reasonable." Grifoni *et al.* suggest that two lymphocyte populations are in conflict[27] and mention that their observations support the view of Hamilton Fairley that "lymphocytes may be committed to react against Hodgkin's tissue."[28] This theme of autoaggressive activity recurs in the literature on Hodgkin's disease.[29 30]

## Graft-versus-host Disease

In a series of experiments graft-versus-host disease was induced in adult mice by injecting parental lymphoid cells into the first generation hybrids. The injected cells colonized the spleen and lymph nodes, and mounted an immunological attack on host tissues. Even in the early stages of the disease, striking histological changes have occurred. Widespread infiltration by lymphoid cells in many organs was seen—liver, pancreas, adrenal, and maxillary glands, and even muscle. Atrophy of the intestine occurred early and is probably important in the wasting syndrome. When we contrast the main features of graft-versus-host disease with Hodgkin's disease there are certain features in common (see Table).

*Comparison of Hodgkin's Disease and Graft-versus-host Disease*

| | Disease | Features |
|---|---|---|
| Similarities | Hodgkin's Disease | Invasive nature of growth<br>Occasional presence of splenic amyloid<br>Wasting<br>Depletion of lymphocytes in terminal state |
| | Graft-versus-host Disease | Invasion of multiple organs by small round cells<br>Presence of splenic amyloid<br>Wasting<br>Depletion of lymphocyte in terminal state |
| Differences | Hodgkin's Disease | Large masses at necropsy<br>Reticulum cells and Reed-Sternberg cells<br>Necrosis common<br>Eosinophils common<br>Gut changes uncommon, exception primary form |
| | Graft-versus-host Disease | No large masses at necropsy<br>Pyronophilic mononuclear cells and histiocytic proliferation<br>Necrosis rare<br>Eosinophils rare<br>Gut changes common |

Dr. Regunathan and I have investigated the function of macrophages in animals suffering from early graft-versus-host disease.

Firstly, the macrophages are bigger and more pleomorphic than normal with an increased affinity for particular matter. Secondly, they no longer discriminate between self and not-self, surely reflecting a fundamental change in behaviour. When macrophages from normal animals are mixed with lymphocytes from normal animals of the same strain, little or no interaction occurs—that is, there is no adherence or death of cells. On the other hand, when macrophages from animals with graft-versus-host disease are used, their interaction with lymphocytes results in the death of the cell—a singularly unphysiological state of affairs. Furthermore, the serum of animals with this disease contains a factor, presumably antibody, which promotes adherence of lymphocytes to macrophages. This antibody reduces the severity of the cell-mediated necrotizing reaction, presumably by coating the cell with a layer of protective protein.

Perhaps these cell-culture techniques can be applied to the study of the cellular pathology in reticulum cell neoplasia and to the problem of autoaggression amidst the turbulent cell population of Hodgkin's disease.

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REFERENCES


1 Symmers, D., *Journal of the American Medical Association,* 1945, **128,** 1248.
2 Sirtori, C., *Lancet,* 1970, **1,** 92.
3 Aisenberg, A. C., *Journal of Clinical Investigation,* 1962, **41,** 1964.
4 Aisenberg, A. C., *Cancer Research,* 1966, **26,** 1152.
5 Chase, M. W., *Cancer Research,* 1966, **26,** 1097.
6 Kelly, W. D., Lamb, D. L., Varco, R. L., Good, R. A., *Annals of the New York Academy of Sciences,* 1960, **87,** 187.
7 Smithers, D. W., *British Medical Journal,* 1967, **2,** 263 and 337.
8 Crowther, D., Fairley, G. H., and Sewell, R. L., *British Medical Journal,* 1969, **2,** 473.
9 Eggerth, G., Kuhbock, J., and Pokorny, D., *Wiener Zeitschrift für innere Medizin und ihre Grenzgebiete,* 1969, **50,** 314.
10 Szur, L., Harrison, C. V., Levene, G. M., and Samman, P. D., *Lancet,* 1970, **1,** 1016.
11 Fazio, M., and Bachi, C., *Nature,* 1967, **215,** 629.
12 Thomas, J. W., Boldt, W., and Horrocks, G., *Canadian Medical Association Journal,* 1968, **99,** 303.
13 Havemann, K., *Deutsche Medizinische Wochenschrift,* 1969, **37,** 1867.
14 Barr, M., and Fairley, G. H., *Lancet,* 1961, **1,** 1305.
15 Irunberry, J., and Colonna, P., *La Presse Medicale,* 1970, **78,** 187.
16 Blefari, D., and Gambertoglio, G., *Il Cancro,* 1968, **21,** 529.
17 Castuma, J. C., Cicchetti, G. E. H., and Bergna, L. J., *Sangre,* 1967, **13,** 275.
18 Ferrari, S., Foggi, C. M., and Serafini, N. A., *Annali dell'Instituto Carlo Forlanini,* 1968, **28,** 292.
19 Goldman, J. M., and Hobbs, J. R., *Immunology,* 1967, **13,** 421.
20 Philipson, L., and Ponteri, J., *Life Sciences,* 1967, **6,** 2635.
21 Pisi, E., Feliciantonio, R. D., Figus, E., and Ferri, S., *Minerva Medica,* 1968, **59,** 944.
22 Stiehm, E. R., and Fudenberg, H. H., *Pediatrics,* 1966, **37,** 715.
23 Stuart, A. E., *Journal of Pathology,* 1970, **101,** 1.
24 Stuart, A. E., and Davidson, A. E., *Journal of Pathology,* 1970, **102.** In press.
25 Stuart, A. E., and Davidson, A. E., *Journal of Pathology,* 1970, **103.** In press.
26 Kaplan, H. S., and Smithers, D. L., *Lancet,* 1959, **2,** 1.
27 Grifoni, V., Del Giacco, G. S., and Tognella, S., *British Medical Journal,* 1969, **3,** 414.
28 Fairley, G. H., *British Medical Journal,* 1969, **2,** 467.
29 Johnson, A. G., *Radiological Clinics of North America,* 1968, **6,** 41.
30 Woodruff, M. F. A., *Lancet,* 1964, **2,** 265.


# Host Defence Mechanisms in Burkitt's Lymphoma and Kaposi's Sarcoma : The Clinical Evidence

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Choriocarcinoma and Burkitt's lymphoma are unique among malignant tumours in the high rate of cures that can be obtained with chemotherapy. The former is in a category of its own since it develops from fetal rather than host cells. Thus, with this exception, Burkitt's lymphoma is the only form of cancer in which a high proportion of apparent cures can be obtained with chemotherapy alone.

Two other tumours, malignant melanoma and Kaposi's sarcoma, also have a tendency to occasional spontaneous remission. I propose to discuss some aspects of Kaposi's sarcoma together with Burkitt's lymphoma, having had considerable clinical experience of both these tumours.

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## Burkitt's Lymphoma

Characteristically Burkitt's tumour responds to a wide range of cytotoxic agents and a high proportion of patients survive apparently free from tumour. Thus there are almost 100% of long-term survivals in patients with one or more tumours limited to the face.[1] Even in patients with intra-abdominal, intrathoracic, or skeletal tumours (other than face) there was a survival rate of over 50%. Moreover, Williams has shown that

impressive results can be obtained even in a simple mission hospital with limited facilities.[2] These results should dissuade doctors from denying treatment to these patients who have no access to specialized centres. Finally, chemotherapy can also achieve remarkable recovery in grossly destroyed bone, a feature particularly evident in jaw tumours.[3]

The next important feature is the effectiveness of even single doses of cytotoxic drugs. Most long-term survivors in my own series[4] received only one or two injections of cyclophosphamide or vincristine sulphate or equivalent oral doses of methotrexate. This sustained response following minimal treatment is one of the strongest arguments suggesting the existence of host defence mechanisms, since it would be unreasonable to postulate that these minimally toxic doses killed all the tumour cells. This is supported by the reports that some tumours have regressed some time after chemotherapy had been stopped.[5,6]

Spontaneous remission of malignant tumours inevitably implies some form of host defence against cancer. Two patients admitted to Mulago Hospital, Kampala, left against advice without treatment following diagnostic biopsy. One had a maxillary tumour and the other had massive bilateral breast tumours.[7] Both remain well seven and four years later.

Non-specific treatment may also be effective in Burkitt's lymphoma. A patient with a histologically confirmed jaw lymphoma was discharged from hospital when no cytotoxic drugs were available. A local practitioner, yielding to the persuasive pleas of the child's mother, gave injections of a remedy containing hexamine, sodium benzoate, and saccharose, which had been used decades earlier for a wide variety of diseases. A month later the tumour began to regress and subsequently disappeared. The child was well seven years later. David then treated seven more unselected patients with Burkitt's lymphoma using this proprietary drug Septicemine.[8] One was alive and well three years later, one after total clinical remission died from unknown cause two and a half years after treatment, and one died from bowel perforation a year after clinical remission of tumour. These patients are believed to have had spontaneous remissions.

Though it is rare, lymph node involvement always appears to have poor prognostic significance.[9] This may be a result or cause of impaired tumour immunity.

Fass *et al.* gave 12 patients with Burkitt's lymphoma intradermal injections of autologus tumour extracts.[10] One patient only, with a small maxillary tumour, showed a positive delayed hypersensitivity reaction. All the others, with large tumours, failed to react. Seven of these patients developed positive reactions after successful treatment and remained in sustained remission. Four of the five who failed to react subsequently relapsed. These observations were interpreted as indicating a cellular immune response against the tumour, and a close relationship between this response and the clinical behaviour of the disease.

## Kaposi's Sarcoma

Like Burkitt's lymphoma, Kaposi's sarcoma is a multifocal lesion. Though most patients present with cutaneous nodules on the limbs, these may or may not be associated with considerable oedema locally and widespread visceral deposits. Kyalwazi[11] has pointed out that the differences in clinical behaviour almost warrant a subdivision into two diseases since some tumours remain relatively stationary for many years, whereas others run a fulminating course to early death.

Williams[12] agrees with this view, and from his long experience is impressed by the similarities between the behaviour of both leprosy and Kaposi's sarcoma. Since the differing manifestations of leprosy are now believed to depend on the patient's immunological response, Williams believes that the varying behaviour of Kaposi's sarcoma suggests a similar explanation. It is particularly noteworthy that Kaposi's sarcoma is rapidly fatal in children.[13,14]

The proportion of long-term survivals following chemotherapy is much higher than in other forms of cancer, except in Burkitt's lymphoma and choriocarcinoma. Thus Kyalwazi[15] has recently reported that over 60% of the patients he and his colleagues have treated with triaziquone during the last three and a half years still survive. Over half of Williams's patients are classified as long-term survivals.[2] Unlike patients with Burkitt's lymphoma most long-term survivors retain some evidence of disease. On the other hand, the prospect of sustained remission is closely related to the content of tumour, and in Kyalwazi's experience visceral tumours have been invariably fatal.[15] Again, small doses of treatment may be effective, Williams[2] reporting three patients with severe disease alive and well seven to eight years after receiving small doses of nitrogen mustard or cyclosphophamide.

Both Cook and Williams have reported total spontaneous remissions of this tumour,[2,16] though how often they occur is not known. The frequency with which single tumour nodules atrophy and disappear is a particularly characteristic feature of Kaposi's sarcoma.

Lymph node involvement also carries a poor prognosis. The rapidly fatal course in children may be related to the fact that peripheral adenopathy is the commonest mode of clinical presentation.[13]

Master *et al.* showed a striking impairment in the delayed hypersensitivity response to dinitrochlorbenzene in patients with rapidly growing massive lesions, whereas a good reaction was obtained in patients with localized and relatively stationary tumours.[17] These results suggested that the cellular immune mechanisms were impaired in the more malignant cases as compared with the more stationary ones.

## Discussion

There are several obvious similarities between the behaviour of Burkitt's lymphoma and of Kaposi's sarcoma: such as the response to chemotherapy; the relative frequency of long-term survivals and spontaneous remissions; the simultaneous regression of some lesions and the enlargement of others; the fact that the successful eradication of one tumour can be followed by the development of another at a different site; the positive results of hypersensitivity skin reactions in patients with small tumours in remission, compared with the negative results in the presence of large and actively growing lesions, suggesting the presence of cellular immunity; the geographical distribution, which suggests at least partial dependence on some local environmental factor; and the poor prognostic significance of lymph node involvement in both tumours.

All these suggest the operation of some form of host defence mechanism. Possibly in Burkitt's lymphoma the development of the tumour means that this has been overcome. But if treatment can kill sufficient tumour cells probably the balance can often again be tipped in favour of the patient's defences. Kaposi's sarcoma seems to represent a fine adjustment of balance between the growth potential of the tumour and the host defence mechanisms. This allows an apparently stable situation to persist for many years, with some lesions regressing and others remaining static. The occasional spontaneous remissions could represent a tipping of the balance in favour of the host, whereas rapid growth and visceral involvement could reflect a tipping of the scales in the opposite direction.

The tumour rejection phenomena observed in Burkitt's lymphoma appear to be related to a high degree of antigenicity, which is characteristic of virus-induced animal tumours and is consistent with the evidence pointing to a virus as an aetiological factor. There is as yet no indication which if any environmental factors may be responsible for Kaposi's sarcoma.

No satisfactory theory has been suggested to explain how in both these diseases a tumour in one site may be regressing while one elsewhere is growing, or why tumours should recur in another site after satisfactory treatment of the original lesion.


REFERENCES

[1] Ziegler, J. L., Morrow, R. H., jun., Fass, L., Kyalwazi, S. K., and Carbone, P. P., unpublished report, 1970.
[2] Williams, E. H., personal communication, 1970.
[3] Adatia, A. K., *British Dental Journal*, 1966, **120**, 315.
[4] Burkitt, D. P., *Cancer*, 1967, **20**, 756.
[5] Burkitt, D. P., Hutt, M. S. R., and Wright, D. H., *Cancer*, 1965, **18**, 399.
[6] Ngu, V. A., Burkitt, D. P., and Osunkoya, B. O., in *Burkitt's Lymphoma*, p. 158. Edinburgh, Livingstone, 1970.
[7] Burkitt, D. P., and Kyalwazi, S. K., *British Journal of Cancer*, 1967, **21**, 14.
[8] David, J., and Burkitt, D. P., *British Medical Journal*, 1968, **4**, 288.
[9] Burkitt, D. P., and Kyalwazi, S. K., in *Neoplasia in Childhood*, Chicago, Year Book Medical Publishers, 1969.
[10] Fass, L., Herberman, R. B., Ziegler, J. L., and Morrow, R. H., jun., *Journal of the National Cancer Institute*, 1970, **44**, 145.
[11] Kyalwazi, S. K., *East African Medical Journal*, 1969, **46**, 459.
[12] Williams, E. H., Albert Cook Memorial Lecture, 1969.
[13] Slavin, G., Cameron, H. McD., and Singh, H., *British Journal of Cancer*, 1969, **23**, 349.
[14] Kyalwazi, S. K., *East African Medical Journal*, 1969, **46**, 450.
[15] Kyalwazi, S. K., personal communication, 1970.
[16] Cook, J., *Journal of the Royal College of Surgeons of Edinburgh*, 1966, **11**, 185.
[17] Master, S. P., Taylor, J. F., Kyalwazi, S. K., and Ziegler, J. L., *British Medical Journal*, 1970, **1**, 600.


# Immunological Features of Choriocarcinoma

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In mammalian pregnancy the fetus inherits from its father strong antigenic markers which are foreign to the mother and which might be expected to excite an immune response. Yet clearly the fetus must not be damaged or rejected by immune attack. This suggests that under certain circumstances the mammalian organism does not eliminate allogeneic cells, and raises the question whether weakly antigenic tumours may escape immune rejection.

Since choriocarcinoma is a tumour of the fetus which invades the mother it appears to forge this link between the feto-maternal relationship and the tumour-host relationship. The concept has arisen that choriocarcinoma differs from its host not only by weak antigens acquired during malignant transformation, but also by strong and readily definable antigens inherited from the father. Some of the assumptions underlying these proposals will now be considered.

## Evidence that Fetal Tissues are Antigenic

In 1958 Woodruff showed that the rabbit fetus was antigenic to its still pregnant mother,[1] and histocompatibility factors inherited from the father have been found on mouse fetal cells as far back as the two-cell stage embryo.[2-5] On the other hand, E. Moller found that some embryonic tissues were less antigenic than adult tissue.[6]

## Evidence that Trophoblast is an Exception to the General Antigenicity of Fetal Tissue

Choriocarcinoma arises from the trophoblast, the tissue at the interface of the feto-maternal junction, and which may therefore play a special part in the escape of the fetus from immune rejection. This was examined in a series of experiments by transplanting early mouse embryos to ectopic sites in allogeneic recipients. The embryo proper provoked a dense cellular reaction and was resorbed, whereas the trophoblast proliferated and survived for about the normal gestational period, provoking little or no cellular response.[7 8] Moreover, inoculation of mice with trophoblast derived from the mother did not induce immunity to paternal allo antigens. These findings led to the conclusion that trophoblast has an intrinsic deficit of such antigens.[2 4 9] Attempts to detect HL-A antigens on human trophoblast have also been unsuccessful.[10]

Other studies have examined the possible immunological role of fibrinoid,[11 12] which is particularly abundant in the placenta. Histochemical studies suggest that placental fibrinoid may be rich in sialic and hyaluronic acids.[13 14] Sialic acid groups mask trypsin-sensitive sites on sialomucins[15] so it was suggested that immunogenic sites on trophoblast and other cells might be similarly masked.[16] If so, inoculation with trophoblast which has had its sialic acid group removed by treatment with neuraminidase would immunize male strain isoantigens and this proved to be the case.[17]

## Histocompatibility of Parents and Children in Choriocarcinoma

In Europe choriocarcinoma is a rare tumour and it was suggested that it might occur only where matings resulted by chance in exceptionally good "matching" of the tissue types. But in over half the matings studied the husband has been found to carry HL-A antigens not present on the patient's cells and there is no evidence so far of unusually good matching.[18-22] These studies indicate that major antigenic discrepancies between patient and tumour are possible, but they do not prove that such discrepancies exist. More direct evidence is obtained when choriocarcinoma follows a successful term pregnancy and when the child's cells can be examined in parallel with the patient's. In our series these children have also been found often to have one or more HL-A factors which have not been identified on the maternal cells.[23]

ABO blood group substances are strong histocompatibility factors[24] and Group A substance has been shown on early human trophoblast though not on late trophoblast.[25 26] Patients with trophoblastic tumours have been found to show a shift away from Group O,[22 27 28] though this does not reach significance. The shift had been interpreted as indicating increased compatibility between conceptus and patient, but we have seen two instances where rapidly disseminating choriocarcinoma has occurred following an ABO-incompatible first pregnancy.[23] Even so, there may be a deficit of ABO-incompatible pregnancies followed by choriocarcinoma.

The only evidence we have so far that blood group factors influence prognosis, as opposed to tumour occurrence, is that the failure rate with chemotherapy in our few patients in blood group AB is three times that of patients in the other groups.

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