SPONTANEOUS AND INDUCED WATER INTOXICATION IN TWO CASES OF HYPOPITUITARISM

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It has been known for many years that patients with adrenocortical failure, whether this be primary or secondary to anterior hypopituitarism, are unable to excrete ingested water at the normal rate (Rowntree and Snell, 1931 ; Robinson *et al.*, 1941 ; Levy *et al.*, 1946). Less recognized is the possibility that patients with hypopituitarism may retain water in excess of electrolytes while on ordinary diets and without apparent forcing of their fluid intake. Such water retention* would lead to dilution of body fluids (hypotonicity) and, finally, to symptoms of water intoxication. Whittaker and Whitehead (1954) have described the case of a patient with hypopituitarism whose death they attributed to spontaneous water intoxication. The present report describes two such cases in which a similar, though reversible, abnormality was observed.

Apart from its spontaneous occurrence, water intoxication is occasionally precipitated by water-diuresis tests in patients with hypopituitarism. Pickford and Watt (1950) have reported this complication, which also occurred in both of our patients.

In primary water retention the plasma sodium concentration falls, although the total body sodium may not be reduced. The plasma sodium concentration may also be low in severe sodium depletion, a finding which, by itself, is often regarded as evidence of depletion of this ion. It is important, therefore, to distinguish between these two hyponatraemic states, since they differ in cause, metabolic effects, and treatment (Wynn and Rob, 1954).

Briefly, sodium depletion leads to loss of body water and haemoconcentration. The patient loses weight, looks haggard, and shows loss of tissue turgor. The circulation is impaired, the blood urea rises, the plasma potassium may be raised, and there is usually a metabolic acidosis. If the kidneys behave normally there is little fall in plasma sodium concentration until loss of this ion is more than 300–500 mEq (McCance, 1936), because water is at first excreted to maintain a normal osmotic pressure of the body fluids.

With primary water retention there is no dehydration but the reverse. The body weight exceeds normal, and the circulation does not fail unless hypotonicity is extreme. The plasma sodium concentration is always low ; acidosis and urea retention may be absent, and the plasma potassium concentration may be normal or low. The symptoms of water intoxication are not unlike those of sodium depletion, but with certain differences (Wynn and Rob, 1954). Gross hypotonicity causes weakness or great prostration, lethargy, anorexia, vomiting, mental disturbances, and, finally, convulsions and coma, which may prove fatal.

The following two cases of hypopituitarism illustrate the occurrence of water intoxication, both spontaneously and after a water-excretion test.

Case 1

M. W., a woman aged 53, had suffered from anterior hypopituitarism since 1941, when her pituitary gland was removed for mild acromegaly. In May, 1953, she came into St. Mary's Hospital for investigation, having had no specific treatment for her condition. She had had amenorrhoea since the operation and had long complained of weakness, tiredness, and difficulty in keeping warm ; her incapacity was such that she had hardly left her bed for many years. On examination there were slight skeletal signs of acromegaly. She was thin, pale, and expressionless. Her speech was slow, monotonous, and slurred. There was loss of eyebrows and of axillary and pubic hair. The thyroid gland was not palpable. There were no abnormal cardiovascular, urinary, or neurological findings, and the blood pressure was 130/70. There were no signs of dehydration, and her weight was 52.3 kg.

The following investigations were made : urinalysis negative ; Hb, 12.6 g.% ; plasma sodium 116, potassium 4.1, chloride 83, and total CO_2 26.2 mEq per litre ; plasma non-protein nitrogen, 20 mg. per 100 ml. (Table I).

TABLE I.—*Case* 1: *Blood and Plasma Chemistry, Blood Pressure, and Weight*

Day	Hb. (g./%)	Haematocrit	Na (mEq/l.)	K (mEq/l.)	Cl (mEq/l.)	Total CO_2 (mEq/l.)	N.P.N. (mg./100 ml.)	Protein (g./100 ml.)	B.P. (mm. Hg)	Weight	
										kg.	lb.
−14*	12·6	—	116	4·1	83·0	26·2	20	—	130/70	52·3	115·2
1	10·5	—	125	4·2	88·5	28·0	20	6·2	130/70	52·3	115·2
2	10·6	35·5	125	4·1	88·0	27·2	20	6·5	140/85	52·3	115·2
3	11·4	36·5	132	4·7	95·0	26·4	21	7·1	135/80	50·2	110·5
5	11·5	36·5	136	4·3	97·0	27·8	22	7·3	138/85	50·2	110·5
9	11·2	35·5	136	3·7	98·0	28·1	26	6·5	130/75	50·6	111·3
21	12·4	40·5	122	3·6	85·0	25·7	20	7·2	116/75	50·8	111·8
22	12·8	40·0	130	3·7	93·5	25·1	24	8·0	117/77	49·2	108·3
23	12·2	39·5	136	3·9	96·0	27·6	24	7·3	118/70	49·1	108·0

* Day −14 was soon after admission to hospital. The metabolic balance study began 2 weeks later (Day 1). Cortisone (100 mg. daily) was given on day 2 to day 9, and again on day 21 and subsequently.

TABLE II.—*Endocrine Function in Cases* 1 *and* 2

Tests of Endocrine Function	Case 1	Case 2
Gonadotrophic:		
Urinary F.S.H. excretion (m.u./24 hrs.)	—	<4
Adrenal cortex:		
Urinary 17-ketosteroids (mg./24 hrs.)	1·5 1·3	0·7 1·2
Urinary 17-hydroxycorticoids	Trace only*	Trace only†
Plasma 17-hydroxycorticoids‡ (μg./100 ml.)	1	0
Water diuresis: % dose excreted in 3 hrs.:		
(a) without cortisone (normal = 70% excretion of 20 ml. water/kg. in 3 hrs.)	9·5	6; 8·5; 12
(b) with cortisone	69	80; 66
Fasting blood sugar (mg./100 ml.)	89	60; 61; 64
Insulin tolerance (0·1 unit/kg.)	Hypoglycaemic —unresponsive	Hypoglycaemic —unresponsive
E.C.G. voltage	Low	Low
Thyroid:		
B.M.R. (% normal)	—	−48
I^{131} neck uptake at 48 hrs. (% dose) (lower limit of normal = 25%)	0	5·1
Urinary excretion 0–48 hrs. (% dose) (normal range = 35–70%)	82·7	73·3
"T" factor (normal range = 3–14)	1·8	1·4
Plasma cholesterol (mg./100 ml.)	207	389

* By courtesy of Dr. C. H. Gray.
† By courtesy of Dr. C. L. Cope.
‡ By courtesy of Dr. R. I. S. Bayliss.

*Unfortunately the term "water retention" is used in two senses in clinical medicine. Most commonly it is used to imply isotonic retention of both water and sodium, a condition which finally results in pitting oedema. The second sense, used in this report, means that water is retained alone or in excess of electrolytes. Since about two-thirds of this water is located in the cells (Wynn and Rob, 1954) the result is not pitting (extracellular) oedema but intracellular overhydration and dilution of body fluids.

Tests of endocrine function, showing adrenal and thyroid failure, are summarized in Table II. A water diuresis test of adrenal function, performed in ignorance of the low plasma sodium concentration, caused severe symptoms of water intoxication, including great prostration, nausea, vomiting, mental confusion, and a fall of blood-pressure to 80/50. Only 9.5% of the litre of water given was excreted in three hours.

Experimental Observations

Methods.—Fourteen days after the episode of water intoxication described above a metabolic balance study was carried out. The patient was put on a diet containing about 50 mEq of sodium a day. Duplicate diets were bulked for three days and analysed for sodium, potassium, chloride, and nitrogen. Aliquots of three-day stool and 24-hour urine

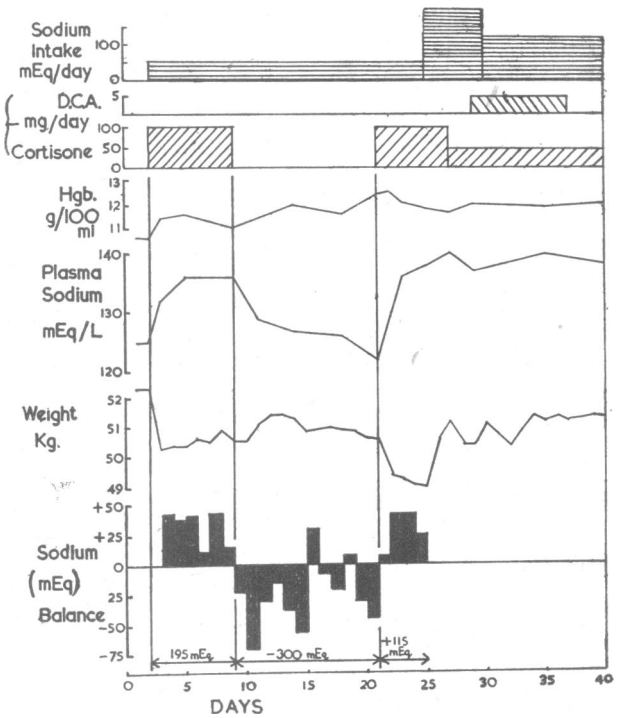

FIG. 1.—Metabolic balance data in relation to cortisone therapy in Case 1.

collections were also analysed. The patient was weighed daily before breakfast, after emptying the bladder, and when possible after defaecation, on scales sensitive to 30 g. (1 oz). After 24 hours on this diet, body weight and plasma electrolyte concentrations having stayed constant, she was given 100 mg. of cortisone a day by mouth, in four divided doses, for one week; cortisone was then discontinued. After a 12-day interval with no treatment the cortisone therapy was repeated.

Results (Fig. 1, Table I).—Twenty-four hours after starting cortisone the following changes were observed. The body weight had fallen by 2.05 kg. (4.5 lb.) owing to a large water diuresis (4,200 ml. of urine in 24 hours, which contained a total of 48 mEq of sodium and 74 mEq of potassium). The balance of water and electrolytes was: water −2 litres; sodium ±0; potassium −30 mEq. The plasma sodium had risen from 125 to 132, and chloride from 88 to 95 mEq per litre.†

During the next 48 hours there was no further change in body weight, and the plasma sodium rose to 136 mEq per litre. At this point—that is, 72 hours after starting cortisone—the cumulative balances were: water −2 litres; sodium +80 mEq; potassium ±0. The serum protein and Hb concentrations had risen slightly, suggesting haemoconcentration. The patient felt very much better whilst on cortisone; there was an increase in muscle power and animation, and her facial colour improved.

During the seven-day period of cortisone treatment 195 mEq of sodium was retained and 38 mEq of potassium lost, and during the latter half of this period the gain in weight was 0.4 kg. (0.9 lb.).

On stopping cortisone for 12 days the plasma sodium fell from 136 to 122 mEq per litre. There was a negative sodium balance of 300 mEq. However, instead of the expected fall in body weight, there was a small rise (0.2 kg., Table I). Thus, the usual renal regulation of osmotic pressure did not occur and water was retained in excess of electrolytes, resulting in severe hypotonicity. The patient's previous symptoms of weakness and lethargy returned.

On repeating the cortisone treatment (100 mg. a day) there was a prompt water diuresis, loss of weight (1.7 kg.), and a rise in plasma sodium concentration from 122 to 136 mEq per litre during the first two days (Fig. 1), during which time only 55 mEq of sodium and 45 mEq of potassium were retained. Clinical improvement was immediate.

These data suggest that the low plasma sodium concentrations present on each occasion before cortisone treatment were due mainly to spontaneous water retention. They also

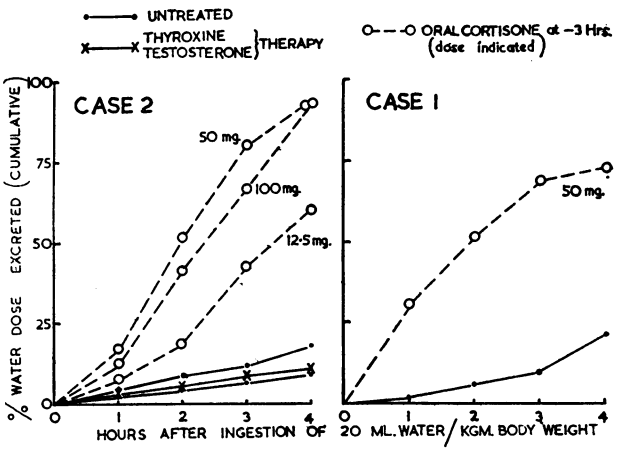

FIG. 2.—Effect of cortisone on water diuresis in Cases 1 and 2.

show that cortisone acutely corrected the sodium dilution. Further tests showed that cortisone acutely restored the ability to excrete a water load rapidly (Fig. 2). Since clinical improvement followed restoration of a normal plasma sodium concentration, it is possible that the symptoms were attributable, partly at any rate, to hypotonicity.

During six weeks of treatment with cortisone (50 mg. a day), later supplemented by D.C.A. (2.5 mg. a day), and a sodium intake of 125–200 mEq a day, the highest weight recorded was 51.5 kg. (113.3 lb.). This was less than the patient's initial weight (52.3 kg.), which further supports the interpretation that there was originally excessive water retention.

Case 2‡

J. B., a housewife aged 53, was admitted to Hammersmith Hospital in January, 1953, with an initial diagnosis of myxoedema. However, at 40 she had had a severe postpartum haemorrhage which had needed blood transfusion and which was followed by complete failure of lactation. The menopause at 51 was followed by the onset of myxoedema, which had become gross by the time of her admission.

†On simple osmotic theory, the expected and the observed rises in plasma sodium were close. Thus, assuming the total body water initially to be 65% of body weight—that is, 34 litres—then the final sodium should have been approximately $\frac{34 \times 125}{32} =$ 133 mEq per litre.

‡This case has already been described briefly in relation to her episodes of hypopituitary coma (Caughey and Garrod, 1954).

Her behaviour, voice, and appearance were those of classical myxoedema, with superadded features of hypopituitarism. In addition to loss of eyebrows and partial baldness of the scalp, there was total loss of axillary and pubic hair and absence of cutaneous pigment. There were no abnormal findings in the cardiovascular, urinary, or neurological systems, and the blood pressure was 140/90.

The following investigations were made: urinalysis, negative; Hb, 11.4 g.%. Tests of endocrine function showing gonadotrophic, adrenal, and thyroid failure are summarized in Table II.

Clinical Observations

The patient gained 3 kg. (6.6 lb.) in weight during her first three days in hospital. Two days later she became nauseated and stuporous after a water diuresis test, and the blood pressure fell to 100/70. She had excreted only 9% of the water dose of 1,320 ml. during four hours, and had remained oliguric during the next 24 hours. The plasma sodium was 116 and the chloride 85 mEq per litre, and blood urea was 21 mg. per 100 ml. She was then given 100 mg. of cortisone by mouth, 5 mg. of D.C.A. by intramuscular injection, and an infusion of 600 ml. of 5% glucose in 0.3% saline. Within 24 hours of starting treatment she passed large volumes of urine, lost 1.9 kg. (4.2 lb.) in weight, and regained full consciousness. Later she was discharged on thyroxine and a testosterone implant.

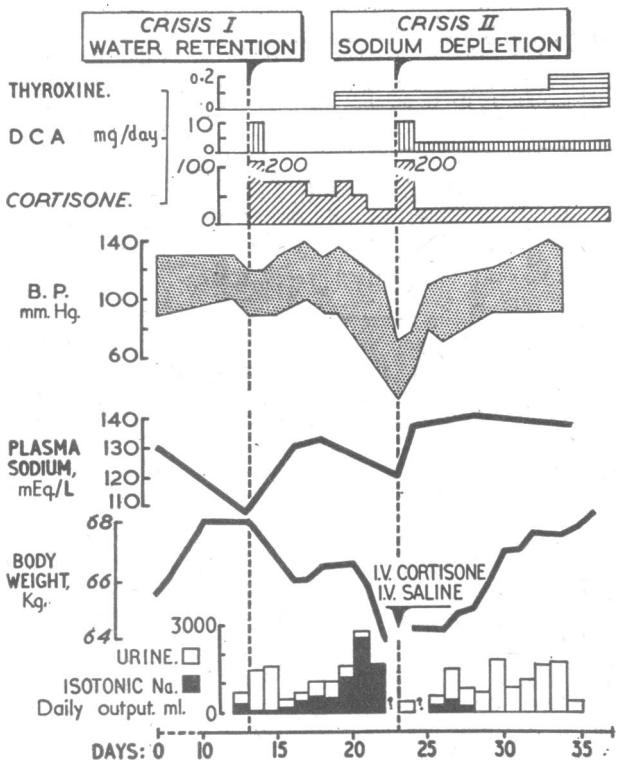

FIG. 3.—Metabolic changes in relation to therapy in Case 2.

In November, 1953, she was readmitted in relapse, having omitted to take any treatment for five months. The blood urea was 16 mg. per 100 ml., plasma cholesterol 389 mg. per 100 ml., and B.M.R. −36% (Robertson and Read). Her subsequent course is charted in Fig. 3. By the 13th day in hospital, while on a normal diet and without specific treatment, she had gained 2.5 kg. (5.5 lb.) in weight. The plasma sodium had fallen from 130 to the very low level of 107 mEq per litre, and potassium from 5.7 to 4.2 mEq per litre. On the 12th day she was nauseated, and during the 13th day she became irritable, then drowsy and stuporous, with a blood pressure of 120/90. She was given 200 mg. of cortisone by mouth in divided doses and one 10-mg. injection of D.C.A., followed by 75 mg. of cortisone a day for three days. During the first two days on cortisone she passed 3.1 litres of urine containing only a trace of sodium, and by the third day she had lost 2 kg. (4.4 lb.) in weight and the plasma sodium had risen to 130 mEq per litre. Full consciousness returned within 24 hours of starting treatment with cortisone. The loss of weight, due to excretion of water without sodium, accompanied by a rise in plasma sodium of 23 mEq, suggests that the hypotonicity was due mainly to water retention.

While still on cortisone, an episode of true sodium depletion occurred, the signs of which differed from those just described. Seven days after starting cortisone therapy the patient became aggressive and mentally confused and began to pass large amounts of sodium in her urine (784 mEq in three days). The body weight fell by a further 2.5 kg. (5.5 lb.) in two days. The exact negative sodium balance was not known, but probably exceeded 500 mEq. On the 10th day of cortisone therapy she needed forcible restraint, and four hours after an injection of paraldehyde (10 ml.) became comatose and pulseless. Her appearance was that of severe dehydration. The systolic blood pressure fell to less than 70 mm. Hg, and at one time could not be measured. The plasma sodium had fallen only to 117 mEq per litre, as compared with 107 mEq during the previous episode of water retention when the circulation was relatively normal. This classic crisis of sodium depletion and dehydration was successfully treated with saline infusion, D.C.A., and intravenous cortisone.

Subsequently, tests showed that normal water diuresis could be restored within three hours by intravenous or oral cortisone, but not by prolonged treatment with testosterone (300-mg. implant) and thyroxine (0.3 mg. a day) (Fig. 2).

Discussion

Both of these patients retained water in excess of electrolytes while on ordinary ward diets. This was shown by a large gain in weight accompanied by a profound fall in plasma sodium concentration—to 116 mEq per litre in Case 1, and to 107 mEq per litre in Case 2. In both patients the water retention was corrected by cortisone, which caused a large water diuresis. The plasma sodium concentration rose towards normal, although there was little change in total body sodium. The stupor which accompanied the hypotonicity in Case 2, and the symptoms of weakness and prostration in Case 1, were relieved when the excess of water was excreted.

Following a water-excretion test, and superimposed on the chronic water retention, there were acute symptoms of water intoxication, including nausea, vomiting, severe prostration, mental confusion, and, in Case 1, a sharp fall of blood pressure. These untoward effects probably occurred because hypotonicity was already significant in both patients when the test was carried out. This interpretation is supported by the fact that later, when the plasma sodium concentration was normal, there were no symptoms from water-excretion tests, although retention of the water dose was roughly the same as before.

Despite much investigation, the cause of the failure of water diuresis in hypo-adrenal states is still uncertain (Lewis, 1953). Cortisone corrects this failure, whereas deoxycortone acetate, testosterone, and thyroid extract are largely ineffective (Slessor, 1951; Garrod and Burston, 1952). Since cortisone also prevents chronic over-retention of water in hypopituitarism, it is likely that the failure of water homoeostasis is mainly conditioned by inadequate adrenal secretion of 17-hydroxycorticosteroids.

In hypopituitarism it would appear that adrenocortical secretion of steroids may fail in a selective manner. Thus, androgen secretion, measured by 17-ketosteroid output (in the female), fails early; and 17-hydroxycorticosteroid secretion (cortisone and hydrocortisone), as measured in the blood (R. I. S. Bayliss and A. W. Steinbeck, 1954, personal communication) and urine (Cope *et al.*, 1951) is usually very low. Yet mineralo-corticoid secretion, now believed to be

aldosterone (Simpson *et al.*, 1953), which may not be dependent on pituitary control, seems to be adequate for the patient's normal needs; because severe sodium depletion, such as occurs regularly in untreated Addison's disease, is an unusual feature of adrenal failure secondary to hypopituitarism, unless it is provoked by infections, gastroenteritis, or surgical stresses (Peters *et al.*, 1954; Caughey and Garrod, 1954). This conclusion is supported by the results of Luetscher and Axelrad (1954), who found normal amounts of aldosterone in the urine of two cases of severe hypopituitarism, although this steroid was absent in the urine of patients with primary adrenal insufficiency. It is not surprising, therefore, that pure water retention without significant sodium depletion can occur in hypopituitarism. That it may not be uncommon is suggested by reports of very low plasma sodium concentrations, without evidence of dehydration or crisis, in patients with this condition—for example Bartter *et al.* (1950), Waterhouse *et al.* (1952), Peters *et al.* (1954), and Aber *et al.* (1954)—a state of affairs which has usually been attributed to sodium depletion.

As though to protect themselves from water retention, and because of their lowered metabolism, which reduces the solute load to the kidneys, patients with advanced hypopituitarism usually drink very little, and their urinary volumes are correspondingly small (Case 1 was exceptional in that her urine output, when not on cortisone, was around 1.5 litres a day). Admission to hospital may present a definite hazard to such patients because of a tendency to force the fluid intake, especially when urine output is low. This should be avoided by special instructions to the nursing staff.

Daily weighing of the patient is the simplest way to detect large changes in water balance. A gain in weight accompanied by a fall in plasma sodium concentration suggests primary water retention. It should be stressed that dangerous hypotonicity can exist without clinical signs, and that peripheral oedema is not a manifestation of primary water retention (although the two conditions may occur together).

Once the danger of forcing fluids in hypopituitary patients is recognized, it follows that water-excretion tests are unwise when plasma sodium estimations show that significant hypotonicity already exists. If the plasma sodium exceeds 130 mEq per litre the diluting effect of a litre or so of water is unlikely to cause untoward symptoms. Since cortisone acts rapidly to cause water excretion in adrenal failure, it should be available for use whenever water-excretion tests are performed in these patients.

Conclusions and Summary

An abnormality of water balance is described in two patients with anterior hypopituitarism. Although their intake of fluids was not forced, they retained water in excess of electrolytes, causing dilution of the body fluids and symptoms of water intoxication. The diagnosis was suggested by a gain in weight and a very low plasma sodium concentration. When cortisone was given there was a prompt water diuresis and the plasma sodium concentration rose to normal, though there was little change in the total body sodium. Water retention may not be very rare in anterior hypopituitarism, although it appears to have been reported as such in only one other case (Whittaker and Whitehead, 1954).

In addition to chronic water retention, acute symptoms of water intoxication, including nausea, vomiting, extreme prostration, mental confusion, and stupor, were precipitated by water-excretion tests of adrenal function. This untoward effect of the test probably occurred because there was already excessive dilution of body fluids which was not recognized when the tests were performed. To avoid this complication, a water-excretion test should not be carried out until the plasma sodium concentration is known. If symptoms due to water retention occur in patients with hypo-adrenal function, cortisone should be given, whereupon the excess water will be excreted rapidly.

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RESULTS OF PARTIAL GASTRECTOMY IN TREATMENT OF PEPTIC ULCER

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Partial gastrectomy has now gained general acceptance as the operation of choice in the treatment of gastric ulcer, and although it is widely used in the treatment of duodenal ulcer its results therein are not so universally acclaimed. Because of its wide usage, much information has accumulated about the effects of the operation, particular attention being focused on the various disturbing after-effects produced.

This investigation was begun in an attempt to assess the value of the operation, and to determine whether partial gastrectomy was capable of relieving the patient of his ulcer symptoms, freeing him from irksome dietary rules, and restoring him to a satisfactory economic life.

Method of Follow-up

This survey is based on a personal follow-up of cases of peptic ulcer submitted to gastrectomy of the Polya type in one surgical unit in the years 1940 to 1951 inclusive. Of 481 patients surviving partial gastrectomy, both elective and emergency, 23 were found to have died of intercurrent disease. Of the remaining 458, 415 (90.6%) were traced and interviewed. Of these, 379 were interviewed personally by one of us with the aid of an agreed schedule of questions, and the results were graded jointly. Information regarding 36 patients who lived too far away to travel was obtained through the courtesy of their own practitioners. Because mild post-gastrectomy symptoms are common in the immediate post-operative period and usually improve or disappear