Attributes of Embryonic Tissues after Growth and Development in Heterologous Hosts*

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Embryonic tissues grow readily on heterologous transplantation to the eye or brain and undergo differentiation into adult structures without the inflammatory reaction that invariably attends the direct transfer of foreign adult tissues (1, 3). The present investigation was undertaken in an attempt to determine whether the failure to evoke such a reaction related to the transplantation site or to changes in the transplant associated with its maturation in the alien species. To this end, two approaches were followed. Embryonic tissues from a variety of species, including man, dog, cat, and rabbit, were transplanted to the subcutaneous space of heterologous species, and the local reaction of the host as well as the fate of the transplant was studied. In other experiments, designed to investigate possible modifications in the constitution of the tissue incident to development in the foreign environment, the susceptibility of the transplant to an infectious agent specific for the donor species was tested.

MATERIALS AND METHODS

It has been noted in previous heterologous transplantation experiments that the incidence of takes in the subcutaneous space bore a relationship to the species of the recipient. Takes were rare in the guinea pig and the rabbit but occurred with relative frequency in the hamster and the DBA mouse. Accordingly, the latter two species were selected as recipient hosts in the present investigation.

Human embryos were obtained from the operating room of the Grace-New Haven Hospital following therapeutic abortion; other embryos were delivered by caesarian section or removed from freshly killed animals. Fragments of tissue measuring approximately 1 mm. in diameter were trans-

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RESULTS

Heterologous subcutaneous transplants.—Embryonic skin from all of the species tested (man, dog, cat, rabbit, guinea pig, and mouse) survived and grew on subcutaneous transfer to hamsters and DBA mice. Takes occurred in approximately 60 per cent of the hamsters and 40 per cent of the mice. The growing fragments were palpable within a week of transfer and increased in size throughout the experimental period. The mass attained by transplants from the same embryo varied greatly and ranged from 2 mm. to 1 cm. at the end of a month.

The majority of transplants resembled dermal cysts and consisted of a core of keratin and hair lined by epidermis and dermis containing hair follicles and glands (Figs. 1–11). Others were distinguished grossly by the presence of long tufts of hair protruding from the transplant into the fat of the axilla. In such cases, giant and inflammatory...
cells were present in the host tissues surrounding the hair shafts, but, when all hair and keratin were confined in the core of the transplant, there was no evidence of an inflammatory reaction in surrounding host tissues.

Retransfer of embryonic rabbit skin after infection.—The results of the retransfer of fragments of embryonic rabbit skin after growth in a heterologous host for varying periods of time and subsequent in vitro infection with the Shope papilloma virus are shown in Table 1. The incidence of takes on retransfer was considerably less than in the first generation, 47.8 per cent in hamsters and 20.8 per cent in mice, but in all except three instances the living transplants showed typical papillomatous transformation (Fig. 1).

A lower incidence of takes in the second generation transplants was expected, and its probable explanation lies in the difficulty of separating proper fragments for transfer. The transplants are intimately associated with host tissues and contain a large amount of keratin as well as a thick envelope of transplanted connective tissue. Epidermis is present in relatively small amount and the selection of fragments containing epithelium is largely by chance. However, the occurrence of papillomatous transformation is highly significant and, from the point of view of susceptibility to infection, identifies the transplants as rabbit in nature.

DISCUSSION

The present investigation was instituted in an attempt to explain the persistence of mature eye and brain transplants of heterologous embryonic tissue without the foreign body reaction characteristic of the transfer of analogous adult tissue. The special conditions obtaining in the eye and brain were found not to be pertinent factors, for the maturation of heterologous embryonic tissue, in the subcutaneous space also failed to elicit an inflammatory response.

The foreign body reaction incident to the transfer of adult rabbit tissue to the hamster derives from the antigenic qualities of the tissue, and the failure of maturing embryonic rabbit tissues to evoke such a reaction indicates that the antigens characteristic of the parent species were not evolved in the alien environment of the hamster. Embryonic rabbit tissue developing to maturity in an alien host prior to removal, infection, and retransfer retains the antigenic attributes of the species, whereas embryonic rabbit tissue developing to maturity in the hamster or mouse fails to evolve such qualities.

It was of interest to determine whether other species characteristics were affected by residence of a transplant in an alien species. Susceptibility to the Shope papilloma virus is a special attribute of the rabbit and is not shared by the hamster. (Susceptibility to this virus is a property of embryonic rat skin but not of adult rat skin or of any developmental stage in the hamster [2].) A ready means of determining whether this property was retained following development in a naturally resistant host was afforded by the retransplantation of embryonic rabbit skin after continued residence in the hamster and in vitro infection. It was found

### Table 1

<table>
<thead>
<tr>
<th>Rabbit Series</th>
<th>Residence of Skin in Alien Host Prior to Removal, Infection, and Retransfer</th>
<th>Retransfer After Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of animals</td>
<td>No. of executions</td>
</tr>
<tr>
<td>20 DBA mouse</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>20 DBA mouse</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>22 DBA mouse</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>21 DBA mouse</td>
<td>58</td>
<td>10</td>
</tr>
</tbody>
</table>

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that susceptibility to the virus was retained and that, with respect to susceptibility to infection, the transplant remained rabbit in nature. It would appear, therefore, that the species factors determining susceptibility to infection are different from those determining antigenicity, and that expression of the latter factors depends on the nurture rather than the nature of the tissue.

SUMMARY

The transplantation of embryonic skin from man, dog, cat, guinea pig, and rabbit to the subcutaneous space of the hamster and the DBA mouse resulted in growth and differentiation without attendant inflammatory reaction. Typical papillomas occurred in mature transplants of embryonic rabbit skin following exposure to the Shope virus and, from the point of view of susceptibility to infection, identified the transplants as rabbit in nature.

REFERENCES

FIG. 5.—Transplant of embryonic cat skin from subcutaneous space of hamster killed 291 days after transfer. Mag. $\times 30$.

FIG. 6.—Higher power view of transplant shown in previous figure. Mag. $\times 145$.

FIG. 7.—Transplant of embryonic cat skin from subcutaneous space of hamster killed 70 days after transfer. Note sebaceous glands. Mag. $\times 165$.

FIG. 8.—Transplant of embryonic dog skin from subcutaneous space of hamster killed 60 days after transfer. Mag. $\times 145$. 
Fig. 9.—Transplant of embryonic dog skin from subcutaneous space of hamster killed 190 days after transfer. Mag. ×145.

Fig. 10.—Transplant of embryonic human skin from the subcutaneous space of a hamster killed 128 days after transfer. Mag. ×30.

Fig. 11.—Higher power view of transplant shown in Figure 10. Mag. ×145.

Fig. 12.—Shope papilloma arising in embryonic rabbit skin following in vitro infection and retransfer to the subcutaneous space of a DBA mouse. The tissue had previously been grown for 36 days in the subcutaneous space of another mouse of this strain. Mag. ×85.
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