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.

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THE WATER REQUIREMENTS OF SURGICAL PATIENTS*

BY

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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

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five-minute readings to the whole twenty-four-hour period. Also it was sometimes impossible to obtain results because the patients would not tolerate the procedure.)

6. If, as is the rule in the ill patient, the calorie requirements are not met by the food intake, then the water formed from the oxidation of body tissues must be estimated. This requires a knowledge as to which of the body constituents are providing the necessary energy, in itself a laborious investigation.

7. The solid intake.

8. The solid output in the urine, faeces, sputum, vomitus, and other discharges. (The solids lost in the sweat have been ignored.)

9. The fluid output in the urine, faeces, and insensible perspiration from the skin and lungs. (Insensible perspiration and insensible loss of weight are not the same. Insensible perspiration implies lost water only. Insensible loss of weight is equal to lost water plus carbon dioxide minus gained oxygen, and varies with the respiratory quotient. In this paper insensible perspiration has been taken to be equal to insensible loss of weight.)

10. The body weight under standard conditions of nudity, after emptying the bladder, and at fixed times during the day.

The direct method of estimating water balance may be expressed in the following two equations:

$$1. \text{ Change in weight} = \left\{ \begin{array}{l} \text{solids in} \\ \text{fluids in} \end{array} \right\} - \left\{ \begin{array}{l} \text{solids lost (urine, faeces, vomitus, etc.;} \\ \text{body solids metabolized)} \\ \text{fluids lost (urine, faeces, vomitus, etc.,} \\ \text{insensible perspiration)} \end{array} \right\}$$

For insensible perspiration this equation may be expressed:

$$\text{Insensible loss} = \left\{ \begin{array}{l} \text{solids in} \\ \text{fluids in} \end{array} \right\} - \left\{ \begin{array}{l} \text{solids lost} \\ \text{visible fluid lost (urine,} \\ \text{faeces, vomitus)} \end{array} \right\} - \text{change in weight}$$

$$2. \text{ Water balance} = \text{fluids available} - \left\{ \begin{array}{l} (1) \text{ in fluid drunk} \\ (2) \text{ in food} \\ (3) \text{ formed by meta-} \\ \text{bolism of either} \\ \text{food or body tissues} \end{array} \right\} - \left\{ \begin{array}{l} \text{visible fluid lost} \\ \text{insensible fluid} \\ \text{lost} \end{array} \right\}$$

Indirect methods are perhaps more complex; they require that a number of no doubt allowable assumptions be made, and are essentially a study of the metabolism of certain electrolytes from which the water exchanges may be calculated (Laviertes, 1935, 1935a). In this investigation the first direct method has been followed.

At this stage it is necessary to study more closely the water gained and lost through the various channels.

WATER GAINED

(a) The volume of the fluids drunk varies considerably with the individual. In health from 800 to 2,000 c.cm. may be taken daily. After operations the patient may be able to tolerate only 200 c.cm. or less during the first twenty-four to forty-eight hours without nausea.

(b) The metabolic mixture provides in water content and from water of oxidation 1,000 c.cm. to 2,000 c.cm. daily.

During starvation about 500 c.cm. of water becomes available from the tissue katabolism made necessary by the energy requirements.

WATER LOSS

1. *In the Urine.*—The water lost in the urine is the amount which remains after insensible perspiration has withdrawn its quota from the body water available for excretory purposes. It follows, therefore, that if the body is seriously dehydrated the patient is often anuric, and the dehydration should be overcome before other measures are taken to promote the secretion of urine. It is here pertinent to point out that the kidneys are required to excrete daily in health about 35 grammes of waste materials. Unless sufficient water is available for this

purpose retention of these waste products occurs. Where renal damage exists more water is required to excrete the same quantity of waste material. The following table is interesting in this connexion:

	Maximum Concentrating Ability	Minimum Water Required to Excrete 35 grammes of Waste Products
Normal kidneys	c.cm. 1,032—1,029	c.cm. 473
Diseased kidney	1,028—1,025 1,024—1,020 1,019—1,015 1,014—1,010	595 605 850 1,439

It follows from these observations that, knowing the degree of renal damage in any given patient, we must never allow the urinary volume to fall below the minimal water volume which is necessary to excrete the patient's urinary waste products. Indeed, as the waste products to be excreted in the post-operative period may greatly exceed 35 grammes, the surgeon's aim must be to ensure that the patient has at least double the above minimal volume of water available for urinary excretion.

2. *In the Faeces.*—On an average 150 c.cm. of water are lost daily in the faeces.

3. *From the Skin and the Breath.*—Normally the volume of water vaporized from the skin and in the breath varies from 800 to 1,500 c.cm. daily; but in abnormal conditions of high external temperature or humidity, or in diseased states such as thyrotoxicosis, fever, etc., these figures may be greatly exceeded. Indeed, as much as 3,500 to 4,000 c.cm. may be lost daily in the breath and from the skin. This water of vaporization is responsible for the thermal control of the body, and dissipates about 24 per cent. of the body heat. Each c.cm. of water requires 0.58 large calorie for its vaporization; therefore, if the insensible water loss be 100 c.cm. it will require 58 calories to effect its vaporization. Owing to its all-important function of temperature regulation the insensible perspiration exercises preferential rights over all water available for excretion. It is not until over 6 per cent. of the body weight has been lost in fluids that any decrease in water vaporized occurs. At this stage the patient is grossly dehydrated, is febrile, is anuric, has sunken eyes, a dry skin, and a dirty dry-leather-like tongue. If water be now given it is retained by the body until the deficit is made good before any becomes available for the restoration of the other excretory processes, such as renal excretion, the faeces, etc.

4. *Loss by Other Channels.*—The loss of water by other channels such as by vomiting and from fistulae, etc., may be great. It is said that severe and rapid dehydration does not occur except by these methods, especially by vomiting. Where there is excessive vomiting, etc., the volume lost must be estimated and added to the fluid intake if water balance is to be maintained.

Results of the Investigation

In the present investigation ten unselected cases were taken, all of which were treated by the usual routine methods of the surgical wards of the Royal Infirmary, Edinburgh. The accompanying table abstracts the pertinent results.

From an inspection of the table it will be seen that:

(a) Following operation each patient became increasingly dehydrated during the period of study, the smallest

		Case 1, aged 65. Carcinoma of Stomach. Lapar- otomy; Inoperable.	Case 2, aged 70. Appendi- ectomy.	Case 3, aged 48. Carcinoma of Stomach. Lapar- otomy; Inoperable.	Case 4, aged 43. Carcinoma of Head of Pancreas. Cholecyst- gastrostomy	Case 5, aged 27. Carcinoma of Pelvic Colon. Colostomy	Case 6, aged 41. Chronic Cholecys- titis. Cholecys- tectomy.	Case 7, aged 47. Right Inguinal Hernia.	Case 8, aged 57. Gastric Ulcer. Partial Gastrec- tomy.	Case 9, aged 61. Appendi- ectomy.	Case 10, aged 10. Osteo- myelitis Right Femur.	
From 9 a.m. of day before operation to 9 a.m. day of operation	State of tongue	Moist	Furred	Dry	Moist	Moist	Moist	Moist	Moist	Moist	Dry	
	Thirst	Nil	Slight	Slight	Nil	Nil	Nil	Nil	Nil	Nil	Slight	
	Blood chemistry { Urea N ₂	22	17	13	16	12	13	17	14	10	13	
	CO ₂ combining power	60	58	60	61	60	56	59	58	60	54	
	Calorie needs and R.Q.	2,219 0.89	909? 0.95	1,500? —	1,346 0.67	1,416 0.86	1,518 0.79	1,678 0.82	1,465 0.78	1,851 0.75	962 0.74	
	Water intake {	By mouth	1,516	540	420	600	911	745	1,317	1,016	965	1,336
		From metabolic mixture	289	129	162	20?	170	222	216	203	212	119
		By rectum	—	600	1,200	—	1,500	600	600	600	600	—
		Intravenous	—	—	—	—	—	—	—	—	—	—
	Water loss {	Total available water	1,805	1,269	1,782	620	2,581	1,593	2,133	1,819	1,777	1,480
		Urine	1,500	740	455	320	1,490	527	970	680	970	165
		Faeces	954	579	1,133	—	747	554	856	749	383	510
Vomitus, etc.		—	—	—	208	173	—	—	—	—	—	
Insensible loss	1,383	491?	272?	?	231?	322?	422?	64??	3??	756		
Water Balance	-2,032	-541	+78	?	-60	362?	-115	+326	+421	+59		
First day	State of tongue	Dry	Dry	V. dry	Dry	Dry	Dry	Dry	Dry	Dry	V. dry	
	Thirst	Marked	Parched	Parched	Great	Moderate	Great	Slight	Great	Great	Great	
	Blood chemistry { Urea N ₂	24	21	21	20	19	21	17	17	19	17	
	CO ₂ combining power	53	56	47	56	47	42	54	53	47	36	
	Calorie needs and R.Q.	2,148 0.69	1,102 0.65	1,500? —	1,500? —	1,239 0.70	1,931 0.73	1,865 0.73	1,930 0.76	1,593 0.67	1,277 0.86	
	Water intake {	By mouth	712	501	621	368	923	775	1,766	874	390	1,028
		From metabolic mixture	224	134	163	171	130	220	239	234	184	155
		By rectum	—	180	—	720	—	180	—	—	—	180
		Intravenous	—	—	—	—	—	—	—	—	—	—
	Water loss {	Total available water	936	715	784	1,259	1,053	1,175	2,005	1,108	574	1,363
		Urine	660	—	330	500	—	—	820	250	60	170
		Faeces	—	—	156	—	21	—	—	—	—	—
Vomitus, etc.		—	74	—	106	177	66	—	367	—	10	
Insensible loss	822	2,019	2,377	1,785	1,379	1,768	1,591	953	972	1,911		
Water Balance	-546 -2,578	-1,378 -1,919	-1,979 -1,901	— -1,132	-524 -584	-656	-406 -521	-452	-452	-658 -559		
Second day	State of tongue	V. v. dry	V. dry	V. dry*	V. dry	V. dry	Dry	Clean	V. v. dry	V. dry	Dry	
	Thirst	Parched	Parched	Parched	Parched	Great	Great	Nil	Parched	Parched	Great	
	Blood chemistry { Urea N ₂	26	25	20	26	25	25	14	24	16	14	
	CO ₂ combining power	49	54	52	51	45	39	57	50	51	48	
	Calorie needs and R.Q.	2,100 0.72	1,194 0.56	1,500? —	1,500? —	1,316 0.74	1,525 0.71	1,710 0.77	2,060 0.66	1,414 0.74	974 0.82	
	Water intake {	By mouth	1,043	961	789	866	960	661	1,565	1,416	1,345	1,321
		From metabolic mixture	237	143	168	154	144	173	237	242	165	133
		By rectum	300	—	480	360	—	—	—	180	180	—
		Intravenous	—	—	—	—	—	—	—	—	—	—
	Water loss {	Total available water	1,583	1,104	1,437	1,380	1,104	834	1,802	1,836	1,690	1,454
		Urine	770	104	580	1,000	130	170	1,360	590	410	320
		Faeces	202	—	433	232	232	—	—	337	400	—
Vomitus, etc.		—	—	—	—	211	—	—	329	—	—	
Insensible loss	1,362	1,784	408	750	1,017	1,170	600	532	1,199	1,571		
Water Balance	-751 -3,329	-784 -2,703	+16 -1,885	-602 -1,734	-254 -838	-506 -1,162	-158 -679	-48 -500	-319 -777	-437 -1,036		
Third day	State of tongue	V. dry	Dry	V. dry	V. dry	—	Less dry	—	V. v. dry	Dry	Dry	
	Thirst	Less	Great	Great	Great	—	Slight	—	Parched	Great	Slight	
	Blood chemistry { Urea N ₂	27	29	14	27	—	17	—	24	19	11	
	CO ₂ combining power	48	56	56	50	—	48	—	47	54	55	
	Calorie needs and R.Q.	2,100 0.72	1,201 0.65	1,500? —	1,500? —	—	1,503 0.75	—	1,734 0.68	1,500 0.75	953 0.84	
	Water intake {	By mouth	1,877	1,007	624	1,804	—	1,436	—	1,280	1,276	1,691
		From metabolic mixture	216	141	195	156	—	168	—	185	180	124
		By rectum	—	—	180	480	—	720	—	600	180	—
		Intravenous	—	—	—	—	—	—	—	1,600	—	—
	Water loss {	Total available water	2,138	1,148	999	2,440	—	2,324	—	2,910	1,636	1,815
		Urine	210	300	440	790	—	560	—	490	450	1,380
		Faeces	359	—	124	537	—	540	—	554	290	405
Vomitus, etc.		—	514	—	—	—	—	—	240	7	—	
Insensible loss	1,333	576	488	1,671	—	972	—	2,179	873	712		
Water Balance	+236 -3,565	-242 -2,945	-53 -1,938	-558 -2,292	—	+252 -910	—	-553 -1,053	-23 -800	-277 -1,313		

negative water balance at the end of the second day after operation being 679 c.cm. and the largest 3,565 c.cm. at the end of the third day. No patient maintained normal water balance. Each case varied considerably, but even with an uneventful convalescence it was not usually until the fifth day that normal water balance was re-established.

(b) The insensible water loss was very considerable, especially in the first twenty-four hours, possibly from the effects of the anaesthetic. This insensible water loss was always very great when the patient perspired profusely, and varied from 1,000 to 2,400 c.cm. (1.65 to 4 pints).

(c) Coincidentally with dehydration there was a noticeable decrease in urinary secretion (even to its abolition); a rise in blood urea nitrogen, indicating waste-product retention; and a decrease in the CO_2 combining power of the blood.

(d) Not shown on this table, but coincidentally with dehydration and the limitation of the patient's calorie intake, there was very marked katabolism of body protein, to facilitate the katabolism of body fat for energy requirements, as the carbohydrate reserves are rapidly exhausted. Amounts up to 250 grammes of body protein burnt per day were observed in the first twenty-four to forty-eight hours after operation. With the restoration of water balance it was remarkable that this excessive destruction of body protein ceased.

(e) Clinically the state of the tongue and oliguria and the subjective sensation of thirst indicate dehydration.

Conclusions

1. Under the existing post-operative regime dehydration occurs, and may be severe.
2. Although each case must be separately considered the minimal fluid intake in the days following operation should be from 3,000 to 4,000 c.cm. a day (approximately 5 to 7 pints), if necessary by the intravenous route. (In a further communication the most suitable fluid will be discussed.)
3. If excessive loss from vomiting, etc., occurs the extra volume of fluids so lost must be added to the amount which the patient in any case requires.
4. Oliguria, thirst, and a filthy dry tongue are a real approach to the septon.

A most pleasant duty is the acknowledgment of my debt to others. To Sir John Fraser for the privilege of working in his wards, and to his staff for their patient help; to the technical staff of the Biochemical Laboratories; and to Professor Melville Dunlop for his unfailing encouragement, my grateful thanks are due.

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Clinical Memoranda

Insulin in the Local Treatment of Persistent Septic Cutaneous Conditions

The use of insulin for the treatment of diabetes mellitus is now world-wide, but the extraordinary effect of this substance in securing the cure of persistent cutaneous septic conditions seems up to the present time not to have been realized.

The work of da Costa and others in connexion with the insulin treatment of epitheliomatous ulcers first drew attention to the possibility of using it in cases of chronic cutaneous sepsis that had proved resistant to all other remedies. The following four cases are typical and represent the varying types of septic conditions treated, the clinical features and treatment being given in detail.

ILLUSTRATIVE CASES

Case 1.—A boy aged 14 was involved in a motor accident in October, 1936, and on November 11 following underwent an exploratory operation in the region of the left elbow. Subsequently the wound broke down. Ultra-violet rays and sun-light treatment as well as the usual dressings were tried, with no success. The patient was admitted to the Westminster Hospital for excision of the skin in the region of the unhealed area. This was done and the wound again sutured, but it broke down immediately. The patient was subsequently readmitted for twice-daily dressings. First cod-liver oil was tried and then antipeol, with no success at all. Insulin dressings were started on March 20, 1937, and applied twice daily by the nursing staff. Rapid healing took place, and the patient was discharged on April 8, with the wound closed for the first time since November, 1936. He has been seen since, and has had no further recurrence of the breaking down of the wound.

Case 2.—This patient was seen in the casualty department, which she had been attending for over a month with a septic finger. In spite of all forms of treatment it was getting worse, to the despair of the casualty officers and the sister in charge. I saw it, and suggested that daily insulin dressings should be tried. These were started at once, and within ten days the finger was quite well and the patient had returned to work.

Case 3.—A man aged 57 was first seen by me in March, 1936, with an amputation of the right leg following arteriosclerosis. He had an infected bunion on the left leg opposite the head of the first metatarsal which had ulcerated and was giving him considerable pain. Ordinary dressings were continued until August, 1937—that is, for sixteen months. The patient was in some pain all this time, particularly when he attempted to walk. He came into my hands again on August 27, 1937, when I suggested insulin treatment locally. This was started on August 29, the man dressing the foot himself three times daily with single-strength insulin on gauze. When seen five days later the patient said he was much more comfortable, and one week after this the pain had gone. The ulcer was shallower, and the area of inflammation surrounding it had entirely disappeared for the first time. It is scarcely to be expected that the ulcer will heal, owing to the continual movement and lack of any pulsation in the peroneal and tibial arteries.

Case 4.—A married woman aged 27 was first seen by me on September 14, 1937. Her history was a peculiar one. After working for some time in a blanket factory she found that whenever she knocked herself the bruised place became septic. This condition was a surface inflammation which took a long time to heal, and when it did it left a white scar. Her right arm was covered with these scars. When examined at the Radcliffe Infirmary a diagnosis of low-grade streptococcal infection was made. At the time I saw her she had one of these septic areas on her left arm, irregular in outline and about two inches by one inch in extent, raw, with a yellow-