PHYSIOLOGICAL AND PHARMACOLOGICAL STUDIES OF THE PROSTATE GLAND

III. EFFECT OF PROSTATECTOMY ON THE BEHAVIOR OF ALBINO RATS

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INTRODUCTORY

The recent advances in our knowledge of internal secretions have caused not only physiologists but also clinicians to be on the lookout for manifestations pointing to a possible derangement in the functions of various glands. To this the prostate gland is no exception. There is an increasing tendency to regard the prostate gland as possessing an internal secretory activity as well as an external one, and a multitude of symptoms noticed in the course of prostatic diseases on the one hand and the sequelae after prostatectomies on the other have been sometimes ascribed to the lack of such a hormone.

Among the commonest symptoms of such a character that have been correlated with an internal secretion of the prostate gland are various manifestations of a psychopathic or neuropathic type. Thus Guisy (1) in an interesting monograph gives some very interesting data on the subject. He found among 31 cases of prostatic hypertrophy in patients between fifty-seven and sixty-seven years of age, 3 subjects exhibiting psychopathic disturbances of the hallucinatory and melancholic type. Out of 7 cases of prostatic cancer, 1 patient was found to suffer from melancholia and optic hallucinations. Among 4 cases of tuberculosis of the prostate the same author found also 1 man suffering from cerebral depression. Guisy further states that he encountered 2 cases with profound depressive psychoses among

17 patients in whom complete prostatectomy had been performed some time previously, and the same author quotes statistics from other writers who have also noted psychic disturbances after transvesical prostatectomy. Similar experiences are reported by Rovsing (2), Voelker (3), and Rumpel (4). On the other hand, probably the vast majority of urologists are inclined to the view that complete extirpation of the prostate gland has no bearing on the character and mental efficiency of the patients, and others such as Fréyer and Ertzbischoff (5) go even so far as to state that, on the contrary, they have often known psychopathic patients to improve in health of body and mind after prostate operations.

It is obvious that clinical data are very unreliable in drawing conclusions as to the relationship of prostatic disease or extirpation of the prostate and the changes in character, mentality, and neuromuscular coördination of the patients. In the first place, the extirpation of the prostate is performed generally in men of advanced age who may already have been suffering from various senile pathological changes. In the second place, any alteration in the health of the patient may very justly be ascribed to the shock of the none too gentle operation. Again, the anesthetics may well bear some responsibility for the after effects. Lastly, the occurrence of psychic disturbances in the patients may be ascribed to a variety of other causes or may even be purely a coincidence. Thus for instance, one reads with a smile the statement of Guisy, that he found 4 cases of melancholia among 51 patients suffering from acute gonorrheal prostatitis.

METHOD OF APPROACH

Perhaps the most satisfactory method of approaching the question of the relationship between an internal secretion of the prostate and the mental efficiency of an individual is to study the effects of the complete extirpation of the prostate on the functions of lower animals. An attempt in this direction has been made by the authors in the present investigation. The most suitable animal for use in conducting such experiments is

the rat. This little rodent possesses a prostate gland which can be easily and completely extirpated. Furthermore, the prostate of the rat is enormously large in proportion to the weight of the animal when compared with that of man. The authors have often removed prostates from rats which weighed as much as one four hundredth of the weight of the whole animal. If we assume the weight of an average man to be 70 kilos and the average weight of the human prostate to be 20 grams, the ratio between the weight of man to the human prostate is 3500 to 1, a figure very small in comparison with that of the rat (400 to 1). It is therefore fair to assume that if the prostate gland elaborates an internal secretion, the complete extirpation of that gland in the rat would lead to much more greatly accentuated disturbances than a similar operation in man. Furthermore, the effects of prostatectomy in rats can be studied in perfectly normal and young adults; so that it may be possible to exclude the effects of senility and other pathological changes which must always be taken into consideration in making deductions from clinical data. The position and size of the prostate gland has been well described by Walker (6), whose plate is here reproduced with his permission (fig. 1).

The authors accordingly selected a number of healthy young adult male rats and performed complete prostatectomies on them. The behavior of these animals was studied before and after the operations and in this way the effects of prostatectomy on the neuromuscular and cerebral efficiency of the animals was investigated. The most convenient method for the study of such phenomena was by the use of a circular maze, such as has been invented by Professor Watson of the Psychological Laboratory of this University. This apparatus is described in detail as follows.

DESCRIPTION OF THE MAZE

The circular maze shown in figure 2 is made with wooden base and aluminum walls. The base is 150 cm. in diameter and 4 cm. in thickness. Its upper surface is marked off by grooves into a series of concentric circles. The diameter of each of the

circles is as follows, beginning with the outermost one: 140 cm., 120 cm., 100 cm., 80 cm., 60 cm., 40 cm., and 20 cm. Into the

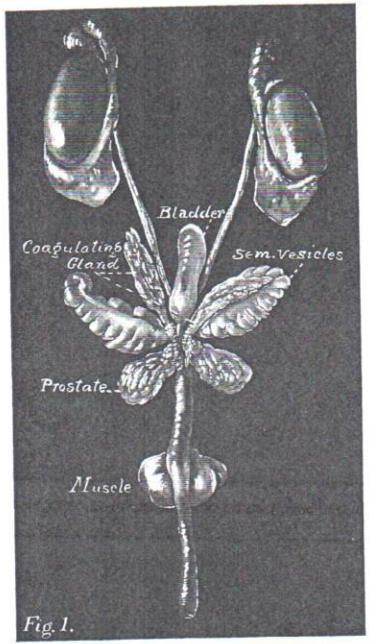

FIG. 1. GENITO URINARY ORGANS OF THE RAT, SHOWING PROSTATE GLAND, ETC.
After Walker; by permission of the author and publishers

circular grooves are inserted sheets of aluminum 18.5 cm. high and 0.8 mm. thick. Each strip of aluminum is cut just 10 cm. shorter than the length of the circular groove into which it is to

be fitted, thus giving an opening into the alley. By means of this arrangement it is possible to slide the aluminum around its groove and thus to place the entrance in any desirable position. In the present investigation, the openings or entrances to the alleys were placed in the position indicated in figure 1, there being 7 openings so arranged that the rat had to make alternate turns turns and left, in the order indicated by nos. 1 and 7. In

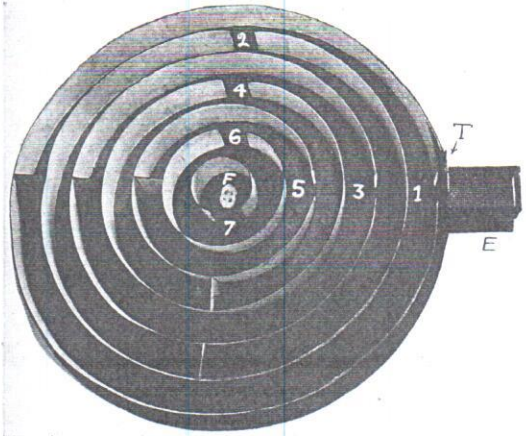

FIG. 2. CIRCULAR MAZE

addition to the doors or openings, the alleys are provided also with obstructing partitions, which form a number of blind culde-sacs. A wire screen half of which is shown (*W*, fig. 3), prevents the animals from crawling over the top.

The camera lucida attachment invented by Professor Watson is illustrated in figure 3. A large plate-glass mirror *M*, 91 cm. wide and 121 cm. in length, was placed at an angle of 45 degrees,

directly over the center of the maze. At a certain distance from this mirror a second mirror, *M*, 60 cm. by 75 cm., is placed at an angle of 45 degrees above the maze, at such a distance from

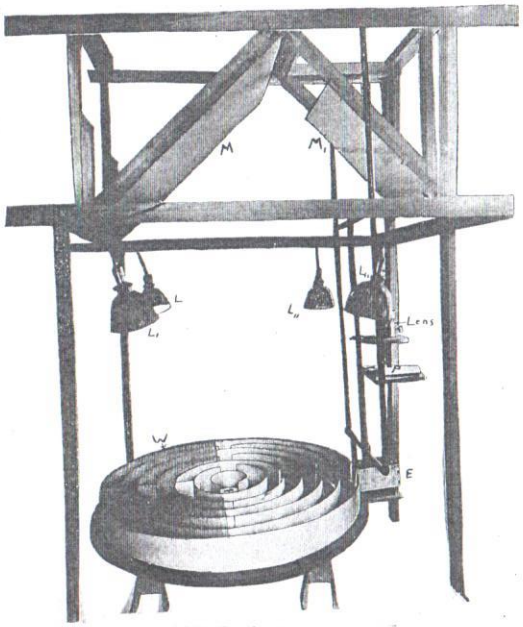

FIG. 3. CIRCULAR MAZE WITH CAMERA LUCIDA ATTACHMENT

the first mirror that the light reflected downward from it falls outside of the maze. Below *M*, and in the light reflected from it, is placed a single achromat, 6 cm. in diameter and 50 cm.

focus. The lens is placed in a barrel and the barrel is attached to a wooden disc 30 cm. in diameter. This board is attached to an iron collar which slides freely up and down and gives a very easy means of adjusting the size of the image. A circular piece of paper is laid upon a wooden shelf, below the lens, and the distance is so adjusted that the reduced image of the maze is focused upon the paper. Extraneous light is excluded by means of a soft dark flannel curtain, not shown in the figure. As may readily be seen from the figure, the maze must be illuminated quite highly in order to produce a clear image. This illumination is obtained by means of four powerful electric lamps, with opaque shades placed symmetrically around the maze. By means of the camera lucida attachment, the movements of an animal in the maze can be traced upon white paper with a soft pencil. Such tracings are especially useful in the study of the learning of the maze problem, such as has been done by Miss Hubbert and others. In the present investigation, where the effect of drugs on the behavior of the animals was studied after the rats had been trained, the use of this attachment was not essential and it was therefore dispensed with in a great many of the experiments.

The study of the behavior of the rats in the circular maze is begun by placing an animal in the center of the maze and feeding it from the bowl *F* for three successive days. During these three preliminary feedings, which last from ten to fifteen minutes, the entrance 7 is blocked off, so that the animal may not roam around. On the fourth day, the rat is placed in the cage *E*, then the trap-door *T* is raised and the animal allowed to enter the first alley. The animal then gradually learns to find its way to the center of the maze, when it is taken out and the experiment is repeated. Generally three trials are made on each day. For work with the maze, albino rats, which are very tame must be employed. The animals must be handled gently with the hands and under no circumstances must they be picked up with forceps or similar instruments. The most suitable animals are found to be rats approximately sixty to ninety days old. Older animals are apt to be sluggish while very young

rats do not learn the maze problem so readily. Ordinarily the albino rats learn the maze problem in about two weeks, and sometimes within a shorter period of time. An animal is considered to have solved the maze problem when it has learned to find its way into the center of the maze by the shortest route, that is, without any errors, on three successive trials. The technic of training is described more in detail by Hubbert (7).

ANALYSIS OF THE DATA FURNISHED BY THE MAZE

The maze problem enables the psychologist to study the mode of learning of a rat. In studying the effect of drugs ,the maze problem can be utilized in two ways. Animals may be subjected to the influence of drug action first and then trained in the maze with the purpose of ascertaining the effect on the rate of learning. Again, animals may be first taught to solve the maze problem and then the effect of a drug is studied in reference to its influence on their behavior, memory-habit, etc. Furthermore other data can be obtained from the maze, after administering drugs to rats, which may show the effect on neuromuscular coördination, and various somatic changes. As to exactly what the mechanism of learning the maze problem may be, the explanations given by various psychologists differ widely. Among the hypotheses which have been advanced to account for the reintegration of conduction paths in learning, there are at least three which stand out as rather opposed to one another in respect to the neural processes which they imply (8). The hypothesis suggested by Ladd and Woodworth (9) assumes inhibition of successive activities as the fundamental process which results in the selection and fixation of random activities. The second hypothesis, given by Angell and others (10), assumes nervous reinforcement as the fundamental process by which successive acts become linked together in habit-formation. The third hypothesis (Watson, (11) depends chiefly upon the chance spreading of nervous excitation, or the simultaneous activation of two afferent pathways in such a way that the final common part of one is able to divert the discharge of the other and so bring about a permanent connection between itself and this afferent path. These hypotheses by no means exhaust the theoretical considerations of the maze problem (Dashiell (12)). For the study of drug action, however, the various theoretical considerations are of secondary importance and the data obtained are of a much more definite nature, as will be seen from the following exposition.

EFFECT OF PROSTATECTOMY ON MEMORY HABIT

Two series of experiments were conducted by the authors. In one series the animals were first trained to solve the maze problem and after having acquired perfect facility in doing so the same animals were prostatectomized and their subsequent behavior studied. In another series of experiments a number of rats were first prostatectomized and then allowed to recover completely from the effects of the operation. They were then left alone for a considerable number of weeks in order to permit a deficiency in the internal secretion of the prostate (if there be any) to manifest itself. Finally these animals were trained in the maze and their rate of learning was compared with that of a series of control rats which were either not operated at all or which underwent the operation of laparotomy but without the extirpation of the prostate.

In the first series of experiments six young, adult, male albino rats were trained in the circular maze. After the animals had learned to run through the maze by the shortest route in the shortest period of time without committing any errors, they were etherized and the complete extirpation of the prostate gland was performed on each rat, under aseptic precautions. The wounds were then closed and allowed to heal and the animals were left undisturbed in their cages for sixteen days. Two other rats were trained in the maze in exactly the same way and after having learned the problem were also etherized and operated on. In this case however, a laparotomy was performed and the various organs examined but no prostate gland was removed. The incision then was closed and the animals allowed to recover

and were used as controls. On the seventeenth day both the prostatectomized rats and the control rats were put in the maze and their behavior was studied. It was found that all the rats retained their memory and ran quickly to the center of the maze without committing any errors, even though they had not practised in the apparatus for sixteen days. On the following, or eighteenth day, all the rats were again put through the maze and were found to have recovered completely their original normal behavior. They ran through the maze by the shortest route in the shortest period of time without making any mistakes, just as if they had not been operated upon, No difference in behavior or effect on the memory-habit between the prostatectomized rats and the control rats was noticed.

EFFECT OF PROSTATECTOMY ON THE RATE OF LEARNING

In this series of experiments a total number of 34 rats were used. Of these 6 rats were studied by Macht and Mora but the record of the experiments was lost. The results, however, agreed completely with those obtained in the 28 rats used in the experiments by the present authors. Fourteen of the animals were prostatectomized. In performing this operation the animals were given ether as an anesthetic and antiseptic precautions were observed. Great care was taken to remove the prostate completely. After the operations the wounds were closed and the animals were allowed to recover. In each case the wounds healed satisfactorily. The other 14 rats were used as controls. Of these 8 were operated on, a laparotomy being performed and the bladder and prostate being handled and examined but *not* excised, so as to subject the animals to as much operative shock as the prostatectomized ones. The 6 other animals were used as unoperated controls.

All of the animals were left undisturbed in their cages, without training, for periods of time ranging from five to nine weeks. After this prolonged rest, training was begun and observations were made on the rate of learning the maze problem. The animals were put in the maze 6 times a week and wherever possible three successive trials were given each rat, on each day.

When the animals, however, were sluggish, in a few cases only two trials were made on some days. The results obtained are exhibited in table 1.

It will be seen that the average time of learning the maze in the case of the prostatectomized rats was 8.2 days and this represented the average number of 22.7 trials. The average time of learning the problem in the case of the control rats was 9.9 days, representing an average of 25.8 trials. The operated and unoperated controls were averaged together as little difference was found between the two.

TABLE 1

PROSTATECTOMIZED RATS			CONTROL RATS			
Rat number	Trials to learn	Days to learn		Rat number	Trials to learn	Days to learn
I	31	11	Laparotomy only	A	29	12
II	40	15	Laparotomy only	B	19	8
III	52	18	Laparotomy only	C	23	9
IV	18	8	Laparotomy only	D	30	12
V	36	12	Laparotomy only	E	12	4
VI	15	7	Laparotomy only	F	22	9
VII	16	6	Laparotomy only	G	38	14
VIII	12	4	Laparotomy only	H	21	8
IX	12	4	Unoperated control	I	18	7
X	18	6	Unoperated control	J	21	8
XI	15	5	Unoperated control	K	38	15
XII	12	4	Unoperated control	L	32	12
XIII	22	8	Unoperated control	M	31	11
XIV	19	7	Unoperated control	N	37	10
Average	22.7	8.2		Average	25.8	9.9

A comparison of the figures obtained reveals the interesting fact that the rate of learning after prostatectomy was *not impaired* and was just as good as in case of the control rats. Indeed if any differences were to be noted it would seem that the prostatectomized rats learned a little more quickly than the control animals.

DISCUSSION

The authors studied the effect of prostatectomy on the rate of learning on the one hand and on the memory-habit and general behavior on the other. The data obtained in both

series of experiments show no difference between the prostatectomized and nonprostatectomized rats. It is to be born in mind that in this investigation young adult males were used; thus excluding the possible effect of senile changes. Again in both the prostatectomized and the control animals care was taken to produce the same amount of surgical shock so that any difference due to such a cause might be eliminated. Furthermore, in choosing the control animals the authors have taken pains to select rats of approximately the same ages. Lastly, the effect of anesthesia was the same in both cases so that any changes produced could not be ascribed to the ether. This, however, was unnecessary inasmuch as Macht and Mora (13) had previously studied the effect of anesthesia on the subsequent behavior of rats and found that ether produces no changes in the behavior of the animals. The above experiments therefore, lead to the conclusion that if the prostate gland possess an endocrine function, its internal secretion bears no relation to the mental efficiency of the animal, in as much as prostatectomized rats behave in all respects the same as the rats which were operated on but in which the prostate was left intact. The conclusions derived from the present research agree with the experiences of the majority of urological surgeons in general and with the experience of the surgeons in the Brady Urological Institute, in particular.

SUMMARY

1. The effects of prostatectomy were studied on albino rats in the circular maze.

2. In one series of experiments the effect of prostatectomy on the rate of learning was investigated.

3. In a second series of experiments the effect of prostatectomy was studied in relation to behavior and memory-habit.

4. It was found that in both series of experiments no difference in the behavior between prostatectomized and control rats occurred.

5. These observations lead to the conclusion that the endocrine function of the prostate gland bears no relation to the mental efficiency of the animals.

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