Hormonal Dependence of Adrenal Cortical Tumors of CE and BALB/c Mice in Serial Intraocular Transfer

HENRY C. BROWNING

(University of Texas Dental Branch and Baylor University College of Medicine, Texas Medical Center, Houston, Texas)

Tumors of endocrine tissues induced by hormonal imbalance often require a similar imbalance in isologous hosts for successful transfer. Such tumors have been called "hormonally dependent" and those that do not require an imbalance "autonomous" (9). A hormonally dependent tumor may become autonomous during successive transfers (1, 23). These same terms, "dependent" or "autonomous," have been used in reference to the absence or presence of the ability of embryonic, normal, and neoplastic tissue to grow in heterologous hosts (13, 14). Progression from this type of dependence to autonomy may be seen in neoplastic tissue (3) and from autonomy to dependence in embryonic tissue (4).

Adrenal cortical tumors of CE and BALB/c mice, induced by early castration (18), may or may not show "hormonal dependence." The following report concerns four such tumors in serial isologous transfer.

MATERIALS AND METHODS

The adrenal cortical tumors used, all arising in castrated males and, if already transplanted, being carried in castrated males (18), were: CE 1, the original neoplasm in a CE mouse; BALB 5880/1, a first-generation subcutaneous transplant in a BALB/c; BALB 5880/2, a second-generation subcutaneous transplant of the same tumor in a BALB/c; and CE 366/2, a second-generation subcutaneous transplant in a CE mouse.

Except as specified, all transfers were made into the anterior chambers of groups of six to eight isologous hosts, 2–4 months of age, by the technic previously described (5). These hosts might be castrated or intact males or females. Most groups were castrated at the time of transfer, but in some castration preceded transfer by a month or more, and in others castration was not performed until approximately 2 weeks or a month after transfer. Certain other groups were treated with exogenous androgen. Occasionally, subcutaneous transplants were made into isologous male or female hosts of castrate or intact status.

Growth measurements, as percentage of takes and as percentage of anterior chamber filled by actively growing transplants, were made at intervals ranging from 1 week to 1 month.

RESULTS

Autonomy and dependence.—All four tumors were initially transplanted intraocularly into cas-

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>Castrated</th>
<th>Intact</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per cent</td>
<td>Per cent</td>
</tr>
<tr>
<td></td>
<td>ant. takes filled</td>
<td>ant. takes filled</td>
</tr>
<tr>
<td>CE 1</td>
<td>75</td>
<td>83</td>
</tr>
<tr>
<td>BALB 5880/1</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td>BALB 5880/2</td>
<td>100</td>
<td>79</td>
</tr>
<tr>
<td>CE 366/2</td>
<td>100</td>
<td>66</td>
</tr>
</tbody>
</table>

GROWTH OF ISLOGOUS INTRAOCULAR TRANSPLANTS OF ADRENAL CORTICAL TUMORS

Measurements were made at the end of 2 months in castrated and intact CE and BALB/c mice (CE 1 in males and females, BALB 5880/1 and BALB 5880/2 in males, CE 366/2 in females).

<table>
<thead>
<tr>
<th>HOST CATEGORY</th>
<th>Castrated</th>
<th>Intact</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUMOR</td>
<td>Per cent</td>
<td>Per cent</td>
</tr>
<tr>
<td></td>
<td>ant. takes filled</td>
<td>ant. takes filled</td>
</tr>
<tr>
<td>CE 1</td>
<td>75</td>
<td>83</td>
</tr>
<tr>
<td>BALB 5880/1</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td>BALB 5880/2</td>
<td>100</td>
<td>79</td>
</tr>
<tr>
<td>CE 366/2</td>
<td>100</td>
<td>66</td>
</tr>
</tbody>
</table>

The figure following the tumor number indicates the subcutaneous transplant generation.

Received for publication November 9, 1957.
Characteristics of intraocular growth of dependent tumors.—Regardless of the endocrine status of hosts, tumor fragments rounded off and diminished in size from approximately 25 per cent to between 10 and 15 per cent of the anterior chamber during the 1st week after transfer. Simultaneously, they became vascularized, showing a few minute vessels. The transplants remained in this latent phase for from 3 weeks to 4 months; the length of this latency varied with individual transplant series and with host sex and castrate status. During latency some further attrition of transplants occurred, often with reduction in size to less than 10 per cent of the anterior chamber.

The end of latency was marked by an increase in size and number of blood vessels and moderate enlargement of the transplants which came to occupy approximately 20 per cent of the anterior chambers. Usually, this post-latency phase occupied from 1 to 2 weeks in castrated hosts. In intact hosts, however, like the preceding latency period, it might be more than twice as long. The post-latency phase was followed by an active phase of continuous growth. The establishment of such growth was certain only when the transplants had come to occupy 25 per cent of the anterior chamber. Arbitrarily, until this point had been reached, transplants were not considered to have taken.

In the subsequent 1–4 months, transplants gradually filled the anterior chamber and usually ruptured the cornea, protruding from it. Usually after 2–4 weeks, with or without corneal rupture, the transplants partially regressed to fill only half the anterior chamber. In this state they remained

**Chart 1.**—Serial transfers of three adrenal cortical tumors in isologous hosts. T: testosterone-treated after mean latency period; a, b, c: castrated 3, 17, and 51 days after transplantation; d, e, f: castrated 75, 47, and 38 days before transplantation; g, h, i, j: castrated 10 months before transplantation.
quiescent or entered upon another similar growth cycle. Only rarely did transplants invade periorbital structures in uninterrupted growth.

The general growth pattern is illustrated graphically in Chart 2 by active transplants of tumor BALB 5880/2 in castrated and intact males (series II, 1, Chart 1). This tumor had the most rapid growth of the three carried serially but differed in no other respect (see also Charts 3, 4, and 5). The growth pattern of individual transplants in the same series is shown in Table 2 for the 32d and 57th days.

In castrated hosts no growth was seen on the 12th day, but by the 25th day three of fourteen (21 per cent) transplants were active. Eight of the remaining eleven were in the post-latency phase; three were still latent. By the 32d day, ten of fourteen (71 per cent) were active; three of the remaining four were in the post-latency phase (Table 2). The mean size of the active transplants at this time was 30 per cent of the anterior chamber. By the 57th day all transplants were actively growing, with 76 per cent of the anterior chambers filled (Table 2). By the 81st day 99 per cent of the anterior chambers was filled.

In intact hosts no transplant was actively growing, even on the 32d day, although five of sixteen were in the post-latency phase (Table 2). On the 46th day five of sixteen (31 per cent) were growing, and three of the remaining eleven were in the post-latency phase. By the 57th day, seven of sixteen (44 per cent) were actively growing, and three of the remaining nine were in the post-latency phase. Not until the 203d day were all transplants growing when the mean amount of the anterior chamber filled was 94 per cent. In this and other series, homogeneity of individual transplant growth was greater in the castrated than in the intact hosts; there also was no clear correlation between the growth of the two transplants in an individual as compared with growth in all individuals in a series.

The above figures, while differing in actual values, were relatively similar for all transplants of the three adrenal cortical tumors in castrated and intact male hosts. In the latter, latency and post-latency were prolonged, and actual growth was somewhat slower than in castrated animals. The number of days taken for one-half of the transplants in a series to enter the active growth phase has been taken arbitrarily as an index of latency in the subsequent results. For tumor BALB 5880/2 in series II, 1 (Chart 1), this latency was 29 or 31 days in castrated males and 66 days in intact males.

### Table 2

<table>
<thead>
<tr>
<th>Days</th>
<th>Castrated</th>
<th>Intact</th>
<th>Castrated</th>
<th>Intact</th>
</tr>
</thead>
<tbody>
<tr>
<td>32d</td>
<td>Right</td>
<td>80</td>
<td>X</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>40</td>
<td>X</td>
<td>100</td>
</tr>
<tr>
<td>57th</td>
<td>Right</td>
<td>30</td>
<td>X</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>30</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>30</td>
<td>X</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>25</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>25</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>35</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>-</td>
<td>-</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>25</td>
<td>-</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>-</td>
<td>-</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>-</td>
<td>-</td>
<td>55</td>
</tr>
</tbody>
</table>

**Chart 2.—** Percentage of takes and mean percentage of anterior chamber filled by actively growing transplants of tumor BALB 5880/2 in castrated and intact males (series II, 1, Chart 1).
Dependency in Relation to Sex or Castrate Status of Donor and Recipient

Transplants from castrated males to males.—Tumor BALB 5880/1 was transferred from a castrated male to castrated and intact males in the original series (original host to II, 1, Chart 1) and in five other series (II, 1, to III, 2 and 3; III, 3, to IV, 4; III, 3, to IV, 6 and 7, Chart 1). Tumor BALB 5880/2 was similarly transferred in the initial series (original host to II, 1; Chart 1) and in three other series (II, 1, subcutaneous to III, 1, subcutaneous; III, 1, subcutaneous to IV, 1, intraocular; and, from another animal of III, 1, subcutaneous to IV, 2, intraocular; Chart 1). In all series except the last, latency was at least twice as long in intact as in castrated hosts (Chart 1). In the last series (III, 1, subcutaneous to IV, 2, intraocular; Chart 1) latency was equal in castrated and intact hosts, its length being more typical of that found in intact series in general. The tumor had lost its dependency.

Transplants from castrated males to females.—Tumor BALB 5880/1 was transferred from castrated males to females twice (III, 1, to IV, 1 and 2; Chart 1) and tumor CE 366/2 from an intact male to castrated and intact males and females (III, 1, to IV, 1 and 2; Chart 1). In all cases latency was prolonged in the intact recipients.

Dependency appeared equally in castrated males and castrated females. It was unaffected by the sex of the donor or by sojourn in intact hosts in these series.

Relative Dependency in Male and Female Hosts

Tumor BALB 5880/1 was transplanted to male and female castrated and intact hosts in the same series twice (IV, 1 and 4; Chart 1) and into castrated and intact males and intact females once (IV, 7; Chart 1). In these series latency increased in the recipient in the following order: castrated male, castrated female, intact female, and intact male. The mean latency period for all transfers to these host categories showed the same sequence (Chart 1 and Table 8). Generally latency in intact males was twice, or more than twice, as long as in castrated males, while that in intact females was less than twice as long as in castrated females.

Tumor BALB 5880/2 was transplanted subcutaneously to similar host categories (series III, 1; Chart 1). The mean diameters of the transplants in ten animals of each host category at 6 and 9 months and the mean weights of the same transplants at autopsy at 12 months (Table 4) show the same sequence as for tumor BALB 5880/1.

Tumor CE 366/2 was transferred to similar host categories in only one series (IV, 1; Chart 1); here intact females showed the longest latency.

Time of Castration and Latency

Tumor BALB 5880/1 in series III, 3 (Chart 1) was transplanted into four groups of intact male mice. One group was castrated on the 3d, one on the 17th, and one on the 31st day after transfer, and one group remained intact. Latency was 52,
67, and 73 days for the castrated groups, and 118 days for the intact group. Latency from the time of castration, however, was of the same order (49, 50, and 42 days) for the castrated groups.

Tumor BALB 5880/1 in series IV, 5 (Chart 1) was transplanted into four groups of male mice, one being castrated 75 days, one 47 days, and one 32 days before transfer, and one group remaining intact. Latency was of the same order in all groups, i.e., 68, 62, 59, and 67 days (Chart 1). Either castration preceding transfer by a month had no effect on latency, or this tumor had lost dependency in this series. However, transplants in series IV, 4, derived from the same group (III, 8, males castrated at time of transfer), showed no such loss.

Tumor BALB 5880/2 in series III, 2 (Chart 1) was transferred into male and female hosts castrated 10 months previously and into intact male and female hosts of the same age (1 year). Latency in intact and castrated females was 62 and 69 days, but latency in castrated males was about twice as long as in intact males (92 and 52 days) in these relatively old hosts.

**Effect of Androgen on Latency**

Tumor BALB 5880/1 in series III, 2 (Chart 1) was transplanted into a group of castrated and intact animals. Each of the castrates received 7.5 mg. of testosterone phenylacetate2 subcutaneously in aqueous suspension shortly after the end of the mean latency period (on the 56th day; latency period, 47 days) and on two subsequent occasions (77th and 123d days). The percentage of takes (actively growing transplants) and mean percentages of anterior chamber filled by these are represented graphically in Chart 3. The percentage of takes decreased slightly by 21 days after the initial testosterone administration and markedly by 10 days after the second administration. It remained low until 94 days after the third and last administration. After an interval without testosterone administration growth was resumed.

Tumor BALB 5880/2, in series II, 1 (Chart 1), was transplanted into two castrated groups and one intact group. One castrated group received the same dose of testosterone phenylacetate at a similar time in the growth phase (32d day; latency period, 29 or 31 days) as the above series (tumor BALB 5880/1, III, 2) and at subsequent intervals (41st and 58th days). While the percentage of takes and of anterior chamber filled steadily increased in the untreated castrated group, no further takes or size increase occurred in the treated group on the 14th day after the initial administration of testosterone (Chart 4). At this time (46th day after transfer), transplants in the intact group were beginning to become active. The percentage of takes and of anterior chamber filled decreased after the second and third administration of testosterone and began to rise again 56 days after the third and last administration. During this period transplants in the castrated group had all taken and completely filled the anterior chambers, and most of the transplants in the intact group were growing with over half the anterior chamber filled. The same partial regression of active transplants and inhibition of those in the latent or post-latent phases in the testosterone-treated hosts was seen as in the previously described series (tumor BALB 5880/1, III, 2; Charts 1 and 3). Similarly, too, after an interval without testosterone administration growth was resumed.

---

2Generously supplied by Ciba Pharmaceutical Products, Inc., through the courtesy of Dr. Robert Gaunt.
Tumor BALB 5880/1, in series IV, 7 (Chart 1), was transplanted into a castrated and intact male group and an intact female group. The latter received the same dose of testosterone phenylacetate as the above two series, but at a later time in the growth phase (125th day; latency period 104 days) and on two subsequent occasions (148th and 167th days). At the time of the initial administration, the transplants in the castrated males were all actively growing and the anterior chambers were nearly full (Chart 5). The transplants in the intact males were beginning to become active, and they progressed steadily to 100 per cent takes and 95 per cent of the anterior chambers filled by the 302d day. Eight days after the first hormonal administration transplants in testosterone-treated castrated males, and in untreated intact males (series II, 1, Chart 1).

DISCUSSION

The induction of neoplasms of the thyroid, adrenal, and pituitary glands and of the ovary and testis by hormonal imbalance in experimental animals has been reviewed by Gardner (11), Furth (9), and, more recently, Kirschbaum (16, 17). During induction the tissues may show histological progression through hyperplasia, adenoma, and carcinoma. Transplantation of the induced tumors is often only possible in hosts with an imbalance similar to that found in the original host. Such tumors are hormonally dependent.

The adrenal cortical tumors used here were induced by castration, at 4–6 weeks of age, of BALB/c or CE mice (18). Presumably, elevated or abnormal pituitary gonadotropins, in the absence of a normal target organ and acting over a long period, induced neoplasia (8, 26, 30). Initiation of an endocrine neoplasm, and the growth of the same neoplasm either in the original host or as a transplant, do not necessarily require the same environment. In initiation, certain conditions produce changes in a tissue that is already part of the host. The process can be inhibited. Woolley and Little (33) found that adrenal cortical tumorigenesis did not follow castration of CE mice if evo-
nous stilbestrol was administered. Monsen (21) showed that testosterone, if administered from the time of ovariectomy, prevented the formation of adenomas in NH mice. The same hormone did not affect established adenomas. Kirschbaum, Liebelt, and Fletcher (19) could similarly inhibit tumorgenesis by testosterone administered to NH mice soon after castration. These authors found that the process became irreversible, probably before any histological changes in the adrenal cortex were detectable. Furthermore, tumors developing in castrated hosts despite continuous testosterone administration from 3 months after castration might still show dependence on castration as transplants. The process became autonomous, although the resultant tumor was dependent.

The hormonal dependence of the adrenal cortical tumors used here was never absolute in transplantation. In intact hosts, as compared with castrated hosts, the latent period before growth was simply prolonged. When transplant entered the active phase, the growth rates in castrated and intact hosts were very similar.

The latency before active growth was extremely long, even in castrated animals. The shortest period recorded was 29 days (tumor BALB 3880/2, series II, Chart 1). Mammary tumors, transplanted directly from the spontaneous neoplasms into the anterior chamber of the mouse eye, had latencies of from 4 to 14 days (3). The greater length of this period for adrenal tumor transplants did not appear to be due to slow reaction by host tissues. Vessels were visible in transplants by the 7th day.

During the long latency, changes may occur in the host, in the tumor, or in endocrine interaction between them. Latencies in castrated hosts ranged, approximately, from 1 to 2 months; in intact hosts, from 3 to 4 months. Host mice were between 2 and 4 months of age. It seems unlikely that endocrine changes of the host per se were related to latency. Modification of the tumor itself also seems improbable, for retransplantation from intact to castrated hosts showed that dependency still persisted. Interaction between host and transplant is possible, despite the small size of the latter during latency. Further (9) found that fragments of a TSH-producing pituitary tumor, only a few millimeters in diameter, would produce thyroid adenomas despite lack of growth of these transplants. Anterior chamber transplants of one quarter of one ovary will restore vaginal cycling in ovariectomized mice (6). Further, adrenal cortical tumors induced by castration usually produce androgenic and estrogenic hormones (7, 31, 92).

On the other hand, different latencies in castrated and intact hosts could be due to heterogeneity of the tumor cell population. Some cells might be responsive to the castrate status and some independent of it. However, persistence of latency after passage through intact hosts makes this improbable.

Shortened latency in castrated hosts of either sex may result from removal of inhibiting hormones or to high levels of stimulating hormones. Testosterone or estrogen-progesterone may inhibit tumor cell multiplication directly. Indeed, the first hormone inhibited transplant growth in both sexes for as long as it was administered, i.e., to a greater extent than the endogenous testosterone of the intact male. The tumor was controlled but not destroyed. The shorter latency in intact females as compared with intact males suggests that endogenous levels of estrogen-progesterone are not as potent inhibitors as endogenous testosterone.

More probably, dependency is related to pituitary gonadotropins. Monsen and Kirschbaum (22) showed that, in parabiosis experiments, the secretion of sex hormones by adrenal tumors is probably under pituitary control. The effect of castration on pituitary output of gonadotropins is complex. Witschi (28) found that, when a castrated rat was parabiosed with a hypophysectomized female, there was excessive follicular stimulation but no luteinization (after an initial period of luteinization before modification of the pituitary of the castrated partner). Without specifying the particular gonadotropin, Gardner (11) estimated that, postcastration, pituitary gonadotropin in males castrated sexually, pituitary gonadotropin in males castrated parabiosically rises to 3 times the level found in the intact and females rises in the intact male or female rat, subsequent to castration as transplants may be stimulated by FSH. Monsen and Kirschbaum (22) found that, in parabiosis experiments, the secretion of sex hormones by adrenal tumors is probably under pituitary control. The effect of castration on pituitary output of gonadotropins is complex. Witschi (28) found that, when a castrated rat was parabiosed with a hypophysectomized female, there was excessive follicular stimulation but no luteinization (after an initial period of luteinization before modification of the pituitary of the castrated partner). Without specifying the particular gonadotropin, Gardner (11) estimated that, postcastration, pituitary gonadotropin in males castrated sexually rises to 3 times the level found in the intact and females rises in the intact male or female rat, subsequent to castration as transplants may be stimulated by FSH. Monsen and Kirschbaum (22) found that, in parabiosis experiments, the secretion of sex hormones by adrenal tumors is probably under pituitary control. The effect of castration on pituitary output of gonadotropins is complex. Witschi (28) found that, when a castrated rat was parabiosed with a hypophysectomized female, there was excessive follicular stimulation but no luteinization (after an initial period of luteinization before modification of the pituitary of the castrated partner). Without specifying the particular gonadotropin, Gardner (11) estimated that, postcastration, pituitary gonadotropin in males castrated sexually, pituitary gonadotropin in males castrated parabiosically rises to 3 times the level found in the intact and females rises in the intact male or female rat, subsequent to castration as transplants may be stimulated by FSH. Monsen and Kirschbaum (22) found that, in parabiosis experiments, the secretion of sex hormones by adrenal tumors is probably under pituitary control. The effect of castration on pituitary output of gonadotropins is complex. Witschi (28) found that, when a castrated rat was parabiosed with a hypophysectomized female, there was excessive follicular stimulation but no luteinization (after an initial period of luteinization before modification of the pituitary of the castrated partner). Without specifying the particular gonadotropin, Gardner (11) estimated that, postcastration, pituitary gonadotropin in males castrated sexually rises to 3 times the level found in the intact and females rises in the intact male or female rat, subsequent to castration as transplants may be stimulated by FSH. Monsen and Kirschbaum (22) found that, in parabiosis experiments, the secretion of sex hormones by adrenal tumors is probably under pituitary control. The effect of castration on pituitary output of gonadotropins is complex. Witschi (28) found that, when a castrated rat was parabiosed with a hypophysectomized female, there was excessive follicular stimulation but no luteinization (after an initial period of luteinization before modification of the pituitary of the castrated partner). Without specifying the particular gonadotropin, Gardner (11) estimated that, postcastration, pituitary gonadotropin in males castrated sexually rises to 3 times the level found in the intact and females rises in the intact male or female rat, subsequent to castration as transplants may be stimulated by FSH. Monsen and Kirschbaum (22) found that, in parabiosis experiments, the secretion of sex hormones by adrenal tumors is probably under pituitary control. The effect of castration on pituitary output of gonadotropins is complex. Witschi (28) found that, when a castrated rat was parabiosed with a hypophysectomized female, there was excessive follicular stimulation but no luteinization (after an initial period of luteinization before modification of the pituitary of the castrated partner). Without specifying the particular gonadotropin, Gardner (11) estimated that, postcastration, pituitary gonadotropin in males castrated sexually rises to 3 times the level found in the intact and females rises in the intact male or female rat, subsequent to castration as transplants may be stimulated by FSH. Monsen and Kirschbaum (22) found that, in parabiosis experiments, the secretion of sex hormones by adrenal tumors is probably under pituitary control. The effect of castration on pituitary output of gonadotropins is complex. Witschi (28) found that, when a castrated rat was parabiosed with a hypophysectomized female, there was excessive follicular stimulation but no luteinization (after an initial period of luteinization before modification of the pituitary of the castrated partner). Without specifying the particular gonadotropin, Gardner (11) estimated that, postcastration, pituitary gonadotropin in males castrated sexually rises to 3 times the level found in the intact and females rises in the intact male or female rat, subsequent to castration as transplants may be stimulated by FSH. Monsen and Kirschbaum (22) found that, in parabiosis experiments, the secretion of sex hormones by adrenal tumors is probably under pituitary control. The effect of castration on pituitary output of gonadotropins is complex. Witschi (28) found that, when a castrated rat was parabiosed with a hypophysectomized female, there was excessive follicular stimulation but no luteinization (after an initial period of luteinization before modification of the pituitary of the castrated partner). Without specifying the particular gonadotropin, Gardner (11) estimated that, postcastration, pituitary gonadotropin in males castrated sexually rises to 3 times the level found in the intact and females rises in the intact male or female rat, subsequent to castration as transplants may be stimulated by FSH. Monsen and Kirschbaum (22) found that, in parabiosis experiments, the secretion of sex hormones by adrenal tumors is probably under pituitary control. The effect of castration on pituitary output of gonadotropins is complex. Witschi (28) found that, when a castrated rat was parabiosed with a hypophysectomized female, there was excessive follicular stimulation but no luteinization (after an initial period of luteinization before modification of the pituitary of the castrated partner). Without specifying the particular gonadotropin, Gardner (11) estimated that, postcastration, pituitary gonadotropin in males castrated sexually rises to 3 times the level found in the intact and females rises in the intact male or female rat, subsequent to castration as transplants may be stimulated by FSH.
trated males, equal but less stimulation in intact males and castrated females, and almost none in intact females (6). This certainly indicates a higher FSH output in castrated than in intact males. In castrated females vaginal cycling is restored; probably the transplant is elaborating sufficient estrogen and progesterone to control pituitary gonadotropin output. In intact females pituitary gonadotropins may be used preferentially by the host ovaries.

When hosts were castrated from 1 to 2½ months before transfer, stimulation of the tumor was lost, although FSH levels should have been maximal. When hosts were castrated a year before transplantation, latency was longer than in intact hosts of the same age. At this time the level of circulating FSH may have fallen, as it apparently does in rats. Alternatively, the adrenals of the hosts may have been secreting sex steroids, so that the animals were anatomically but not physiologically castrate.

Testosterone has been shown to depress pituitary gonadotropin potency in female rats, causing increased FSH storage and decreased LH content (20, 29), and to maintain a normal level of gonadotropins in castrated female mice (27). Such inhibition of pituitary output might account for inhibition of transplants by exogenous testosterone. In initiation of adrenal cortical neoplasms testosterone and stilbestrol are inhibiting (19, 33); progesterone, cortisone, and deoxycorticosterone are not (21, 29). Experiments to determine whether sex steroids other than testosterone inhibit dependent adrenal cortical tumor transplants in intact hosts, and whether the action of testosteron in castrated hosts is direct or mediated via the pituitary, are being undertaken.

Furth (9) defines a dependent neoplasm as one that will grow only in a hormonally altered host. He states that some can become able to grow in normal hosts and look as if they had then acquired autonomy. Condition as such implies that autonomy is a condition acquired during the life cycle of a neoplasm. It is indicated by capability for metastasis and growth on transplantation to the anterior chamber of the eyes of alien species or strains. These two concepts of autonomy are unrelated. Hormonally dependent testicular (10) and thyroid tumors (2, 23) will metastasize.

Adrenal cortical tumors of the type under discussion ultimately grew in normal hosts; they might be considered partially autonomous. Autonomy may have been facultative for all cells or some may have been autonomous and others dependent. Like most other endocrine tumors of mice they exhibited very slow growth under any conditions, e.g., pituitary tumor transplants in estrogen-treated hosts required a year before becoming detectable (12). These long latencies or slow growth rates raise the question as to whether complete independence really exists. Gardner (10) found that testicular tumor grafts remain dormant for several months until stimulated by exogenous estrogen. Once growing, cessation of estrogen treatment had no effect. If these grafts would not have grown without estrogen stimulation, then under it they must have immediately acquired autonomy. Furth (9) found that thyroid hormone would restrain but not arrest dependent pituitary tumors. On the other hand, adrenal cortical tumors were arrested in the present experiments by exogenous testosterone, but they were not destroyed. Initiation itself can only be reversed at a very early phase. Subsequently, restoration of hormonal balance affects only growth rates, or, in transplants, latency. Possibly all "dependent" tumors, given sufficient time in normal hosts, will grow and show "partial autonomy."


32. ———. The Incidence of Adrenal Cortical Carcinoma in Gonadectomized Male Mice of the Extreme Dilution Strain. Ibid., pp. 211-19.

33. ———. Prevention of Adrenal Cortical Carcinoma by Diethylstilbestrol. Ibid., 5:401, 1946.
Hormonal Dependence of Adrenal Cortical Tumors of CE and BALB/c Mice in Serial Intraocular Transfer

Henry C. Browning


Updated version

Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/18/7/781

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/18/7/781.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.