normal condition. The tough but extensile nature of the pellicle may be further demonstrated by inflating the cell with distilled water injected through a micropipette. From a cell ruptured under pressure the entire pellicle may be removed. In every case recorded the nucleus came away with the pellicle. Injection of various solutions usually causes an immediate inflation of the Amoeba, the fluid collecting in an area beneath the pellicle, while the endoplasm contracts into an irregular mass containing the nucleus.

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The reaction of the endocrine system of the rabbit to tumor inoculation and the relation of this reaction to malignancy.

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Within recent years, a great deal of evidence has been accumulated from both clinical and laboratory sources which has tended to show that some kind of connection exists between the occurrence and growth of tumors and the system of organs regulating animal economy. For the most part, the evidence bearing upon this problem has been circumstantial. In a few instances a definite relationship appears to have been established as in the case of the experiments reported by Loeb[1] concerning the effects of castration on the incidence of mammary tumors in mice and those of Rohdenburg, Bullock, and Johnson[2] on the effects of operative removal of various organs upon the growth of transplanted tumors and the immunity of tumor animals. There are also therapeutic observations on the use of thyroid and of thymic products alone or combined with castration[3] which might be regarded as equally suggestive were it not for the fact that similar results have been obtained by the use of a variety of means.[4]

1 Loeb, L., *J. Med. Res.*, 1919, xxxv, 447.

2 Rohdenburg, G. L., Bullock, F. D., and Johnson, P. F., in *Studies in Cancer (George Crocker Research Fund)*, 1913, iii, 87.

3 Beatson, G. T., *Glasgow Med. J.*, 1913, n. s. lxxvi, 81, and earlier reports.

4 A more recent article on this subject has been published by Enge in the *Ztschr. f. Krebsforsch.*, 1923, xix, 339.

Two years ago, we reported the occurrence of a malignant tumor in the scrotum of a rabbit infected with *Treponema pallidum.*[5] Since that time, a careful study has been made of the conditions presented by this animal[6] and a long series of investigations based upon the behavior of transplanted tumors derived from this stock has been carried out which have shown that there is an essential connection between the growth of transplanted tumors and certain members of the endocrine system on the one hand, and the mechanism of animal defense on the other.

In the animal with the spontaneous tumor, there was a notable tendency to atypical epithelial proliferation in many parts of the body associated with a deficiency in the reaction of the surrounding connective tissues and a widespread tendency to degeneration. There were also very striking alterations in such organs as the thyroid, the thymus, the suprarenals and the lymphoid tissues, which might have been regarded as part of a general organic deterioration attributable to one or both of the diseases present. From our knowledge of the biology of syphilitic infections and from what is known as to the influence of this system of organs on animal economy, however, we were led to suspect that the changes present might not be entirely incidental. This suspicion was strengthened when it was found that inoculation of other animals gave rise to decided alterations in a number of the organs of internal secretion as well as in the lymphoid tissues. With a view to determining whether these changes were consequences of disease or possessed a functional significance in tumor-bearing animals, especial attention was given to the alterations that occurred in this system of organs.

EXPERIMENTAL

Since the fall of 1921, the thyroid, the parathyroids, the suprarenals, the hypophysis, the pineal, and the thymus of all animals inoculated with this tumor have been studied grossly and histologically, including determinations of weight per unit of body weight. As a means of control, like observations were made upon normal rabbits derived from the same stocks and

[5] Brown, W. H., and Pearce, L., PROC. SOC. BIOL. AND EXPER. MED., 1921, xviii, 201.

[6] Brown, W. H., and Pearce, L., *J. Exper. Med.*, 1923, xxxvii, 601.

kept under the same conditions as the tumor animals. The sacrificing of these animals was so arranged as to provide control observations on the condition of the glands existing at the time inoculation was carried out as well as at the time of determining the effect of the inoculation. The results of tumor inoculations were further controlled by the examination of a large series of animals with various forms of spontaneous disease and of animals inoculated with *Treponema pallidum* as reported elsewhere.[7]

Some of the experimental animals died as a result of tumor growth while others were either arbitrarily killed at intervals of from 48 hours to 4 weeks after inoculation or at some critical period during the progress of the disease. The results thus obtained were analyzed with reference to the growth and the malignancy of the tumor as indicated by the clinical course of the disease and the conditions existing at the time of death. The control animals with other diseases were handled in much the same way.

RESULTS

Stated briefly, these investigations showed conclusively that the growth of the tumor was associated with the occurrence of marked alterations in the size and the general appearance of such organs as the thyroid, the thymus, and the suprarenals and that less pronounced changes took place in the parathyroids and the hypophysis. Distinct histological changes also occurred in the thyroid, the thymus, and the hypophysis, but no definite change could be made out in the other glands.

In general the initial change was of the nature of a hyperplasia associated at first with a reduction in the weight of the gland which was followed by hypertrophy, or an increase in weight, while the ultimate condition presented depended upon the course of the disease. Thus, where the tumor progressed for a considerable period of time with the formation of metastases, there was a marked increase in the weight of such organs as the thyroid and the suprarenals while the thymus remained small or diminished in size. If the disease assumed a highly malignant character as indicated by the early appearance

[7] Brown, W. H., and Pearce, L., PROC. SOC. EXPER. BIOL. AND MED., 1923, xx, 476.

of widespread metastases, all of the organs enumerated above showed a sharp reduction in weight suggesting an exhaustion. This occurred before the animal exhibited any clinical signs of physical deterioration.

If, on the other hand, the disease terminated in recovery, the picture presented was quite different. The thyroid invariably showed a hypertrophy which persisted through the early stages of resolution; it then diminished in size but increased again as healing was completed. The suprarenals showed a similar series of changes except that the reduction in size and the secondary increase occurred earlier than the corresponding changes in the thyroid. In these animals, the thymus showed an increase in weight which was proportional to the extent of the growth at the time regression set in and this was a striking feature of the reaction seen in animals capable of controlling the growth of the tumor as compared with those in which the reaction was ineffectual.

Again, in recovered animals and in animals that had been subjected to repeated inoculations of tumor emulsions (immune animals), the weights of the thyroid, the parathyroids, the thymus, the suprarenals, and the hypophysis were all found to be greater than in normal controls and they apparently retained this increased size indefinitely.

Finally, a similar series of changes occurred in the superficial lymphnodes and in the spleen. The lymphnodes showed an initial hyperplasia and enlargement followed by a terminal atrophy in acutely fatal cases. The spleen, on the other hand, showed comparatively little change during the early stages of the disease but later became enlarged. It was a notable fact that the enlargement was usually proportional to the atrophy of the thymus except in cases of fulminating malignancy where both organs not infrequently showed a reduction in size.

The alterations described showed clearly that there was an intimate relation between the reaction that occurred in these organs and the malignancy displayed by the tumor or the ability of the animal to control or suppress its growth. Viewed from another standpoint, a similar relation was found to exist between the occurrence of periodic variations in malignancy and the prevailing state of the endocrine mechanism as indicated by the weights of the glands of normal rabbits. For example,

during the 2 years that the tumor has been under investigation, it has shown distinct seasonal variations in malignancy which have followed a definite order. During the summer, the disease has been more benign than in winter while each spring and fall there has been a marked increase in malignancy as determined by such criteria as the rate of growth of primary tumors, the incidence and distribution of metastases, the proportion of cases of fulminating malignancy and the mortality of inoculated animals.

These variations in malignancy, or in animal resistance, coincided with the existence of a given state of equilibrium or the occurrence of readjustments of endocrine balance as shown by the weights of these organs in control animals. But, the periods of greatest malignancy occurred at the time of readjustment from winter to summer or from summer to winter conditions, that is, at periods of unstable equilibrium.

From these observations, the general conclusion was reached that the malignancy displayed by this tumor was largely a function of animal economy and that the resistance of the animal to the growth of the tumor was conditioned upon the activity of those organs ordinarily concerned in the regulation of growth and maturity.

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Animal resistance and the endocrine system of the rabbit in experimental syphilis.

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In the course of the work that has been carried out in this laboratory during the past 8 years, it has become more and more apparent that of the several factors concerned in determining the general course and severity of syphilitic infections, th spirochete is of minor importance as compared with ber of other influences, especially the factor of animal re.