neither of these things and is best avoided, nor should any other form of aperient be prescribed. Opium is the most useful drug in cases of this disease, and it may be taken with bismuth or a reliable brand of kaolin. Fluids should be given so far as the vomiting permits, and as soon as there is a desire for food a bland diet may be ordered. In debilitated patients special measures to combat the dehydration may be required. The use of anti-dysenteric serum is neither necessary nor of value in cases of Sonne dysentery.

REFERENCES

- Nabarro, D., and Signy, A. G. (1932). *Arch. Dis. Childh.*, 7, 327.
Smith, R. E. (1931). *Lancet*, 2, 925.

THE ABSENCE OF ANTI-GONADOTROPIC SUBSTANCES IN THE BLOOD SERUM OF MAN INJECTED WITH GONADOTROPIC EXTRACTS

BY

A. W. SPENCE, M.A., M.D., F.R.C.P.

Assistant Physician, St. Bartholomew's Hospital

E. F. SCOWEN, M.D., M.R.C.P.

Assistant Physician and Assistant Director, Medical Professorial Unit, St. Bartholomew's Hospital

AND

I. W. ROWLANDS, Ph.D.

National Institute for Medical Research, Hampstead

Recent work has demonstrated that the prolonged administration of gonadotropic hormones to animals produces a state of insensitivity, so that the initial hypertrophy of the gonads disappears and may even be followed by atrophy (Collip, 1934). Moreover, the serum of an animal injected for about three months with a gonadotropic extract acquires the property of inhibiting the action of the gonadotropic extract when both are separately injected into a test animal, such as the immature rat; when the serum alone is injected into a normal adult animal it may cause atrophy of the reproductive organs (Rowlands, 1937). These phenomena are due to the production of anti-gonadotropic substances in the blood as a result of the continued administration of the gonadotropic extract.

These facts might be of clinical importance in the treatment of patients for a prolonged period with gonadotropic hormones. Should such anti-gonadotropic substances be formed in the human it would appear advisable to intersperse rest periods of several months, during which the patient receives no treatment, to enable him to reacquire sensitivity and to prevent any possible damage to the gonads. On the other hand, should there be no indication of the production of such substances as a result of prolonged treatment these rest periods would be unnecessary. In the elucidation of this problem samples of blood from nine patients with undescended testes who were receiving treatment with gonadotropic hormones were tested for anti-gonadotropic activity.

Methods

The patients were injected intramuscularly twice a week with extracts of human urine of pregnancy (pregnyl or antuitrin S) or with extracts of pig anterior pituitary (ambinon or antuitrin gonadotropic). Details of their treatment are given in Table I.

TABLE I.—*The Treatment of the Patients with Gonadotropic Preparations*

Case No.	Age (Years)	Preparation	Dose (Rat Units, R.U.) twice weekly
1	19	Pregnyl	1,000
2	12	Pregnyl	500 for first 9 weeks, then 1,000
7	14	Pregnyl	1,000
8	20	Pregnyl	1,000
9	12	Pregnyl	500
10	14	Pregnyl	500
5	13	Antuitrin S	200
3	14	Ambinon	50
4	10	Antuitrin gonadotropic	30 for first 14 weeks, then 50 for 9 weeks

Where possible a sample of blood was obtained before treatment and thereafter at intervals of one to two months for as long as was practicable in each case (Table II). About 20 c.cm. of blood was obtained from the basilic vein, and kept in a sterile flask at 0° C. until the following morning, when the serum was separated. The activity of the serum was measured by its capacity to neutralize, in the immature rat, the power of a gonadotropic extract similar to that injected into the patient. Each sample of serum and gonadotropic extract was injected into a group of five immature female rats (40–50 grammes) once daily for five days; the two injections were given on opposite sides of each animal. The rats were killed twenty-four hours after the last injection, and the ovaries dissected, fixed in Bouin's fluid, and weighed the following day from 70 per cent. alcohol.

A gonadotropic extract from human urine of pregnancy (UP10) was used in testing, of which a total dose of 1 mg., divided over five days, produces ovaries weighing 35 mg. in the immature rat. The weight of the normal ovaries of rats of this body weight is 10–12 mg. The activity of the other extracts used is given in Table II.

TABLE II.—*The Effect of Serum from Patients Treated with Gonadotropic Extracts on the Action of Similar Extracts on the Immature Rat Ovary*

Case No.	Date of Sample after First Injection (Weeks)	Assay			
		Substance	Amount (mg.)	Amount of Serum (c.cm.)	Weight of Rat Ovaries (mg.)
1	0	UP10	1	1.25	34
1a	5	"	1	1.25	44
1b	11	"	1	1.00	27
2	11	UP10	1	1.25	40
2a	15	"	1	2.00	33
2b	19	"	1	1.50	22
2c	25	"	1	1.90	26
2d	29	"	1	1.50	30
7	7	UP10	1	1.50	29
8	13	UP10	1	1.00	39
8a	20	"	1	0.80	47
8b	28	"	1	0.75	32
9a	6	UP10	1	1.00	34
9b	13	"	1	1.00	34
5	0	—	—	1.50	12
5a	4	UP10	1	0.75	32
5b	10	"	1	1.00	39
—	—	Saline extract of pig Ant. pit. AP43D	1 gm.	—	43
3	16	"	1 gm.	1.25	65
3a	21	AP44	25	1.50	27
—	—	AP44	25	1.50	44
3b	26	"	25	1.50	32
—	—	—	25	1.50	35
4a	13	AP43D	25	0.75	32
4b	19	AP44	25	1.90	39
—	—	AP51	25	—	21
9 & 10	0	"	25	2.50	27

Results

Serum of Patients Injected with Human Urine of Pregnancy Extracts.—The results of these assays (Table II) show that no appreciable amount of anti-gonadotropic substance is formed in response to the prolonged administration of either pregnyl or antuitrin S. The serum of Case II, which was tested most frequently, showed after nineteen weeks of injections a slight anti-gonadotropic activity, in that it inhibited, in an amount of 1.5 c.cm., the activity contained in about 0.5 mg. of the extract UP10. No further production was found in samples taken at a later date, in spite of the continued injections. This amount of anti-gonadotropic substance is very slight in comparison with that formed in other species receiving continued injection of this material (Rowlands and Parkes, 1937). Direct comparison is difficult, on account of the difference in the amounts given and the method of administration. The development of this small amount of anti-gonadotropic activity might be explained on the assumption that the pregnyl had been denatured to such an extent in its preparation as to become slightly antigenic to man.

These results confirm the work of Twombly (1936) and are in keeping with those of Thompson (1937) and Rowlands (1937a), who failed to produce "anti-hormone" activity in the blood of sheep that had been injected for prolonged periods with sheep pituitary extracts: they uphold the view of the true antibody nature of "anti-hormones."

Serum of Patients Treated with Pig Pituitary Extracts.—The serum of the patient (Case 3) treated with ambinon for sixteen weeks appeared to augment the gonadotropic activity of a saline extract of pig pituitary. When the test was repeated after twenty-one weeks of treatment the serum again appeared to enhance the activity of an extract made from acetone-desiccated pig pituitary (AP43D). A final sample of serum taken five weeks later failed either to augment or to inhibit the action of ambinon (AP44). The injection together with ambinon (AP51) of serum obtained before treatment (Cases 9 and 10) did not increase the effect of the extract on the rat ovary. Very doubtful augmentary effects were given by the serum of the patient (Case 4) treated with antuitrin gonadotropic.

The significance of an augmentary action, such as seems to be shown by these sera, is discussed elsewhere (Rowlands, 1937a).

Summary

No serious amount of anti-gonadotropic activity was demonstrable in the serum of patients receiving gonadotropic extracts of either human urine of pregnancy or pig pituitary for varying periods up to seven months. From this we conclude that in the treatment of undescended testes and other disabilities the administration of gonadotropic hormones may be continued for a considerable period without fear of inducing a phase of insensitivity and damage to the gonads by anti-gonadotropic substances.

We wish to thank Dr. J. Stanley White, of Messrs. Parke, Davis and Co. Ltd., for supplies of antuitrin S and antuitrin gonadotropic, and Dr. A. N. Macbeth, of Organon Laboratories, for supplies of pregnyl and ambinon.

BIBLIOGRAPHY

- Collip, J. B. (1934). *J. Mt. Sinai Hosp.*, N.Y., 1, 28.
Rowlands, I. W. (1937). *Proc. roy. Soc.*, B, 121, 517.
— (1937a). In press.
— and Parkes, A. S. (1937). *Lancet*, 1, 924.
Thompson, K. W. (1937). *Proc. Soc. exp. Biol.*, N.Y., 35, 634.
Twombly, G. H. (1936). *Endocrinology*, 20, 311.

THE WATER REQUIREMENTS OF SURGICAL PATIENTS*

BY

D. L. C. BINGHAM, F.R.C.S.Ed.

Clinical Tutor, Surgical Out-patients Department, Royal Infirmary, Edinburgh

This paper is a preliminary survey of the metabolism of the surgical patient during the immediate post-operative period, and is based upon results obtained while investigating the water balance of such subjects. It became evident very early in the investigation that water metabolism is only one of the many metabolic processes occurring in the surgical patient of which knowledge is far from complete. In this paper only water metabolism will be discussed; other aspects of metabolism will merely be noticed as each becomes relevant.

Water is essential for all the physiological processes of the animal organism, and the regulation of its intake and output is finely adjusted. This delicate regulation of intake and output is called water balance. In spite of its importance, only in the last ten years have accurate investigations been made into this subject, and although much is already known the water exchanges of the ill patient abound in unsolved problems. The researches of Maddock and Coller; Newburgh, Wiley, and Johnstone; and Lavietes, Harrison, and Peters are all of the first importance, and should be consulted by students of the subject.

It is estimated that water forms from 65 per cent. to 70 per cent. of the body weight. This water is distributed in approximately the following proportions:

					Per cent. body weight
Extracellular fluids:	(1) Blood stream	..	..	..	9
	(2) Interstitial tissues	..	..	..	16
Intracellular fluid	..	..	..	..	45
Total	..	..	..	..	70

The functions of the extracellular fluids are threefold: to carry foodstuffs to the cells; to carry waste products away from the cells; and to regulate the stability of certain physico-chemical conditions in the body—pH, osmotic pressure, temperature, etc. For the perfect performance of these functions there is an optimum volume of the extracellular fluids, and departures from this optimum in either direction prejudice and may even threaten the actual life of the body cells. Alterations in the body fluids are largely made up of changes in the extracellular fluids, the intracellular fluids remaining comparatively constant until the approach of death.

The Study of Water Metabolism

Water metabolism may be studied by direct or by indirect methods. The direct method requires a knowledge of the following:

1. Water content of the fluids drunk.
2. Water content of ingested foods which may vary from 5 per cent. to 95 per cent.
3. Water formed by oxidation of this food.
4. Calorie output from its oxidation. (In this investigation it has been assumed that all the food ingested has been completely absorbed and metabolized.)
5. The approximate calorific requirements of the subject. (In the investigation the Douglas bag method was adopted, with due regard to its serious potential error when applying

* Report of work done while in receipt of a British Medical Association research scholarship.