

Chapter XIV

Conditions in which there is a known lowered resistance to infection and an increased liability to both "collagen" and "auto-immune" diseases and malignancy

The depression of immune mechanisms with the development of lymphoma and other malignancies

In cases in which lymphoma, myelomatosis and chronic lymphatic leukaemia develop in subjects suffering from rheumatoid arthritis or other manifestations of rheumatoid disease, RF and organ specific antibodies may disappear from the blood. Talal and Bunim (1964) describe a case of Sjögren's syndrome which developed malignant lymphoma, RF and organ specific antibodies, previously present, disappeared from the serum with the development of the reticulosarcoma. Nilsen et al. (1967) recorded a case of systemic lupus erythematosus which developed Hodgkin's disease ten years later. All clinical and serological signs of systemic lupus erythematosus then disappeared. Fernandez-Herlihy and Kott (1967), Schmidt and Gebhardt (1969), Szegedi et al. (1968) and Klingmuller and Voelander (1965) also record similar cases. In one case successful treatment of the Hodgkin's disease caused a reappearance of the serological changes and antibodies in the blood. Zawadski and Benedek (1969) describe a case of rheumatoid arthritis with RF in the blood, which disappeared with the development of lymphosarcoma, and five cases of seropositive rheumatoid arthritis in which myelomatosis developed and in which the RF titre fell markedly with the onset of the malignancy. In the author's experience, described above, with cases of rheumatoid arthritis developing lymphoma or lymphatic leukaemia and sometimes carcinoma, this phenomenon

has also been noted. Alexander and Fairley (1968) report that in reticulososes, including leukaemia, circulating antibody formation is usually impaired, especially in disease of lymphocytic and plasma cells (chronic lymphatic leukaemia, lymphosarcoma and myelomatosis). In other reticulososes and carcinoma variable results are obtained, but usually only the primary response to antigenic stimulation is impaired. Arenberg (1964) and Hughes and MacKay (1965) point out that in cases of cancer and lymphoma there develops depression of immune mechanisms and tissue energy, which may return to normal with successful treatment of the tumour. Southam (1968) reports that in cases of non-lymphomatous cancer many patients show impaired immune responses, especially those requiring mediation of cells rather than the production of serum antibodies. Lee et al. (1970) report similar findings of depressed antibody-producing capacity in cases of human cancer. It has been shown that limax amoebae infection which exists in cancer cases may depress the formation of immunoglobulins and the humoral mechanisms resisting the growth of cancer cells and thus a cancerous process gains momentum. That this does occur was shown by Dostalova et al. (1970), who found a progressive decrease in IgG and IgM in the serum with advancing cancer. The loss of the immune mechanisms in advanced cancer not only explains the rapid progress of malignant disease after it has appeared, but also why intercurrent infections, which further depress immune mechanisms, may cause a sudden growth of hitherto stationary sec-

ondaries (Gordon-Taylor, 1959; Willis, 1967) or the sudden appearance of Hodgkin's disease (Hoster and Dratman, 1946).

In a number of conditions in man there occurs a depression of bodily resistance to infections and in these there appears to be a special liability to both collagen and auto-immune diseases and to lymphomata and cancer. Among these are:-

- 1) Congenital agammaglobulinaemia, already considered.
- 2) Increasing age, already considered.
- 3) Generalized sarcoidosis.
- 4) The effects of administration of hydantoins.
- 5) The effects of organ transplants and administering immunosuppressive drugs.
- 6) The effects of generalized irradiation.

a) Sarcoidosis and malignant lymphoma and carcinoma

In cases of sarcoidosis with its partial failure of cellular immunity there appears to be an increased susceptibility to the manifestations of collagen and auto-immune disease (see above). There are a number of reports in which disseminated sarcoidosis has been associated with or followed by the development of malignant lymphoma or leukaemia (Poutier, 1934, quoted by Raben et al., 1962; Craver, quoted by Hoster and Dratman, 1948; Lamache et al., 1954, quoted by Raben et al., 1962; Moertel and Hagedorn, 1957; Razis et al., 1959 a; Raben et al., 1962). Buckle (1960) described a patient with sarcoidosis of the lungs who developed generalized reticulosarcoma as the former was regressing. Kissel et al. (1961) reported the case of a patient with lymphoma in which the histological changes of sarcoidosis were present in some of the lymph nodes and the changes of lymphatic leukaemia appeared terminally. Atwood et al. (1966) described the case of a 49 year old negro with generalized sarcoidosis who developed mycosis fungoides and fatal malignant lymphoma. They found 14

previously reported cases of this association. Two cases of co-existent disseminated sarcoidosis and Hodgkin's disease were described by Goldfarb and Cohen (1970) and another in which sarcoidosis was followed by lymphosarcoma by Silver et al. (1967). Five cases of sarcoidosis followed by Hodgkin's disease or chronic lymphatic leukaemia were reported by Brincker (1972), of which one case had both Hodgkin's disease, squamous carcinoma of the lip and leukoplakia of one vocal cord and the other chronic lymphatic leukaemia and carcinoma of the cervix. Sarcoidosis always comes first.

Gresham and Ackerley (1958) and Gregorie et al. (1962) record sarcoid-like lesions within neoplasms and in regional lymph nodes and these have been reported in association with a variety of tumours, for example, tumours of the breast, skin, bronchus, bile ducts, ovaries and neurocytoma. Generalized sarcoidosis may also occur. The former authors report a case of carcinoma of the stomach with sarcoid lesions in the lymph nodes whether or not these were affected by metastases. They were also present in the lung and liver, and Gresham and Ackerley mention ten cases of carcinomatosis in which regional lymph nodes showed diffuse granulomata and giant cell reaction. Granulomatous lesions like sarcoidosis are also described in ovarian dysgerminomata and granulosa cell tumours. In such cases of "sarcoid" in local lymph nodes draining a malignant tumour it seems that the sarcoid changes are a reaction to substances produced by the tumour.

Carcinoma may also exhibit a relationship to disseminated sarcoidosis. Sarcoidosis associated with bronchial carcinoma has also been described by Jefferson et al. (1954) and Sakula (1963). Warner (1962) reports sarcoidosis and malignant teratoma of the lung. Badmaeva (1970) reports a case of sarcoidosis which developed angio-sarcomatosis and Jahn et al. (1969) the case of a patient with gen-

eralized sarcoidosis, ulcerative colitis and carcinoma of the terminal ileum. In a case known to the author multiple shadows were present in both lungs radiologically and a carcinoma of the pylorus was found at operation. Total gastrectomy and splenectomy were performed and histologically the spleen showed the changes of sarcoidosis.

In cases in which generalized sarcoidosis preceded or accompanies the manifestations of malignant lymphoma it may well be that the liability of patients with sarcoidosis to develop the manifestations of rheumatoid disease is related to the subsequent development of lymphoma or carcinoma. As regards the association of generalized sarcoidosis with various malignant tumours this may be ambivalent. It may be that the development of malignant disease with its associated loss of resistance to infection may favour the development of sarcoidosis or vice versa.

b) The effects of administration of hydantoins

It has been suggested that some cases of idiopathic epilepsy may result from *limax amoebae* infection. Hydantoins are, of course, widely used in its treatment. Attention has already been drawn to observations suggesting that they depress both cellular and humoral immunity mechanisms.

Hydantoins and lymphomata

It has been seen that hydantoins may result in the appearance of collagen diseases, including benign lymphadenopathy. A condition closely mimicking malignant lymphoma, clinically and pathologically, following taking of various hydantoins over a prolonged period was described by Saltzstein and Ackerman (1959). The syndrome included lymphadenopathy, fever, exanthemata, eosinophilia in the blood and bone marrow and less often hepato- and spleno-megaly. Pathologically the lymph nodes showed obliteration of their

normal architecture, hyperplasia of reticulum cells and other elements, frequent mitoses, infiltration with eosinophils, focal necrosis and phagocytosis, but no Reed-Sternberg cells or a picture like Hodgkin's disease or reticulosarcoma, or only chronic inflammation. One patient, and another quoted from the literature, showed persistent plasmocytosis in the bone marrow and resected nodes abnormal serum proteins. There was no conclusive evidence of myeloma. Hyman and Sommers (1966), however, report six cases of true Hodgkin's disease and lymphoma developing during anticonvulsant therapy and Rausing and Trelle (1971) another. Brown (1971) reports that there is a spectrum of lymphadenopathies varying from hyperplasia to neoplasm with Reed-Sternberg cells. It may be that depression of resistance to *limax amoebae* by the drug is responsible for the appearance of both collagen disease and lymphoma in such circumstances.

c) Human organ transplants and cancer

In cases of human organ transplants in which therapeutic immunosuppression is used there are now over 40 reported cases of the development of malignant lymphoma (Doll and Kinlen, 1970). Fairley (1971) reports that in about 4,000 renal transplants there occurred 12 reticulum cell sarcomas, 3 other lymphomas, 2 carcinoma of the gastro-intestinal tract, 9 of the lip or skin, 2 of carcinomatosis and 4 of other organs. Inadequate information was available in 5 cases and carcinoma-in-situ of the cervix occurred in 5 cases. Walder et al. (1971) report skin cancer, often multiple, as developing in 7 of 71 cases of kidney allograft recipients receiving immunosuppressive drugs. Tallent et al. (1971) describes a case which developed a carcinoma of the cervix and Hyun-Hank and Williams (1972) the development of endometrioid carcinoma of the uterus and bilateral ovarian carcinoma in a subject of renal transplantation and

Addendum: Multiple myeloma after phenytoin therapy. Aymard JP, Lederlin P, Witz F et al. *Scand. J. Haematol.* 1981, 26 330-332
Authors report a case of multiple myeloma in a 48 years old woman treated with phenytoin 55 months. Association may be fortuitous but depressive effect of drug on immune responses would account for blood changes.

Addendum: Mougeot-Martin, M., Krulik, M., Haronsseau, J.L., et al., *Ann. Med. Interne.*, 1978, 129, 175-80, collected more than thirty examples of acute leukaemia following immunosuppressive therapy for multiple sclerosis and for Behcet's syndrome. The leukaemia was often preceded by a preleukaemic phase.

Addendum: Matzner Y and Polliack A. Monoclonal gammopathy and subsequent multiple myeloma in a patient on chronic diphenylhydantoin therapy. *Isr. J. Med. Sci.* 1978, 14, 1265-1267