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.

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**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.2,3 On the other hand, E. Moller found that some embryonic tissues were less antigenic than adult tissue.4

**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.5,6 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.7,8 Attempts to detect HL-A antigens on human trophoblast have also been unsuccessful.9,10 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 sialomucins8 so it was suggested that immunogenic sites on trophoblast and other cells might be similarly masked.15 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.16

**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.16-20 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.21

ABO blood group substances are strong histocompatibility factors22 and Group A substance has been shown on early human trophoblast though not on late trophoblast.23 Patients with trophoblastic tumours have been found to show a shift away from Group O,23,24 though this does not reach significance. The shift had been interpreted as indicating increased compatibility between conceptus and parent, but we have seen two instances where rapidly disseminating choriocarcinoma has occurred following an ABO-incompatible first pregnancy.25 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.
Responses to Choriocarcinoma

Antibodies to paternal HL-A antigens and to platelet antigens in the sera of patients with choriocarcinoma have been found by various workers.4 20 and in our series by Dr. S. D. Lawler. These antibodies are well known to result from pregnancy and from blood transfusions, and since all these patients had had at least one such stimulus to antibody production (and many have had several) interpretation of their significance is difficult. All that can be said is that choriocarcinoma can grow and kill patients with circulating cytotoxic and agglutinating antibodies to these antigens.

Cellular Response to Choriocarcinoma and Fetus

There has been a striking variability in the mononuclear cell reaction to choriocarcinoma among our patients. In some it was notably less than that seen for instance around some breast carcinomas. A positive correlation was found between the intensity of the reaction before chemotherapy and the outcome of this treatment.29 In other words, a considerable cellular response tends to be favourable. The contribution from the host’s immune defences (if we interpret the mononuclear cell reaction as such) is clearly not obliterated by the chemotherapy.

Evidence of a cellular immune response to the mammalian fetus is not extensive. We have recently found that excision of the uterus of the pregnant rat is followed by an increase in the proportion of immunoblasts in thoracic duct lymph, comparable to that found by Alexander et al.,22 following excision of rat tumours.22 Changes in the lymph nodes have also been observed during pregnancy.13 24

Maternofetal Responses

Immune responses are not severely impaired either during pregnancy or in choriocarcinoma. An immune response to paternal antigens may well be an inevitable consequence of pregnancy. There is indeed a deficit of ABO-incompatible live births23 and possibly ABO-incompatible choriocarcinomas, indicating that if the antigenic differences are great enough the fetus is harmed and that a malignant fetal tumour may be eliminated. It remains to be determined whether HL-A incompatibility also has similar effects.

However, antigenicity sufficient to cause the prompt rejection of normal adult tissue does not usually result in rejection of the fetus. This “failure” has been described as “maternal tolerance”25 or “maternal inertia.”26 Yet it is clearly not a failure to respond to the fetus but a particular type of positive response. This distinctive response is shown in multiparous mice, which are slow to reject skin grafts from the male strain with which they have been mated.27 28 Unfortunately, there are no comparable data for human pregnancy. In patients with choriocarcinoma the primary rejection of skin from the husband is delayed.8 29 30 Second grafts are also rejected slowly and in some instances only after five grafts or more have been placed and rejected did the rejection time fall to 10-12 days.4 41 The same patients rejected unrelated donor grafts normally.

Little can be said here about the immunotherapy of choriocarcinoma but in our patients intradermal inoculation with B.C.G. between successive grafts abolished the delayed rejection of a graft of the husband’s skin more effectively than repeated provocation with skin or leucocytes taken from the husband. Studies with mouse tumours have indicated that the chemotherapy-immunotherapy interval can be critical,8 9 but we have not yet been able to define any clearly beneficial immunotherapeutic regimen in patients with choriocarcinoma.

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