She worked as a typist, earning £6 to £7 per month. Later she married, and had two children. At the birth of the second infant the doctor advised that she should be sent to Valkenberg Mental Hospital. Her mother, however, would not agree to this, and nursed her herself. The patient recovered and returned to her husband. This husband deserted her, and she obtained a divorce from him in 1922. Her life with this man was very unhappy.

"A year after her divorce she married her present husband, who had been divorced from his first wife. His first wife is at present an inmate of the Pretoria Mental Hospital, being mentally disordered, suffering from manic-depressive psychosis of the mixed type. The patient has two children by the first husband living with her. On the advice of the probation officer in Johannesburg the patient applied for admission to the Pretoria Mental Hospital as a voluntary boarder on July 14th, 1927. Previous to this she had become very sleepless, her nerves were all upset; she stated that her husband gave her no money and no servants, that he ill-treated her, and that she had to work very hard. She attempted to cut her throat with a razor.

"On admission to the Mental Hospital in July she was depressed, unhappy, and lacrymose, weeping readily. She conversed rationally, and gave a correct account of herself. Her memory and orientation were intact. No delusions or hallucinations were elicited from her; she slept badly. By August 1st, 1927, she showed some improvement, was more cheerful, and took an interest in her surroundings. She expressed herself as being quite better, and wanted to return home. On August 9th, 1927, she returned home."

It will be noted that on October 9th, 1927, she was admitted to the General Hospital, Johannesburg, after having driven the first nail into her head. Dr. Holmes's notes on her condition on her second admission to the Mental Hospital, on April 19th, 1928, are as follows:

"The patient is acutely depressed, cries easily, and is oriented for time and place. She does not give a correct account of herself, and feigns amnesia. She begins to speak, and then says, 'Oh! I can't remember; my memory has completely gone.' (Obviously not true.) She threatened suicide, and emphatically told the nurse that she would do it properly next time. She is under constant observation. On May 1st the patient was still very depressed and looked miserable. She maintained that her memory was lost. She stated that she was lame, but when she thought she was unobserved her gait and station were normal. She complained readily and was hypochondriacal. She slept badly, and sedatives had to be administered.

"By May 26th she had improved mentally, and occupied her time by reading. She sleeps and eats well and desires to go home to her mother.

"Her emotional tone is unstable, but her consciousness is clear, and her attention can be obtained and retained; her behaviour is irresponsible. She converses rationally, but her reasoning and powers of judgement are slightly impaired. Her memory and orientation are intact; no delusions or hallucinations can be elicited. Her psychomotor reaction is slightly retarded.

"*Diagnosis:* Manic-depressive psychosis—depressed type. *Prognosis:* (1) Immediate favourable; (2) ultimate bad. Will recover from present attack, but will probably relapse."

FURTHER OBSERVATIONS ON ADRENALINE MYDRIASIS AT THE MENOPAUSE.

BY

JOHN H. HANNAN, M.A., M.D., B.CHIR.

(From the Physiological Laboratories of the Middlesex Hospital.)

In a preliminary communication to this *Journal*,¹ and elsewhere,^{2,3} I have presented evidence that women at the menopause show an increase in sensitiveness to adrenaline. It has been shown that no mydriasis occurs in normal individuals following the instillation of adrenaline into the conjunctival sac, whereas I have demonstrated that a transitory mydriasis occurs at the menopause in some women, who complain of severe "flushing."

Our knowledge concerning the internal secretion of the ovaries has been considerably augmented by the work of Allen and Doisy and others working on the mode of action and methods of standardization of the oestrus-producing autacoid. Up to the present, however, the practical value of this work, particularly in connexion with the treatment of women with ovarian extracts, has been somewhat doubtful, since the condition of oestrus, as such, does not occur in women, and the system of standardization based on the production of oestrus in lower animals is, therefore, not strictly applicable to ovarian therapy in women. Furthermore, it has been shown that there is more than one active substance present in the internal secretion of the whole ovary.

It will be seen that some investigation was necessary to determine if a symptom common to both man and to lower animals occurs following oophorectomy. Work was there-

fore undertaken to determine if adrenaline mydriasis following oophorectomy occurs in rats as it does in some women at the menopause.

EXPERIMENTAL TECHNIQUE.

Test for Adrenaline Mydriasis.

One drop of adrenaline hydrochloride was instilled into the animal's conjunctival sac, at five-minute intervals, for twenty minutes. The adrenaline mydriasis reaction was considered to be positive if the pupil on the treated side became obviously dilated within this time when compared with the untreated eye.

Over a period of twelve months a large number of young mature animals—rats, rabbits, and guinea-pigs—have been subjected to this test, but in no instance has mydriasis occurred.

On October 20th, 1927, 6 albino female rats, having regular 3-4 day oestral cycles, were oophorectomized under ether. From this time until June 6th, 1928, the adrenaline mydriasis test has been applied at regular intervals to these animals, 64 individual observations having been made during this period. All the rats in this experiment showed adrenaline mydriasis commencing at different periods; in no instance did a rat which had once shown adrenaline mydriasis fail to reproduce the phenomenon at subsequent tests.

The reaction to adrenaline commenced in the animals under consideration on the 91st day of the experiment, and all rats showed mydriasis by the 154th day.

EFFECT OF ADMINISTRATION OF THE OESTRUS-PRODUCING AUTACOID.

I have recently shown⁴ that the oestrus-producing autacoid is effective when administered in adequate doses by the oral route, and that it will produce changes characteristic of oestrus in the vaginal smears in test rats. The dose which is effective by the mouth is some sixty times larger than that which is effective when given subcutaneously. It was decided to treat the adrenaline sensitiveness of the rats by the oral administration of the autacoid, in doses of the size which had been found necessary to produce oestrus. Only 5 of the 6 rats were at this time available for the experiment, as one had been accidentally killed some time previously.

Experiment I.—Twelve sows' ovaries, rich in follicles, were given to the 5 rats in one cage. The adrenaline mydriasis test was applied on the third day of the experiment, and was found to be positive in four instances, negative in one. An observation on the eighth day showed a return of the mydriatic reaction in all the rats.

Experiment II.—Five hundred rat units of a tested preparation of the autacoid were mixed with the animals' drinking water. On the third day of the experiment no adrenaline mydriasis occurred in any instance; a further observation on the eighth day showed a return in all instances of the mydriatic reaction.

Experiment III.—In this experiment the number of rat units of the preparation administered in water was reduced to 150. Observations on the third and eighth days of the experiment showed adrenaline mydriasis in all instances.

DISCUSSION.

It will be seen from these experiments that 500 rat units of the autacoid cured the adrenaline sensitiveness of all 5 rats; 12 sows' ovaries produced a cure in only one case; 150 rat units of the autacoid failed to produce any effect.

In my experiments on the production of oestrus similar doses of the autacoid and sows' ovaries were administered to batches of 6 rats, as compared with the batch of 5 animals used in this experiment, and it is interesting to note that the dosage of the autacoid which I had found necessary to produce oestrus corresponded roughly to that which was necessary to control mydriasis in the investigation under consideration. It will also be observed that the controlling influence of the autacoid passed off in all instances by the eighth day of the experiment.

In my work on women, to which I have drawn attention previously in this paper,⁵ only 6.2 per cent. of those women at the menopause who were tested showed adrenaline mydriasis, whereas all the rats gave positive results.

In order to explain this phenomenon the point which first arises is that women suffering from the normal menopause have still some ovarian tissue left, and are but

suffering from a diminution in the amount of the internal secretion, whereas the rats had all ovarian tissue removed. If this were the explanation one would expect to find that rats suffering from a normal menopause would not all show adrenaline mydriasis, whereas all women suffering from a surgical menopause associated with total removal of the ovaries should show the reaction.

Dealing with the first point, an effort was made to obtain some rats of menopause age, and here considerable difficulty was experienced, and an interesting point arises which has an important bearing on claims which have been made in the rejuvenation of old animals. I have found that either old animals are pets, and are therefore not available for experimental work at any price, or, if they are not pets, for economic reasons are never allowed to grow old.

After considerable trouble, however, 6 rats, all guaranteed to be 2 years old or more, were obtained, but one of these has had a litter, 4 show oestrous cycles at regular intervals, and only one rat was found to have no oestrous cycles. It is interesting to find that this rat, which has a senile cataract in one eye, gives a constant mydriatic reaction.

With regard to the testing of women who have had all ovarian tissue removed, some difficulty has again been experienced owing to the reluctance with which most surgeons remove all ovarian tissue. Twelve women who have undergone Wertheim's radical operation for carcinoma of the cervix have been tested, however, and in only one instance was adrenaline mydriasis present. It is therefore obvious that some other explanation of the difference in the percentage of reaction between rats and women must be found. As I have shown elsewhere,⁶ adrenaline mydriasis in women invariably passes off when the symptoms of "flushing" cease, and that not all women who suffer from "flushing" at the menopause show adrenaline mydriasis. I have advanced a hypothesis in this *Journal*⁷ that the disturbance of the sympathetic nervous system, in particular the abnormal adrenaline effects, is but a temporary phenomenon consequent upon the withdrawal of part or whole of the internal secretion of the ovaries, and that the duration of the symptoms depends entirely upon the speed at which the compensatory activity of the general endocrine system occurs. It would seem, therefore, that this compensatory activity is much more rapid in women than in rats.

Finally, I would suggest that the experimental work which I have outlined in this paper justifies the following conclusions.

1. The adrenaline mydriasis phenomena associated with the menopause in women occur also in oophorectomized rats.
2. The adrenaline mydriasis reaction occurs with more regularity in rats than in women.
3. The oestrus-producing autacoid can cause rats to lose the adrenaline mydriasis effect if administered in adequate doses.
4. The autacoid is effective when administered by the oral route in doses corresponding to those necessary to produce oestrus.
5. Diminution in the amount of the oestrus-producing hormone is responsible for adrenaline mydriasis at the menopause, and, as this phenomenon is always associated with severe vasomotor phenomena in women, is also probably responsible for these symptoms of the menopause.
6. The oral administration of the oestrus-producing autacoid is rational treatment for the vasomotor symptoms of the menopause.
7. The dose will have to be repeated within seven days if a permanent effect is required.
8. Though administration of the autacoid at the menopause is rational treatment, the enormous doses required will prevent the maximum benefit from such treatment being attained until preparations of increased activity are available.

I wish to record my appreciation of the helpful criticism and advice which I have received from Professor Swale Vincent and from Mr. J. H. Thompson of this department.

REFERENCES.

- ¹ *British Medical Journal*, July 2nd, 1927, p. 14. ² *The Flushings of the Menopause*, Baillière, Tindall and Cox, London, 1927. ³ *Endocrinology*, 12 (1), 59-64, 1928. ⁴ *Ibid.*, 12 (2), 193-198, 1928. ⁵ and ⁶ *Ibid.*, 12 (1), 1928, p. 62. ⁷ *British Medical Journal*, July 30th, 1927, p. 192.

CARDIOSPASM.

BY

H. H. GREENWOOD, B.S.LOND., F.R.C.S.ENG.,
CONSULTING SURGEON TO THE G.W.R. HOSPITAL, SWINDON.

THE use of the term "achalasia" implies a pathology analogous to that of Hirschsprung's disease and of congenital hypertrophic stenosis of the pylorus; both these diseases are probably congenital in their origin, both are accompanied by demonstrable hypertrophy affecting the muscular coat of the alimentary tube, whereas in cardiospasm the condition is certainly not congenital, and the existence of any hypertrophy of the muscular coat remains a subject of contention.

The term "cardiospasm" has an established place in the literature, and clinical observation bears out its descriptive accuracy; it would seem that the term "achalasia" is a premature attempt at generalization, facile and tempting, but quite unjustified by the present state of our knowledge.

The opinions expressed in recent literature by eminent authorities¹ show a lack of unanimity as to the cause of the disease, nor is there general agreement about the counsel of perfection in treatment.^{2 3 4 5}

The symptoms, slowly progressive, fall roughly into three stages: (1) Discomfort, not amounting to pain, in the epigastrium and behind the sternum. (2) Precipitate vomiting, coming at intervals, later occurring at every meal; pain, sometimes severe, usually precedes the vomiting and is relieved by it. (3) The vomiting becomes less precipitate. The oesophagus has become dilated so that it will hold a pint or more; the propulsive power of the oesophageal wall has weakened, and food enters the stomach mainly by hydrostatic pressure.

The disease usually occurs "in individuals of middle and late life" (Wright⁶). The youngest case in the series recorded by Walton⁴ developed symptoms at 21 years of age; the average age of onset was 46 years. In a case sent to me by Dr. Moore the age of onset was earlier—16½ years. The symptoms developed in the manner described above; there were, however, other features of an unusual character that are interesting.

The patient, an unmarried man, now aged 25, became an apprentice at the age of 16 in an engineering works one and a half miles distant from his home. The long hours of hard physical labour and his rapid growth during the period of adolescence demanded abundant food. Half an hour's rapid uphill walk, a similar period to return, left only a few minutes for a substantial meal at noon. In the evening, reaching home tired, at 6 o'clock, he had another hearty and hasty meal, hurrying to reach the technical college for evening classes at 7 o'clock. His teeth were very defective. In consequence all his meals were imperfectly masticated and were followed immediately by active exertion. The penalty of this constant bolting of food was the onset of symptoms of cardiospasm at the age of 16½ years. For several months the dilated oesophagus was emptied from time to time by vomiting, and relief from the pain followed. One day, after running rapidly up and down stairs, he discovered that the usual oppression in the chest and the sense of impending vomiting were suddenly relieved, and he felt something pass on into the stomach. He thereupon adopted the ingenious manoeuvre of springing up in the midst of a meal (when the symptoms invariably had their inception) and jumping with a curious side-to-side action, first on one leg and then on the other, until he felt a mass slide suddenly through an obstruction; he experienced an immediate freedom from pain, and he was able to resume his interrupted meal.

His general health began to suffer and he was obliged to abandon his employment at the works. He went abroad to Malay, and there, although now equipped with efficient dentures and no longer condemned to hurried meals, the symptoms persisted unabated. During the last few years they have, indeed, grown worse, and he has slowly but steadily lost weight; a stature of 6 ft. 1 in. consorted ill with a weight of 9 st. 8 lb. Sometimes pain and oppression were such prominent and urgent features that vomiting would alone serve to relieve his distress. He consulted various medical men and ingenious explanations were offered, but the cause was usually ascribed to "nerves," an attribution probably influenced by his curious saltatory movements.

Whilst on "long leave" he was referred to me, and I had several opportunities of seeing typical attacks during meals, ushered in by a growing expression of distress, and culminating in a sudden spring from his chair; the execution of this curious jumping dance, sometimes lasting a few minutes, sometimes as long as fifteen minutes before sudden relief came, was very striking, and suggested the existence of an oesophageal pouch or of cardiospasm.