Chromophobe Adenoma-Like Lesions of the Rat Hypophysis

Frequency of the Spontaneous Lesions and Characteristics of Growth of Homologous Intraocular Transplants*

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In a study of spontaneous diseases that occur in albino rats with advance in age, chromophobe adenoma-like lesions were found in the hypophyses of many old rats of the Yale strain. The frequency of this lesion in a limited series of animals, and the preliminary results of intraocular transplantation of one of the lesions, have been reported (8). Periods of 7 to 12 months elapsed before growth of these transplants became evident, and it was therefore thought likely that advanced age of the host was necessary for growth of this type of tissue following transplantation. This is contrary to the usual experience that transplanted tumors grow best in young animals, and would suggest that this tissue had little if any autonomy of growth and therefore was not neoplastic.

Experiments have been continued to determine so far as possible by the behavior of transplants whether the spontaneous growths represent hyperplasia of chromophobe cells in response to endogenous stimuli associated with advancing age, or true neoplasia in the generally accepted sense. The experiments were designed to study the character of growth of transplants under varying conditions of age, sex, and strain of the hosts. For comparison, transplants were made of normal hypophyseal tissue. The study of frequency of the spontaneous lesions has been continued to include a larger number of rats of the Yale strain. In addition, the pituitaries of rats of the Sherman strain and of a stock derived from the Wistar albino strain have been examined.

MATERIALS AND METHODS

Three hundred sixty-two albino rats of the Yale strain, ranging from 1 month to about 3 years of age, are included in the study of frequency of spontaneous chromophobe adenoma-like lesions. The pituitaries of all animals were examined in the gross, and the great majority were sectioned and stained with hematoxylin and cosin, and with Heidenhain's modification of Mallory's aniline blue technic (6). The pituitaries of 170 rats of the Sherman strain and of 79 rats of a stock derived from the Wistar albino strain were also examined. A smaller proportion of these were sectioned, and frequency of the lesions is based chiefly upon the gross appearance of the pituitaries. Enlarged pituitaries were rarely seen in rats of these strains.

Intraocular homologous transplantation was carried out in the following manner. The rat was anesthetized with chloroform, the upper part of the cornea was incised with a safety razor blade, and the opening widened with small scissors. Chloroform was preferable to ether because it produced greater dilatation of the pupil and consequently there was less chance of hernia of the iris during manipulations. Pieces of tissue less than 1 mm. in greatest diameter were introduced into the anterior chamber and pressed into the inferior region of the angle of the iris. In a few instances tissue was transplanted into the subcutaneous tissue and into the testis, but none of these transplants was observed to grow. Tissues from 4 spontaneous lesions were transplanted. The transplants from 2 of the 4 lesions, 1 each from the Sherman and Wistar Mendel strain, were obtained from the stock colony of the Department of Animal Nutrition at Cornell University. Some had been used in experiments dealing with the relation of diet to the life span, but could be considered normal for the purposes of this survey. We are indebted to Dr. C. M. McCay for the rats of this strain.

Most of the rats of the Sherman strain, which is a derivative of the Osborne-Mendel strain, were obtained from the Rockland Farms. Others were raised in this Department. Some had been used in experiments where the procedures would not have been likely to influence the frequency of hypophyseal lesions.

These rats were from a stock that was formerly maintained in the Department of Biochemistry of Cornell University Medical College. The animals from which this stock originated were of the Wistar albino strain. We are indebted to Dr. N. F. Blau for rats of this stock.
rived strains, respectively, did not grow. Transplants from lesions in 2 rats of the Yale strain grew in a number of the recipients, and were carried into second and third serial generations by intracocular transfer. These form the basis for analysis of the behavior of the hypophyseal lesions after transplantation. Intracocular transplants of normal hypophyseal tissue were made in the same manner to serve as controls. The details of individual experiments are described with the results.

RESULTS

FREQUENCY AND MORPHOLOGY

Yale strain.—The frequency of chromophobe adenoma-like lesions of the hypophysis in rats of the Yale strain in relation to age and sex is shown in Table I.

Adenoma-like lesions occurred in 92 of 362 hypophyses examined. Two lesions only were found in rats less than 400 days old. These were microscopic in size and occurred in males aged 237 and 241 days respectively. The frequency increased with advancing age to about 50 per cent in males and 30 per cent in females 600 to 800 days old. The lesions included in Table I varied from small nodular areas of chromophobe hyperplasia seen only in microscopic section, to large adenomatous growths of chromophobe cells, the largest weighing 367 mgm. Multicentric origin was common, and the microscopic appearance in most instances resembled that already described (8). The nodules were not encapsulated and did not appear invasive. They were characteristically composed of cords and irregular groups of cells with chromophobe vacuolated cytoplasm and with vesicular nuclei, often of large size, in which the chromatin was usually in the form of coarse granules. Many nuclei contained large eosinophilic nucleoli. A few of the growths were cavernous in structure, whereas most were solid. The former observation that the cytoplasmic vacuoles contained fat was confirmed. Several growths were composed of small cells with relatively scant chromophobe cytoplasm in which no vacuoles were seen. Although differing in appearance from the others, these were considered to be chromophobe adenoma-like lesions on the basis of staining properties, and are included in Table I. It was not possible to trace the origin of any of the lesions observed; but since many of the smaller nodules were embedded deeply in the anterior lobe of the pituitary, it seemed probable that they developed from cells of this lobe. No chromophilic growth was seen in the entire series. The two lesions from which transplants were made were typical of the majority, being composed of rather large cells with chromophobic vacuolated cytoplasm.

Sherman strain.—The age distribution in rats of the Sherman strain was about the same as that in the Yale strain. There were 93 rats, 83 males and 10 females, aged from 1 to 3 years, and 77 rats less than 1 year old. Three chromophobe adenoma-like lesions occurred in this series, all in male rats between 2 and 3 years old. The largest lesion measured 6 mm. in diameter and was composed of chromophobe vacuolated cells with large nuclei containing coarse granules of chromatin. Many large and small vascular spaces were within the lesion. A slightly smaller growth, from which transplants were made, was composed of cells with less cytoplasm and without vacuoles. The nuclei varied somewhat in size and staining properties. Vascular spaces were numerous and usually small. One large organizing thrombus was present. Small fragments of this lesion were transplanted into the eyes of 2 rats of this strain, and into the eyes of 3 males and 1 female of the stock derived from the Wistar strain. All recipients were about 18 months old. No growth was seen at any time, and the rats were discarded after 5 months of observation. The third adenoma-like lesion consisted of a nodule 2 mm. in diameter located in one side of the hypophysis. It was composed of small cells without vacuoles and contained abundant small vascular spaces. There was an infiltration by a few phagocytes laden with brown pigment.

Stock derived from the Wistar strain.—Of the 79 rats of this stock, 13 were over 1 year of age when examined. There were 9 males and 4 females. A large tumor of the pituitary was found in a male rat 17 months old. The pituitary bearing the lesion weighed 191 mgm. The tumor was composed of chromophobe cells without vacuoles, and contained small areas of fresh hemorrhage. Part of the tissue was transplanted to the eyes of 7 male and 5 female rats of the same stock, aged 2 months. In no instance was any growth observed, and the recipients were discarded after periods of 8 to 13 months.

TRANSPLANTATION

Chromophobe adenoma-like lesions.—The results of transplanting one spontaneous adenoma-like lesion from a rat of the Yale strain are shown graphically in Chart I. The first serial transplants of this growth have been described (8). The original lesion was found in a male rat 17 months old. After prolonged
latent periods 3 of the 9 intraocular transplants began to grow slowly. Two of these were used for second serial transfers. In one instance the tissue was transplanted to the eyes of 6 male rats of the Wistar stock 5 months old, with resultant growth in 2 of the rats. In the other case, 21 months after the first transfer, tissue was placed in the eyes of 4 male rats of the Sherman strain 2 months old, and of 4 albino rats of unknown strain, about 18 months old. Growth of the transplants occurred in 3 of the 4 old rats and in 2 of the 4 young rats. After periods of 11 and 14 months the transplants in the younger animals had each reached a diameter of 3 mm. Third serial transplants were made in each case into the eyes of young male rats of the Sherman strain. Growth resulted in 1 of 4 rats receiving tissue from one transplant, but in none of 5 rats receiving tissue from the other. Tissue of this transplant had the typical appearance of the original adenoma-like lesion, but there was in addition an infiltration of lymphocytes. The rat bearing this transplant was killed because of labyrinthitis, and the right middle ear was found to contain pus. It seemed probable that contamination of the tissue had interfered with growth of the transplants, and the 5 recipients are therefore not included in the analysis of the transplantation experiments. The rat bearing the only successful third serial transplant was observed for 13 months. The transplant reached a diameter of 3.5 mm. after 8 months, but during the 12th and 13th months it decreased in size and the color changed from yellowish pink to white. Microscopically, there was degeneration of the transplanted tissue, but the structure of the original lesion could be recognized.

In all transplants where growth was observed the tissue retained the microscopic structure of the original lesion and became vascularized as evidenced in the gross by a pink color and in section by capillaries filled with blood. The transplants usually became surrounded by a thin capsule of fibrous tissue. In this series it was shown that chromophobe adenoma-like tissue would grow after homologous intraocular transplantation; that growth of transplants was extremely slow and might follow long periods of latency; that growth of adenoma-like tissue would occur in second and third serial intraocular transfers; that growth would take place in the eyes of rats of strains other than that in which the original lesion developed; and that intraocular transplants would grow as well in young as in old rats of the male sex.

The second chromophobe adenoma-like lesion to be successfully transplanted occurred in a male rat of the Yale strain 171/2 months old. The lesion was estimated to weigh about 70 mgm. Tissue was placed in the eyes of 4 male rats aged 18 months and of 7 male rats aged 7 weeks, all of the Yale strain. The behavior of the transplants is shown in Chart II. Growth occurred in 4 of the 7 young rats and in 3 of the 4 old rats. The transplants increased in size more rapidly in the young than in the old animals. In general the period of latency was not so conspicuous as in the case of the first lesion transplanted (Chart I). The transplants did not differ appreciably in microscopic appearance from the original lesion, which is illustrated in Fig. 1. One transplant in a young rat measured 5 mm. in diameter 14 months after transfer, and weighed 25 mgm. This transplant in the eye is shown in Fig. 2. Tissue from it was put into the eyes of 4 young male and 4 young female rats of the Yale

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**Chart I.**—Outline of transplantation of chromophobe adenoma-like lesion from rat M264. Relative size of the transplants is indicated by the thickness of the lines. Time in months is shown along the baseline. The letter "x" indicates that transfer was considered negative at time the host was discarded. The letters "K" and "D" indicate whether the rats bearing the transplants were killed or died of natural causes.

**Chart II.**—Outline of transplantation of chromophobe adenoma-like lesion from rat W-D 142. Symbols are the same as for Chart I.
strain. Transplants grew well in 3 of the 4 males, but in one instance there was some regression in size after 4 months of progressive growth. One of these second serial transplants in a male rat, killed 8 months after transfer, is shown in Fig. 3. In but 1 of the females there was growth of the transplant. It reached a diameter of slightly more than 1 mm. in 2 months, but after 4 months had regressed completely. When the recipient was killed 8 months after transfer no tissue could be found in the eye.

From this series it appeared that spontaneous adenoma-like lesions of relatively small size were capable of growth after homologous intraocular transplantation; that the growth of transplants was somewhat rapid in young than in old animals; and that the male rat was a more suitable host than the female.

The two series of experiments were analyzed together to determine the effect of age and strain of the recipient upon the fate of the transplants. Excluding one group of 5 rats, referred to above, which received tissue that was probably infected, there were 21 successful growths in a total of 42 male rats receiving intraocular transplants.

Transplants grew in 15 of 34 rats of less than 1 year of age at the time of transplantation, whereas growth occurred in 6 of 8 rats that were over 1 year of age. Many of the transplants into young animals grew more rapidly and attained greater size than did those in old animals. It is therefore doubtful if age of the host exerted an appreciable influence upon the fate of transplants. The difference in proportion of successful transplants between young and old animals may perhaps be explained by the fact that the eyes of the young rats were smaller and thus presented a greater mechanical difficulty during inoculation.

The results of transplantation were analyzed in relation to the strain of the recipients. Growth of transplants occurred in 13 of 24 male rats of the Yale strain and in 8 of 18 albino rats of other strains. Thus the strain of the host was not an important factor in the survival and growth of transplants.

The relation of growth of transplants to the development of adenoma-like lesions in the pituitaries of the hosts was determined in the two series of experiments. Because spontaneous lesions were rare in pituitaries of rats of other than the Yale strain, these are excluded from the analysis. It was also necessary to exclude animals less than 1 year of age when examined, because of the observed low frequency of spontaneous lesions in young rats. Many of the recipients in which the transplants did not grow had been discarded after observation for 6 or 8 months, and before they were 1 year old. No animal excluded from the analysis bore a spontaneous adenoma-like lesion. There remained 14 old male rats for this analysis. Adenoma-like lesions were present in the hypophyses of 3 of 4 animals in which the transplants failed to grow, and in the hypophyses of 6 to 10 rats in which growth of transplants took place. It would appear from this small series that growth of transplants is no more probable in rats that develop spontaneous hypophyseal lesions than in those that do not. Moreover, it is noteworthy that the frequency of adenoma-like lesions of the hypophysis was not influenced by the inoculation of adenomatous tissue. The frequency of hypophyseal lesions in rats receiving transplants was of the same magnitude as that for the entire survey.

Normal hypophyseal tissue.—To serve as a control, anterior pituitary tissue from a male rat of the Sherman strain, aged 3 months, was transplanted into the eyes of 6 male rats aged 6 to 8 months, and of 5 male rats aged 3½ months. All animals were of the Sherman strain. The transplants were observed over a period of 7 months, and tissue persisted in the eyes of 9 rats throughout the period of observation. During the first 4 months the transplants appeared in the anterior chambers as small rounded pink masses between 0.5 and 1.0 mm. in diameter; subsequently, most of the transplants shrank and became white. One reached a diameter of 1.5 mm. after 1 month, but later decreased in size and at the end of the period of observation appeared as a tiny white speck. After 7 months only two transplants appeared viable. Each was about 0.5 mm. in diameter. One of these was sectioned and was found to be a rounded, encapsulated, and vascularized mass of cells bearing a closer resemblance to normal hypophyseal tissue than to the adenomatous growths. The cells were small, their nuclei of uniform size, and eosinophilic granules were present in the cytoplasm of many cells, usually those near capillaries. The transplant is shown in Fig. 4.

It is concluded from these observations that normal hypophyseal tissue may persist for a considerable period after homologous intraocular transplantation, but may not grow in a manner comparable to adenomatous tissue.

DISCUSSION

In these investigations an attempt has been made to determine whether the nodular chromophobic lesions of the rat's hypophysis are essentially hyperplastic or neoplastic in character. The behavior of the first serial transplants of one lesion, described in the former report (8), indicated that the tissue has little if any autonomy of growth, and was therefore merely hyperplastic. Studies of the morphology and frequency of the lesions, and of the behavior of subsequent transplants, reported here, have indicated that the lesions may be more closely identified with neoplasia than with focal hyperplasia. Nevertheless, the lesions do not completely satisfy the accepted criteria for neo-
Fig. 1. Original adenoma-like lesion from rat W-D 142. × 460.

Fig. 2.—First serial transplant in eye of rat (W-D 142-3), taken about 12 months after transfer.

Fig. 3.—Second serial intraocular transplant from rat W-D 142 (W-D 142-3-1), removed 8 months after transfer. × 460.

Fig. 4.—Intraocular transplant of normal hypophyseal tissue 7 months after transfer. × 460.
plasms. The term "adenoma-like lesion" has therefore been used again to describe the entire group, although it is reasonably sure that the largest lesions are adenomas.

On the basis of structure it has been difficult to classify many of the smaller lesions as hyperplastic or neoplastic. Wolfe, Bryan, and Wright (11) have described two main types of adenomatous reaction in the anterior pituitaries of old rats. Lesions of one type, considered by these authors to be adenomatous foci, ranged in size from 0.4 to 4.0 mm. and were composed of small groups or nests of enlarged chromophobic or occasionally eosinophilic cells. There was no encapsulation and no compression of surrounding tissue. Others, designated as true adenomata, ranged in size from 0.60 to 0.6 mm. and were composed almost exclusively of large chromophobic cells. These were not encapsulated, but were well demarcated from the normal tissue, which was compressed to a variable degree depending upon the size of the lesions. Numerous vascular spaces and areas of hemorrhage were described and the authors have classified these growths as hemorrhagic adenomata (11). The majority of lesions of our series, including those that were transplanted successfully, were generally similar to the hemorrhagic adenomata. Small vascular spaces were common, but areas of recent or old hemorrhage were noted only exceptionally. There was in all cases some distortion of the adjacent normal pituitary tissue. Cells of the smallest lesions of our series were not appreciably different from those of the largest. The small nodules would therefore seem to be young stages of the growth, and it is probable that the morphologic character of the lesion is determined early in its development. In favor of neoplasia is the observation that there was considerable variation in size and staining properties of the nuclei. Invasion of adjacent structures was not observed in any case, but it is significant that the largest lesions produced some erosion of underlying bone. In no instance was there a connective tissue capsule or other evidence of cellular reaction to the presence of the lesion, whereas the formation of a capsule is an almost constant feature of adenomata. The absence of a capsule may perhaps be taken rather as evidence of a low order of neoplasia than as evidence that the lesions are not neoplastic.

In our series, adenomatous changes of the pituitary were observed in but 2 rats less than 1 year of age. Wolfe and his associates (9, 10, 11, 13) have described adenomatous changes only in old rats. It may be inferred either that stimuli resulting in adenoma-like growth must act over a considerable period of time, or that changes occur in older animals favoring their development. The observed distribution in relation to sex would suggest that gonadal hormones may influence the occurrence of the lesions. Experiments of Cramer and Horning (1); McEuen, Selye, and Collip (7); of Wolfe and Wright (13); and of Zondek (15), where chromophobic lesions of the pituitary have developed after long-continued administration of estrogens, support this view. Furthermore, Wolfe (9) has found that adenomatous changes were rare in the anterior pituitaries of old male rats injected daily with testosterone propionate as compared with controls of the same age.

Adenomatous lesions were present in the pituitaries of 56 per cent of old male and of 22 per cent of old female rats of the Yale strain, whereas only 3 of 83 males of the Sherman strain, comparable in age, bore such lesions. Wolfe and his associates (9, 10, 11, 13) have found adenomatous changes in the pituitaries of 14 per cent of males and of 28 per cent of females of the Vanderbilt strain 17 and more months of age. The differences in frequency can be considered significant in that large numbers of animals of each strain were examined. Since the three strains of rats are all derived from the Osborne-Mendel strain, the frequency of adenomatous lesions would appear to have been influenced either by environmental conditions or, less likely, by selective breeding. In neither colony from which our rats were obtained has there been selection for purposes other than to maintain a vigorous stock. The Vanderbilt strain has been maintained by inbreeding (11). The number of animals of the Wistar derived stock that we examined is too small to warrant conclusions. A single adenomatous lesion was found in 1 of 9 old males of this stock. Wolfe, Bryan, and Wright (11) found pituitary lesions in 26 of 38 old females of the Wistar strain, or 68 per cent. In 11.4 per cent of old female rats of the Albany strain, Wolfe and Wright (14) noted adenomatous changes. It is thus apparent that while the lesions are widely distributed in common strains of rats their frequency in relation to strain and sex varies considerably.

The development of pituitary adenoma-like lesions does not appear to be associated with changes in other endocrine organs. No consistent change has been found in animals of our series in which the lesions have developed, although enlarged prostates and seminal vesicles were occasionally present. The Albany strain has been shown by Wolfe and Wright (14) to be characterized by structural and functional abnormalities of the ovaries, and by a high frequency of mammary tumors. Nevertheless, the frequency of adenomatous lesions of the pituitary was found by these authors to be lower than in strains with a normal reproductive function. Harned and Cole (3) have shown that rats of the Yale strain exhibit a lower glucose tolerance, more rapid growth, larger size, and a greater incidence of sterility than do those of the Wistar strain. These authors suggest that hyperfunction of the pituitary may be a common denominator.
for these and some other differences between the two strains. However, Wolfe, Bryan, and Wright (11) have found pituitary lesions in 68 per cent of females of the Wistar strain, whereas we have found pituitary lesions in only 22 per cent of Yale strain females of the same age. Comparable data for males of the Wistar strain are not available. Although differences in endocrine constitution may exist among the various strains studied, these cannot be correlated with the frequency of pituitary adenomata.

The behavior of transplants has given a better indication of the nature of adenoma-like lesions than could be obtained from studies of frequency and morphology of the spontaneous lesions. From the behavior of three transplants described in the first paper (8) it appeared possible that the tissue would grow only in animals of advanced age, where factors perhaps favored the development of spontaneous lesions. It was therefore necessary to determine to what degree the tissue was dependent for growth upon age, sex, and strain of the host. It was important also to determine whether or not growth of transplants took place more readily in animals that developed spontaneous adenoma-like lesions.

It is of some interest that growth of adenoma-like tissue occurred only when this was inoculated into the anterior chamber of the eye. Subcutaneous and intratesticular transplants were introduced but did not appear to grow. The brain and the anterior chamber of the eye represent somewhat specialized sites for the growth of alien tissues in that they appear to be protected by the hematoencephalic barrier (4). Tissues placed in these regions are perhaps less subject to various defenses of the body, and for this reason growth of intraocular transplants may be less conclusive evidence of autonomy than growth after subcutaneous transplantation. However, transplanted tissues that grew had become vascularized, and so were in intimate contact with the blood of the hosts during their growth. Furthermore, the fact that intraocular transplants of normal hypophyseal tissue did not behave like the transplants of adenoma-like tissue can only be interpreted as evidence that the adenoma-like tissue possessed a capacity for growth greater than and independent of that of normal tissues. It is also of significance that normal hypophyseal tissue transplanted to the anterior chamber of the eye underwent much the same changes in appearance as were found by Wolfe, Kirtz, and Loeb (12) in anterior pituitaries of inbred mice transplanted into the subcutaneous tissue of their brothers and sisters. It is thus reasonable to assume that, within certain limits, the site of inoculation is of secondary importance in the behavior of transplants.

In our experiments transplants of adenoma-like tissue behaved in more respects like neoplastic than normal tissue. The growth rate, while characteristically slow, appeared to be independent of the age and strain of the recipients. Greene (2) has described a neoplasm of the rabbit kidney which, while bearing a close morphological resemblance to rapidly growing embryonal renal tumors of man, has been found to grow very slowly after homologous intraocular transplantation. A slow rate of growth after transplantation may thus be characteristic of some neoplasms. Only in respect to sex did transplants of adenoma-like tissue appear to be dependent upon constitutional factors of the host. Tissue did not grow so well in female as in male rats, although the number of females used as recipients was too small to be conclusive. The experiments were terminated before this difference had been adequately tested. For the same reason it is not possible to state that pituitary adenoma-like tissue can be carried indefinitely by serial intraocular transfer. It is conceivable that a hyperplastic tissue may upon transplantation carry with it the factor from the host inciting its original growth. However, such a factor would of necessity become diluted in subsequent passages if it were not a component or product of the tissue. The energy or rate of growth of subsequent serial transplants would thus be expected to diminish. That this was not the case in our experiments is shown by the fact that there was no diminution in the growth rate of second and third serial transplants.

At the time the experiments were discontinued it could not be said that the limit of transplantability of adenoma-like tissue was being approached.

The growth of intraocular transplants appeared to be unrelated to the development of adenoma-like lesions in the pituitaries of the hosts. The tissue grew as well in the strains characterized by a high frequency of pituitary adenoma-like lesions as in strains where the spontaneous lesions were relatively infrequent. It was thus probable that the transplanted tissue did not derive a stimulus for growth from factors of the host that gave rise to the spontaneous lesions, and this may be taken as further evidence of autonomy. Moreover, the presence of growing transplants of adenoma-like tissue did not influence the frequency of pituitary lesions in the hosts. It is therefore unlikely that the tissue carried with it a separable agent that might stimulate growth of chromophobic cells.

From the studies of their behavior after transplantation, it is concluded that the larger growths of chromophobic cells are neoplastic in character. The frequency and morphology of the lesions are compatible with this view. It is doubtful, however, if the smaller lesions are neoplasms. These may represent hyperplasia in response to stimuli from within the endocrine system, since it is well known that disturbances in hormonal balance may induce proliferative changes in tissues upon which various hormones...
may act. Hyperplasia of endocrine origin may lead directly to true autonomy of growth, or may provide a suitable substrate in which other factors may then induce neoplasia (5). When chromophobe hyperplasia as such ends and neoplasia begins was not determined in these experiments. It is probable that a study of transplants from very small or early chromophobic lesions would be of value in this regard.

SUMMARY

Chromophobe adenoma-like lesions of the hypophysis were found in 92 of 362 albino rats of the Yale strain. Two lesions only were observed in rats less than 1 year of age. The lesions increased in frequency with advancing age, and were present in 60 per cent of male rats and in 30 per cent of female rats 600 and more days old. The lesions varied in size from small nodules seen only in microscopic section to large masses, the largest weighing 367 mgm. The majority of lesions were composed of cells with vacuolated chromophobic cytoplasm and large oval nuclei in which the chromatin was usually in the form of coarse granules. Chromophobe adenoma-like lesions were found in the hypophyses of 3 of 83 male rats of the Sherman strain, aged between 1 and 3 years, and of 1 of 9 male rats of a stock derived from the Wistar strain, of comparable age.

Homologous intraocular transplants were made with adenoma-like tissue from two spontaneous lesions in male rats of the Yale strain, and these were carried in males into second and third serial intraocular generations respectively. Including all generations, growth of transplants occurred in 21 of 42 recipients. The transplants grew at an extremely slow rate, requiring from 11 to 19 months to reach a size suitable for serial transfer, and there was frequently a latent period of several months before growth was manifest. All transplants that grew became vascularized. The growth rate was not accelerated in subsequent transfers and the morphology did not change. Although the spontaneous lesions developed only at an advanced age, intraocular transplants grew as well in young as in old male rats. However, there was but slight growth in 1 of 4 female recipients. The strain of the recipient was found not to be a factor in either the percentage of successful transplants or their growth rate. The presence of spontaneous adenoma-like lesions in the pituitaries of the hosts did not influence the fate of transplants of adenoma-like tissue.

Normal hypophysial tissue persisted for a considerable period after intraocular transplantation, but did not grow in a manner comparable to adenoma-like tissue.

Morphological studies have indicated that chromophobe adenoma-like lesions of the rat's hypophysis are more probably neoplastic than hyperplastic in nature. It is concluded on the basis of the behavior of transplants that the larger adenoma-like lesions are true neoplasms in that the growth rate of transplants, while characteristically slow, is independent of the growth rate of tissues of the recipients, and in that the ability of transplants to grow is independent of constitutional factors associated with age and strain of the recipient.

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