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.

This is strikingly illustrated by the experimental infection in the rabbit which, as a rule, is comparatively mild but in exceptional instances may assume a more malignant form or persist in an active state with severe constitutional symptoms for months or even years and in the end cause the death of the animal.

Little has been known as to the nature or source of the forces employed by the animal in combating this disease but there is a great deal of evidence to indicate that resistance to this infection is a function of animal economy and is subject to the same influences as are concerned in the regulation of growth and development, and the maintenance of general metabolic activities. Moreover, there have been specific indications that resistance was influenced to some extent by the endocrine system.

This possibility was first suggested to us by the occurrence of marked seasonal changes in the severity of the disease but was most forcibly impressed upon us by the abnormal resistance displayed at times by pregnant and lactating females. Finally, when we came to investigate the crossed immunity relationships between syphilis and a malignant tumor which had developed in a syphilitic rabbit,[1, 2] we were again impressed by the importance of the constitutional element in resistance. In the case of the tumor, it was perfectly obvious that we had to deal with the endocrine mechanism and this led us to carry out on rabbits infected with *Treponema pallidum* a parallel series of investigations intended in part as a control for the work on the tumor but primarily as a means of determining whether any definite changes which appeared to bear a relation to the resistance displayed by the animal to syphilitic infection could be detected in the animal organism.

EXPERIMENTAL

Since November, 1921, a total of 139 rabbits infected with virulent strains of *Treponema pallidum* has been killed and examined at various stages of the infection, the time ranging from 1 week after inoculation (first incubation period) to several months after the development of complete latency. All organs were weighed and studied grossly and microscopically and the conditions found were analyzed with reference to the

1 Brown, W. H., and Pearce, L., *J. Exper. Med.*, 1923, xxxvii, 601.

2 Pearce, L., and Brown, W. H., *ibid.*, 631.

function of animal resistance as indicated by the course of the disease and the conditions existing at the time the animal was killed.

The results obtained from these examinations were controlled by similar observations made on a larger series (182) of normal rabbits derived from the same sources and comparable as to age, sex, breeds, length of caging, diet, and time and mode of killing. As a further means of control, similar observations were carried out on 51 rabbits with various forms and degrees of acute and chronic infections of spontaneous origin and by a comparison with effects produced by tumor inoculation and by inoculating first with *Treponema pallidum* and then with the tumor or *vice versa.*

RESULTS

The results of these experiments cannot be reported in detail but they show conclusively that, apart from any localized lesions which might be attributed to syphilis, there were definite changes in the weights of such organs as the thyroid, the parathyroids, the suprarenals, the hypophysis and the thymus, as well as in the liver, the spleen, and the lymphoid tissues in general. The majority of these organs showed distinct changes in appearance and structure which were especially noticeable in the thyroid, the parathyroids, and the thymus. Moreover, the status of the organs at one stage of the infection differed from that at another and, in general, the direction and magnitude of the change that occurred was proportional to and parallel with the resistance displayed by different groups of animals. Finally, it was found that the changes which took place as the disease was brought under control and immunity was established were of a more or less permanent character. In other words, such organs as the thyroid, the parathyroids, the suprarenals, and the thymus, did not revert to their normal size and appearance but maintained a condition suggestive of a higher plane of functional activity and of a change in the general relationship of one organ to another.

In severe infections, some of these glands showed unmistakable evidences of injury. This was most noticeable in the case of the thyroid and the parathyroids but on the whole it appeared that the changes were related to alterations in functional activity which had to do with the development and maintenance of the resistance to infection.

Upon the basis of these findings, a further series of experiments was undertaken by Louise Pearce and C. M. Van Allen for the purpose of determining whether the course of the disease could be altered by operative interference with any of the endocrine glands or by the administration of such chemical agents as the iodides and mercury. Neither of these agents possesses any considerable spirocheticidal action in doses below the lethal limits but have been found to produce marked changes in the endocrine glands and the lymphoid tissues.

These experiments are not complete but they show already that, by either of the methods mentioned, the general character and course of the disease may be greatly modified; that the resistance of infected animals may be augmented or depressed by one and the same agency; that the immediate effect is proportional to the stimulation or depression of the activity of this system of organs. In other words, it has been found that the development and resolution of syphilitic lesions are subject to the same influences as are concerned in ordinary processes of growth and maturity. In this instance, it is of interest to note that the lymphoid tissues act in harmony with the endocrines or as though they formed a part of the general system of organs concerned in these reactions.

DISCUSSIONS AND CONCLUSIONS

The experiments referred to open up an enormous field for investigation. They supply us with a concrete basis for dealing with phenomena of disease which are dependent upon animal behavior. In fact, they point to the possible importance of this system of organs wherever the factor of constitutional predisposition or resistance enters into the problem of etiology or resistance to disease. At the same time, the fact cannot be emphasized too strongly that we are dealing here with a system of organs and tissues whose action may be interfered with at a number of points and in a number of ways which in the end may produce effects almost identical in character. In other words, while it is obvious that one or another of the elements of this system may be immediately responsible for a given effect, or of greater importance than another, the integrity and stability of the mechanism and the existing balance in the functional activity of its component parts appear to be the factors of foremost importance.

The deductions which might be drawn from the experiments already carried out are numerous. These experiments not only supply us with a better basis for understanding phenomena of constitutional resistance or susceptibility to syphilitic infection in general but they throw considerable light upon many obscure aspects of the disease. It is not unlikely that differences in individual susceptibility and differences between the sexes and between pregnant and non-pregnant women or even racial and geographical peculiarities of the disease may be explainable upon this basis. In the same way, other features of the disease, such as the abnormalities of detentition in congenital syphilis, may be attributable to the injury inflicted upon this group of organs. Again, it appears that the maintenance of immunity is in some way dependent upon the functioning of this mechanism at a new and probably a higher level which is necessitated by the presence of an infection which must be kept under continuous control. This state of heightened activity or constant stress may in turn account for the eventual physical deterioration and predisposition to other forms of disease which so often occur in syphilitic individuals.

Finally, these experiments also serve to indicate what may be accomplished by a system of therapy that is intended to reinforce the resistance of the patient. At the same time, they serve as a warning of the dangers that may be encountered by attempting to treat syphilis without due regard for the effects of such treatment upon the patient or from ill advised efforts to alter the action of the mechanism concerned in maintaining constitutional resistance.