Stevens et al, 1971). The incidence of leukaemia in patients following infectious mononucleosis is now being studied but no firm data have been reported (Levin et al, 1972; Miller et al, 1972).

The presence of Epstein-Barr virus antibody has been studied in a variety of diseases other than Burkitt's lymphoma and infectious mononucleosis. Nasopharyngeal carcinoma, a disease which as a prominent lymphoid component, is associated with high titres of EBV antibody (Ida et al, 1972). Less than 50% of American children with Burkitt's lymphoma have significant antibody against Epstein-Barr virus. This suggests that the virus does not cause American Burkitt's lymphoma (Tischendorf et al, 1970). On the other hand, high titres of antibody in chronic lymphocytic leukaemia (Johansson et al, 1971), poorly differentiated lymphoma (Johansson et al, 1970), Hodgkin's sarcoma (Levine et al, 1971), and sarcoidosis (Hirshaut et al, 1970), are being reported.

The mononucleosis syndrome includes febrile diseases with atypical lymphocytes in which the EBV titre does not rise. One such disease that has been extensively studied is the post-pump-perfusion syndrome, a febrile illness occurring after cardiac surgery or other massive blood transfusion. Antibodies to the Epstein-Barr virus occur rarely in this illness; however, cytomegalic disease virus (CMV) titres rise quite frequently, suggesting that this virus may be the etiology of the post-perfusion syndrome (Kantor & Goldberg, 1971).

Infectious hepatitis and serum sickness are illnesses commonly considered in the differential diagnosis of infectious mononucleosis. Other conditions in which atypical lymphocytes are found in peripheral blood include virus diseases such as measles and mumps; reactions to drugs such as diphenylhydantoin and para-aminosalicylic acid; bacterial infections such as typhoid, tuberculosis, and listeriosis; neoplasms such as lymphosarcoma. Lastly, about 8% of mononuclear cells in normal blood meet the criteria of 'atypical'. Atypical lymphocytes in the peripheral smear are not diagnostic of one disease but represent an immunologic response to a variety of stresses (Wood & Frenkel, 1967).

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