considered and the history of the use of the measurement is reviewed.

A new instrument, the peak flow meter, for making the measurement is described, and an account given of the method of calibration.

The available figures for the range of normal values are reviewed, and it is noted that the figures obtained with the peak flow meter are much higher than those recorded by most previous observers using other methods.

It is suggested that the maximum forced expiratory flow rate ("peak flow rate") measured with the peak flow meter may be found to be a convenient and reliable way of estimating ventilatory capacity.

This instrument has been developed over a period of several years, and it is impossible to acknowledge the help of all those who have assisted us. We should, however, specially like to thank the following: Dr. J. C. Gilson and the staff of the Pneumoconiosis Research Unit who have assisted in innumerable ways, including offering themselves and their children as subjects on a number of occasions; Mr. V. Gubb, who made two of the early models; and Messrs. Fred Ferraris, who started commercial manufacture and contributed a number of useful features to the design. Mrs. M. McDermott gave much valuable advice and assistance on the physical problems involved in the testing of the apparatus. The calibrations against the pneumotachograph were carried out by Miss M. Collins and Miss P. Edwards, and the drawings were made by Mr. C. W. Couling, Miss M. B. Wilson, and Miss M. Jenkins. Finally, we thank Dr. C. M. Fletcher for arranging numerous clinical trials of the instrument and for his constant help and encouragement. The instrument is distributed by Messrs. Airmed Ltd., of 16, Wigmore Street, London, W.1, who also supplied the photograph.

REFERENCES

- Comroe, J. H., Forster, R. E., Dubois, A. B., Briscoe, W. A., and Carlsen, E. (1955). *The Lung*, p. 130. Year Book Publishers, Chicago.
- Donald, K. W. (1953). *Brit. med. J.*, **1**, 415.
- Gaensler, E. A. (1951). *Science*, **114**, 444.
- Goldsmith, J. R. (1958). *Amer. Rev. Tuberc.*, **78**, 180.
- and Young, A. C. (1956). *J. appl. Physiol.*, **8**, 562.
- Hadorn, W. (1942). *Schweiz. med. Wschr.*, **23**, 946.
- Higgins, I. T. T. (1957). *Brit. med. J.*, **2**, 1198.
- Hildebrandt, G., and Hanke, O. (1956). *Ärzt. Wschr.*, **11**, 439.
- Kennedy, M. C. S. (1953). *Thorax*, **8**, 73.
- Leuallen, E. C., and Fowler, W. S. (1955). *Amer. Rev. Tuberc.*, **72**, 783.
- Lilly, J. C. (1950). In *Methods in Medical Research*, edited by J. H. Comroe, **2**, 113. Chicago.
- Linford, A. (1949). *Flow Measurement and Meters*. Spon, London.
- McKerrow, C. B., McDermott, M., Gilson, J. C., and Schilling, R. S. F. (1958). *Brit. J. industr. Med.*, **15**, 75.
- Shephard, R. J. (1955). *Thorax*, **10**, 258.
- Silverman, L., and Whittenberger, J. L. (1950). In *Methods in Medical Research*, edited by J. H. Comroe, **2**, 104. Chicago.
- Wyss, F. (1950). *Helv. med. Acta*, **17**, 516.

Ten scholarships have been awarded this year by the British Commonwealth Nurses War Memorial Fund, bringing the total awarded since the Fund was founded in 1946 to 94. Four of this year's scholarships go to nurses of the United Kingdom, and six to Commonwealth countries: Canada, New Zealand (two), India, Rhodesia and Nyasaland, and Malta. The four United Kingdom awards go to Miss ANNIE ALTSCHUL (principal sister tutor, Bethlem Royal and Maudsley Hospitals, London), Miss CHARLOTTE BENTLEY (general secretary, National Association of State Enrolled Assistant Nurses), Mr. C. SCOWCROFT (principal tutor, Pinderfields General Hospital, Wakefield), and Mr. O. HUGHES (deputy chief male nurse, Bexley Hospital, Kent).

CASE OF CONN'S SYNDROME

BY

P. K. M. BARRETT, M.B., M.R.C.P.

Late Medical Registrar, Bolingbroke Hospital, London

J. R. REES, M.A., M.D., M.R.C.P.

Late Medical Registrar, Westminster Hospital, London

AND

D. MARRACK, M.D.

Late Senior Registrar in Chemical Pathology, Westminster Hospital, London

The syndrome of potassium depletion and hypertension due to adrenocortical adenoma was first described by Conn (1955a, 1955b). It is characterized clinically by episodes of severe muscle weakness and paralysis, intermittent tetany, and paraesthesiae. Hypertension is the rule, polyuria and polydipsia generally occur, but there is no oedema. The principal biochemical features are hypokalaemia and a varying degree of alkalosis and hypernatraemia. An increased secretion of aldosterone can often be demonstrated, and Conn named the syndrome primary aldosteronism. There is selective impairment of urinary concentration and acidification, and histologically a distinctive tubular vacuolation results from hypokalaemia. An increased liability to urinary infection often leads to progressive renal damage.

About 20 cases have been reported in which an adenoma was found either at operation or at necropsy (Conn and Louis, 1956; Mader and Iseri, 1955; Eales and Linder, 1956; Chalmers *et al.*, 1956; Hellem, 1956; Campbell *et al.*, 1956; Milne *et al.*, 1957; Skanse *et al.*, 1957; Hewlett *et al.*, 1957; Russell *et al.*, 1956, 1957; Fine *et al.*, 1957; Brooks *et al.*, 1957; Kretchmer *et al.*, 1957; Crane *et al.*, 1956, 1958). In two other cases the syndrome was produced by adrenocortical hyperplasia (Wyngaarden *et al.*, 1954; van Buchem *et al.*, 1956) and in two patients a malignant adrenocortical tumour was found (Foye and Feichtmeir, 1955; Brooks *et al.*, 1957). In the following case of Conn's syndrome no increase in aldosterone production could be demonstrated and a firm diagnosis could not be made before operation.

Case History

A spinster aged 47 had several attacks of urinary infection at the ages of 20 and 33. Thereafter she remained well until February, 1955, when at the age of 45 she noted increasing lethargy and nocturnal frequency of micturition. In September, 1955, she developed severe weakness, affecting the legs particularly, with lumbar pain and paraesthesiae in the arms.

She was thought to have poliomyelitis, and was admitted to a fever hospital, where she showed photophobia, and tenderness and paralysis of the leg muscles with absent reflexes. Her blood pressure was 180/100. The illness proved atypical, with normal cerebrospinal fluid and negative virological investigations. She made a spontaneous recovery after six weeks and was discharged. Her lethargy, however, continued and she remained liable to recurrent episodes of weakness in the legs, and in May, 1957, a severe exacerbation occurred after a respiratory infection. She was admitted to the Bolingbroke Hospital, where the hypokalaemia was discovered. Serum electrolyte levels on admission were: potassium, 2.6 mEq/l.; sodium 142 mEq/l.; chlorides, 102 mEq/l.; alkali reserve, 32 mEq/l. She was very anaemic, with an Hb of 31%

and a macrocytic blood picture. Examination of the sternal marrow and a histamine test meal showed the changes of pernicious anaemia and she responded promptly to treatment with cyanocobalamin. In the nervous system there was generalized hypotonia, with weakness and tenderness in the legs and absent knee and ankle reflexes. The heart was normal apart from a basal systolic murmur, and the blood pressure was 150/90. An E.C.G. showed typical hypokalaemic changes.

Over the next 24 hours she was given 250 mEq of potassium as a mixture of potassium chloride and citrate by mouth. Her strength returned and the reflexes became normal. Subsequently she remained well with a potassium supplement of about 130 mEq daily, the serum potassium ranging from 3 to 4.4 mEq/l., but her symptoms returned if the supplement was withdrawn for more than three days.

In December she developed severe headache, became disorientated, and lapsed into a coma over a few hours. She was readmitted to the Bolingbroke Hospital and showed meningeal irritation and a right hemiparesis. She remained semicomatose for 10 days, and food and the potassium supplement were given via a Ryle tube. She eventually made a good recovery, but in January, 1958, whilst in the Westminster Hospital she developed an acute febrile illness followed by confusion and meningitis. The cerebrospinal fluid pressure was 240 mm., with a protein content of 60 mg./100 ml. and pleocytosis (polymorphs 100/c.mm., lymphocytes 40/c.mm.). Culture of the fluid was sterile. There were no localizing signs in the nervous system and she recovered fully in six days.

A month later she once again became confused, with severe dysphasia, followed by a Jacksonian convulsion, which started in the right hand and became generalized. Once again she made a rapid recovery and no further neurological episodes occurred. These incidents were thought to be cerebrovascular, probably thrombotic, and left carotid arteriography showed evidence of cerebral arteriosclerosis.

Metabolic studies were begun in February while she was on her potassium supplement of 130 mEq daily. Examination at this stage showed no weakness and no depression of the reflexes. Mild generalized cutaneous pigmentation was noted, not involving the mouth. There was residual nominal aphasia and slight visual defect in the right temporal field. She showed a labile hypertension, ranging from 130/90 to 220/160 and averaging 175/105. The only evidence of hypertensive heart disease was slight cardiac enlargement. E.C.G.s showed hypokalaemic changes only.

Investigations

Serum Electrolytes.—Serum potassium: Without supplements this was 2.5–2.8 mEq/l. On supplements it rose to low normal figures, but only 4 out of 29 pre-operation readings were over 4 mEq/l., the highest being 5.1 mEq/l. When given enteric-coated tablets of potassium chloride these were not absorbed and the serum potassium fell from 4 to 2.6 mEq/l. in three days. When potassium supplements were stopped after prolonged repletion the serum potassium fell from 4.6 to 2.8 mEq/l. in four days with a calculated negative balance of 180 mEq over this period. Serum sodium, 135–150 mEq/l. (average 145 mEq/l.). Serum chloride 96–110 mEq/l. (average 106 mEq/l.). Alkali reserve, 23–34 mEq/l. (average 28 mEq/l.). Serum calcium, 10.3 mg./100 ml. Serum phosphate, 4.3 mg./100 ml. Serum magnesium, 1.9 mg./100 ml. Blood urea, 14–35 mg./100 ml.

Urine.—Numerous catheter specimens of urine were examined. All showed mild to moderate albuminuria. Occasional specimens showed hyaline and granular casts. All were sterile save one specimen in May, 1957, which grew *Escherichia coli*.

Renal-function Tests.—24-hour urine volume over 10-day period on 230 mEq of potassium intake, 2–3.4 l. (average 2.6 l.). Urine concentration (12 hours), 1020. Urine dilution, 1001. 90% of 1,140 ml. water load (20 ml./kg.)

excreted in four hours. Urinary reaction to litmus: generally neutral, occasionally acid or alkaline. Urinary pH after 5 g. of ammonium chloride orally:

	4–6 hours	6–9 hours
Pre-operative	7.4	6.8
Post-operative	5.9	5.9

Renal response to "pitressin": (pitressin tannate in oil 5 units intramuscularly):

	Urine flow	S.G.
0–2 hours	3.5 ml./min.	1005
2–4 hours	1.0 ml./min.	1011
4–8 hours	1.5 ml./min.	1015
10–11 hours	0.5 ml./min.	1019

Urea clearance test, 66% average normal. Intravenous pyelogram, normal. Presacral pneumogram, normal renal and suprarenal outlines. Percutaneous renal biopsy (February 10, 1958): eight glomeruli were seen, and these and the vessels were normal; the tubules showed slight vacuolation only and in other respects were normal. At this time she had received a potassium supplement for eight months. Urinary aldosterone:—December 17, 1957: with potassium supplement (serum potassium 4.2 mEq/l.), 6.7 µg./24 hours; February 16, 1958: without potassium supplement (serum potassium 2.6 mEq/l., potassium intake 47 mEq/day), 1.8 µg./24 hours; March 30: post-operative (serum potassium 4.3 mEq/l., potassium intake 84 mEq/day), 0.3 µg./24 hours (normal range 3–7 µg./24 hours).

Urinary Steroid Excretion after Intramuscular A.C.T.H. ("Corticotrophin Z")

Date	Dose of Corticotrophin (Same Batch)	17-ketosteroid Excretion (Mg./24 Hours)	17-hydroxysteroid Excretion (Mg. 24 hours)
Pre-op.	18/1/58	Control	7.4
	19/1/58		5.3
	20/1/58	20 units b.d.	7.2
	21/1/58	20 "	3.3
	8/2/58	40 "	4.8
	9/2/58	40 "	6.6
Post-op.	8/4/58	Control	6.6
	9/4/58		6.1
	10/4/58	20 units b.d.	8.2
	11/4/58	" "	12.7
			7.6

Glucose-tolerance test, normal. Liver-function tests and serum electrophoresis, normal. Faecal fat estimation (mean of five days), 5.7 g./24 hours. Sodium/potassium ratios were as follows:

	Daily Potassium Intake	Sodium/ Potassium Ratio	Flow Rate
Saliva:			
Pre-operative	224 mEq	0.9	0.8 ml./min.
Post-operative	47 "	1.6	3.4 "
	84 "	2.3	2.9 "
Faeces during balance studies:			
Pre-operative	47 mEq	0.5	
Post-operative	84 "	0.6	

Renal Potassium Excretion.—Daily potassium excretion related to potassium intake and serum potassium level is shown in Fig. 1. In potassium depletion, when the serum potassium is less than 3 mEq/l., the normal kidneys excrete less than 15 mEq/day. In our patient much higher values were obtained, and, for given levels of the serum potassium, excretion rates rose with the potassium intake, though on high intakes positive potassium balance was achieved. Three of the values on a potassium intake of 86 mEq daily were not conspicuously abnormal, and this may be due to the marked sodium retention over this period when a low-sodium diet was given (27 mEq/day). The fourth value is very abnormal, and this high excretion of potassium (175 mEq/day) was accompanied by sodium diuresis (100 mEq/day) following a convulsion (Day 54, Fig. 2).

Balance Data.—The response to high and low potassium intakes was studied in the pre-operative period (Fig. 3). During the first period of 14 days, on a potassium intake of 224 mEq/day, a positive potassium balance of about 820 mEq was achieved. Sodium balance was negative by 180 mEq on the fifth and seventh days of the study, but later became positive. During the second period of five

FIG. 1.—Relation between serum potassium levels and daily urinary potassium excretion. Normal data for urinary potassium loss, at serum potassium levels of 3.5 mEq/l. and lower, from the papers of Black and Milne (1952), Schwartz and Relman (1953), Evans *et al.* (1954), and Fourman (1954).

Response to Low Sodium Intake.—A diet containing 27 mEq of sodium and 86 mEq of potassium was given for 10 days. Urinary electrolyte excretion was as follows:

Day:	1	2	3	4	5	6	7	8	9	10
Urinary sodium (mEq/day)	60	18	18	4	2	13	19	100	30	4
Urinary potassium (mEq/day)	82	88	49	65	56	47	54	175	34	46

days on a potassium intake of 47 mEq/day there was a negative potassium balance of 88 mEq and a positive sodium balance of 350 mEq. On the 12th post-operative day a further full balance was carried out over five days. On the first day of this balance the total exchangeable potassium measured with radio-potassium was 1,694 mEq (31.4 mEq/kg.). The potassium intake was 84 mEq daily and a positive balance of 70 mEq resulted. Sodium intake was 86 mEq daily and a negative sodium balance of 185 mEq occurred.

FIG. 3.—Balance data over two periods before operation. In the first period it was estimated that 90% of the patient's food was taken and a daily faecal loss of 30 mEq potassium and 10 mEq sodium was assumed. Total exchangeable potassium measured with radio-potassium and extracellular fluid volume with radio-bromine. Between days 17 and 35 she became ill and took little food. Despite continuing the potassium supplement, further potassium depletion occurred, partly explaining the marked increase in extracellular fluid volume.

There was marked sodium retention, with an average urinary sodium excretion of 19 mEq/day in the first week. On the eighth day the convulsion occurred, but, following this, sodium excretion fell again to low figures.

Management

The abnormal renal potassium loss was readily demonstrated, but it was uncertain whether this was due to Conn's syndrome or to potassium-losing nephritis. The absence of pyelonephritic changes in the renal biopsy favoured Conn's syndrome, but no increase in urinary aldosterone excretion was found, nor could an adrenal tumour be demonstrated radiologically. There was no hypernatraemia or alkalosis, and the electrolyte composition of saliva and faeces was normal. Furthermore, the previous

FIG. 2.—Daily urine volumes and sodium and potassium excretion in the pre-operative period. Under conditions of stress a marked sodium diuresis is seen, accompanied on one occasion (following convulsion) by a potassium diuresis. It is suggested that this represents a paradoxical response to increased adrenocortical activity.

history of urinary infection and positive culture on one occasion favoured pyelonephritis.

The investigations were therefore equivocal, but further neurological incidents seemed probable if the hypertension was not controlled, and an adrenal exploration was performed on March 14, 1958. This was done under a cortisone cover, as bilateral subtotal adrenalectomy was planned if no tumour was found. The left adrenal was inspected first by a postero-lateral approach. The gland was enlarged, and on removal was seen to be largely replaced by a round encapsulated tumour with a striking orange colour on transection. The gland weighed 22 g. and the tumour was 1 in. (2.5 cm.) in diameter. The left kidney appeared normal; no further biopsy was taken, and the right suprarenal was not examined.

The histology showed a benign cortical adenoma closely resembling those reported in other cases (Fig. 4). The cells were polyhedral, with rather vacuolated cytoplasm and well-defined rounded nuclei. The tumour appeared to be composed

FIG. 4.—Photomicrograph showing benign cortical adenoma. The cells are polyhedral, with vacuolated cytoplasm and well-defined rounded nuclei. Appearances suggest that the adenoma is formed of cells predominantly from the zona fasciculata and resemble closely those of other reported cases of Conn's syndrome. The adrenal remnant showed no atrophy of the cortical zones.

predominantly of cells from the zona fasciculata. Sections from the adrenal remnant showed no significant abnormality.

After operation the patient remained well on a normal diet without potassium supplements. The serum potassium rose to 5.6 mEq/l. on the fourth post-operative day and thereafter fluctuated between 4.1 and 4.5 mEq/l. There was no change in serum sodium, chlorides, alkali reserve, or blood urea. Urinary potassium loss was high until the fourth post-operative day, when potassium supplements were stopped and the cortisone was gradually withdrawn. The blood pressure fell and fluctuated between 120/70 and 180/100, averaging 140/90. Renal acidification rapidly improved, but concentration remained unaffected. She has been followed up subsequently in the out-patient department and remained well apart from difficulty in reading and writing. The blood pressure after four months was 145/105, and after six months was 135/80. The E.C.G. is normal and serum electrolyte levels have all been normal. The values six months after operation were: sodium, 144 mEq/l.; potassium, 4.7 mEq/l.; chlorides, 108 mEq/l.; alkali reserve, 33 mEq/l.; urea, 41 mg./100 ml.

Discussion

The diagnosis of Conn's syndrome in our patient is justified by the reversal of potassium depletion and

amelioration of hypertension which followed removal of a typical adrenal adenoma. There are, however, several unusual features which prevented a confident initial diagnosis.

The long history of urinary infection was misleading until the results of repeated urine examination and the renal biopsy showed little evidence of pyelonephritis. Paraesthesiae occurred only in the first episode of weakness and she never showed tetany. She did not complain of polyuria or polydipsia, though daily urine volumes were large and occasional nocturnal frequency occurred which subsided after operation.

The changes in serum electrolytes were also unusual, and hypokalaemia was the only abnormality. She never showed hypernatraemia or alkalosis, though these features are sometimes absent in Conn's syndrome. There was no fall in the serum magnesium (Mader and Iseri, 1955; Milne *et al.*, 1957), and no reduction in the serum phosphate, which may occur as a secondary effect of potassium depletion (Mahler and Stanbury, 1956). She did not show hyperglycaemia and glycosuria as reported in the cases of Hewlett *et al.* (1957). Urinary aldosterone excretion was also misleading. The first estimation (6.7 μ g./24 hours) was during high potassium intake when the serum potassium level was normal, and could be interpreted as a normal suprarenal response. The second estimation (1.8 μ g./24 hours) was below the normal range and is a very unusual finding. The marked reduction in urinary aldosterone excretion post-operatively (0.3 μ g./24 hours) does, however, suggest that most of the excreted aldosterone was formed by the tumour. Normal values for this hormone in the urine have been reported in three other cases (Milne *et al.*, 1957; Russell *et al.*, 1957; Brooks *et al.*, 1957), and in a fourth was normal on two out of three occasions (Chalmers *et al.*, 1956). Only a small proportion of aldosterone formed in the body can be recovered from the urine, and the aldosterone content of the tumour in our patient has not been assayed. We are therefore unable to decide whether excessive aldosterone production occurred in our case and have avoided the term primary aldosteronism for this reason.

The electrolyte composition of saliva and faeces was also unusual, and well within the normal range. It has been shown by Pawan (1955) that a marked variation in salivary sodium/potassium ratios (0.15–2.10) may occur in normal subjects depending on diurnal variation and rates of flow.

The urinary findings, on the other hand, were suggestive of Conn's syndrome. A positive culture was obtained on an isolated occasion only and renal function was good, apart from selective impairment of concentration and acidification due to kalopenic nephropathy. The renal biopsy was also helpful in showing tubular vacuolation only. It must be remembered, however, that pyelonephritis may be focal, and that the small fragment obtained at renal biopsy may not be representative of the kidney as a whole. Conversely, even if severe pyelonephritis is found this may be a secondary development in Conn's syndrome.

Bartter (1956) has suggested that urinary sodium excretion during sodium restriction is important in differentiating Conn's syndrome and potassium-losing nephritis. Patients with Conn's syndrome should excrete urine with a minimal sodium content, whereas in

potassium-losing nephritis a salt-losing tendency may be unmasked, though this may also occur in Conn's syndrome when renal damage has occurred (Mader and Iseri, 1955; Milne *et al.*, 1957). Mahler and Stanbury (1956) have shown that severe potassium depletion itself may impair sodium retention, and in our patient the response to sodium depletion was studied after potassium supplements had been given, so that the potassium deficit at this time was probably small. Urinary sodium excretion fell promptly and over the first seven days averaged 19 mEq daily on a sodium intake of 27 mEq daily.

Renwick *et al.* (1955) found no difference between hypertensive and normotensive subjects in their response to sodium restriction and noted that seven to nine days were required before urinary sodium excretion became restabilized at a low level, and Hatch (1954) found the period of restabilization extended over three weeks. The low average daily sodium excretion in our patient in the first week of sodium restriction is striking, and may be contrasted to the average daily sodium excretion in a hypertensive subject (38 mEq daily) and a normotensive subject (39 mEq daily), both free from renal disease and heart failure, in their first week on a similar diet. This suggests that in Conn's syndrome sodium retention may be excessive on a low sodium intake, but further observations are required to confirm this.

Conn (1955a) noted a paradoxical response in electrolyte excretion when corticotrophin was given to his patient. The effect was delayed until the third day, when a heavy sodium diuresis occurred. Our patient was given corticotrophin for two 48-hour periods by the intramuscular route as the veins were poor. No change in electrolyte excretion occurred, but estimation of urinary steroids showed that the corticotrophin had produced no adrenal response. Post-operatively an increase in steroid excretion occurred with 20 units of corticotrophin b.d., and the initial failure to respond to 40 units of corticotrophin b.d. of the same batch is rather surprising. Our patient did show, however, a sodium diuresis whenever subjected to stress. The response occurred on the same day and was generally accompanied by an increase in potassium excretion. This is demonstrated in Fig. 4 accompanying air insufflation, the start of an intercurrent infection, lumbar puncture, renal biopsy, and a convulsion. Mader and Iseri (1955) obtained a similar immediate sodium diuresis, with increased potassium excretion by giving 25 mg. of cortisone intravenously to their patient. This curious response to stress in our case may therefore be a paradoxical effect of increased adrenocortical activity.

The diagnostic problems in Conn's syndrome may be considerable. Excessive renal potassium loss occurs in renal tubular acidosis, the Fanconi syndrome, and following uretero-sigmoidostomy. These conditions are all associated with acidosis and a low serum bicarbonate level, and are readily distinguished. The distinction between Conn's syndrome and potassium-losing nephritis, however, may be very difficult. In patients such as ours, even when renal damage is slight, the diagnosis may only be presumptive when biochemical changes other than hypokalaemia are absent, and when no evidence of an adrenal tumour or increased aldosterone production can be demonstrated. These investigations are of little value if negative, and in these

circumstances the discovery of excessive sodium retention following sodium restriction, and an abnormal electrolyte excretion in response to stress, may be of help.

When pyelonephritis is present the distinction between Conn's syndrome and potassium-losing nephritis may be impossible before operation. The demonstration of increased urinary aldosterone excretion may be of no help at this stage, since chronic pyelonephritis may lead to adrenal hyperplasia and secondary aldosteronism (Luetscher, 1956). Furthermore, secondary aldosteronism may occur in the late stages of hypertension, and potassium depletion with increased aldosterone production, mimicking Conn's syndrome, has been reported by FitzGerald *et al.* (1957) in a case of malignant hypertension. With the present diagnostic methods it appears that an adrenal adenoma can be excluded with certainty only by exploration of the adrenals.

Most cases of Conn's syndrome are progressive, with increasing hypertension and secondary renal damage. Conn (1955a, 1955b) quotes two cases in which the patients died; and the patient of Brooks *et al.* (1957) died after being hypertensive for 15 years. On the other hand, removal of the tumour arrests the process, though hypertension has recurred later in some cases. In the absence of acidosis or severe impairment of renal function, the demonstration of progressive urinary potassium depletion in a hypertensive patient seems an indication for planned exploration of the adrenals. If severe renal damage is already present removal of a tumour or hyperplastic adrenals may precipitate renal failure, as a decrease in renal function may follow operation (Chalmers *et al.*, 1956; van Buchem *et al.*, 1956; Dustan *et al.*, 1956; Milne *et al.*, 1957).

Summary

A case is described of Conn's syndrome due to a benign adrenocortical adenoma. The patient suffered from recurrent episodes of severe muscular weakness and showed marked hypokalaemia without hypernatraemia or alkalosis.

Renal-function tests showed selective impairment of urinary concentration and acidification. Renal biopsy showed slight tubular vacuolation only. No adrenal tumour was demonstrated by air insufflation and no increase in urinary aldosterone excretion was found.

Balance data are given and an excessive renal response to sodium restriction is described. A paradoxical response to stress was noted, with increased urinary sodium loss and a less constant potassium diuresis.

The problems of diagnosis are discussed. At present the distinction from potassium-losing renal disease may be made only at operation.

We thank Dr. R. E. Rodgers for permission to publish this case, and Dr. R. I. S. Bayliss, under whose care the patient was later admitted, for his advice in the preparation of this paper. The adrenalectomy was performed by Mr. Robert Cox. The urinary aldosterone assays were estimated by Professor F. T. G. Prunty and Dr. R. V. Brooks. The serum magnesium level was estimated by Dr. I. McIntyre. Isotope studies were performed by Dr. J. P. Nicholson and Dr. J. F. Zilva. The histological study

of the tumour was made by Dr. D. A. H. Mackenzie. The illustrations were prepared by Miss Jeannette Purkiss.

REFERENCES

- Bartter, F. C. (1956). *Metabolism*, 5, 369.
 Black, D. A. K., and Milne, M. D. (1952). *Clin. Sci.*, 11, 397.
 Brooks, R. V., McSwiney, R. R., Prunty, F. T. G., and Wood, F. J. Y. (1957). *Amer. J. Med.*, 23, 391.
 Buchem, F. S. P. van, Doorenbos, M., and Elings, H. S. (1956). *Lancet*, 2, 335.
 Campbell, C. M., Nicolaides, N., and Steinbeck, A. W. (1956). *Ibid.*, 2, 553.
 Chalmers, T. M., FitzGerald, M. G., James, A. H., and Scarborough, H. (1956). *Ibid.*, 1, 127.
 Crane, M. G., Short, G., Peterson, J. E., and Weiss, S. (1958). *Amer. J. Med.*, 24, 313.
 — Vogel, P. J., and Richland, K. J. (1956). *J. Lab. clin. Med.*, 48, 1.
 Conn, J. W. (1955a). *Ibid.*, 45, 6.
 — (1955b). *Ibid.*, 45, 661.
 — and Louis, L. H. (1956). *Ann. intern. Med.*, 44, 1.
 Dustan, H. P., Corcoran, A. C., and Page, I. H. (1956). *J. clin. Invest.*, 35, 1357.
 Eales, L., and Linder, G. C. (1956). *Quart. J. Med.*, 25, 539.
 Evans, B. M., Hughes Jones, N. C., Milne, M. D., and Steiner S. (1954). *Clin. Sci.*, 13, 305.
 Fine, D., Meiselas, L. E., Colsky, J., and Oxenhorn, S. (1957). *New Engl. J. Med.*, 256, 147.
 FitzGerald, M. G., Fourman, P., James, A. H., and Scarborough, H. (1957). *Scot. med. J.*, 2, 473.
 Fourman, P. (1954). *Clin. Sci.*, 13, 93.
 Foye, L. V., jun., and Feichtmeir, T. V. (1955). *Amer. J. Med.*, 19, 966.
 Hatch, F. T. (1954). *Metabolism*, 3, 160.
 Hellem, A. J. (1956). *Acta med. scand.*, 155, 271.
 Hewlett, J. S., McCullagh, E. P., Farrell, G. L., Dustan, H. P., Poutasse, E. F., and Proudfit, W. L. (1957). *J. Amer. med. Ass.*, 164, 719.
 Kretchmer, N., Dickinson, A., and Karl, R. (1957). *A.M.A. J. Dis. Child.*, 94, 452.
 Luetscher, J. A., jun. (1956). *Advanc. intern. Med.*, 8, 155.
 Mader, I. J., and Iseri, L. T. (1955). *Amer. J. Med.*, 19, 976.
 Mahler, R. F., and Stanbury, S. W. (1956). *Quart. J. Med.*, 25, 21.
 Milne, M. D., Muehrcke, R. C., and Aird, I. (1957). *Ibid.*, 26, 317.
 Pawan, G. L. S. (1955). *Biochem. J.*, 60, xii.
 Renwick, R., Robson, J. S., and Stewart, C. P. (1955). *J. clin. Invest.*, 34, 1037.
 Russell, G. F. M., Marshall, J., and Stanton, J. B. (1956). *Scot. med. J.*, 1, 122.
 — Tucker, J. B., and Fraser, J. D. (1957). *Ibid.*, 2, 403.
 Schwartz, W. B., and Relman, A. S. (1953). *J. clin. Invest.*, 32, 258.
 Skanse, B., Möller, F., Gydell, K., Johansson, S., and Wulff, M. B. (1957). *Acta med. scand.*, 158, 181.
 Wynngaarden, J. B., Keitel, H. G., and Isselbacher, J. (1954). *New Engl. J. Med.*, 250, 597.

Every year fire brigades in the United Kingdom attend about 500 fires in such places as nursing-homes and hospitals of all kinds, clinics and welfare centres, children's and old people's homes, special schools for handicapped children, day nurseries, training centres for ex-Service men, and institutions for the blind. . . . Generally speaking the causes of most of the fires were not peculiar to hospitals but were similar to those of fires in dwellings. Many were the result of carelessness or forgetfulness—for instance, 18 were due to dropped smoking materials, and of these five were started by people who were smoking in bed. An important proportion of fires was concerned with cooking and heating equipment. . . . Six fires originated in hospital boilers or furnaces and seven were caused by chimneys or flues. Two fires arose as a result of a fairly common practice in hospitals—shielding the glare from an electric lamp by draping a cloth or towel round it; and one fire was started by the flame from a lighted sulphur fumigating cone placed on a mattress. Only five of the fires were peculiar to hospitals in that they involved special hospital equipment. There were three fires in sterilizers, two electric and one gas-heated, and the two other fires originated in immersion heaters in x-ray developing tanks. One of the most encouraging conclusions of this survey is that the provision of fire-fighting equipment seems to have been adequate, and most of the fires were tackled by the hospital staff, who were able to extinguish 52 of them without fire brigade assistance. . . . (*Fire Protection Association Journal*, July, 1959.)

A CONTROLLED TRIAL OF IMIPRAMINE IN TREATMENT OF DEPRESSIVE STATES

BY

J. R. B. BALL, M.B., B.S., D.P.M.

Senior Registrar, Department of Psychological Medicine,
Royal Victoria Infirmary, Newcastle upon Tyne

AND

L. G. KILOH, M.D., M.R.C.P., D.P.M.

Senior Lecturer, Department of Psychological Medicine,
University of Durham

Imipramine, an iminodibenzyl derivative, is a distant relative of chlorpromazine. Investigation of this substance was carried out by Kuhn, at Munsterlingen, in 1950, but after an initial and limited assessment it was put aside until interest was rekindled in 1954 after the beneficial effects of chlorpromazine had been established (Kuhn, 1957). Like iproniazid, imipramine inhibits the lowering of the serotonin level in the brain caused by reserpine (van Meter *et al.*, 1959). A number of clinical studies published on the effects of imipramine suggest that the drug is of considerable value in the treatment of depression and that its effects are at least comparable to those of electric convulsion therapy (E.C.T.).

In three years Kuhn (1957, 1958) treated 500 patients suffering from various psychiatric disorders with imipramine. The best results were obtained in endogenous depression, and he states that success can be expected in three-quarters to four-fifths of cases. In reactive depression a significant though less marked response was noted.

Kielholz and Battegay (1958) treated 69 cases of severe depression and found that 67% were improved or became symptom-free.

Lehmann *et al.* (1958) reported the effects of imipramine upon 84 patients in whom depression was a prominent feature. Three-fifths of these suffered from endogenous depression. Within eight weeks 60% had recovered or were much improved.

Fazio *et al.* (1958) found that in 50 cases of depression of varied aetiology 32% showed a full clinical remission and 42% were appreciably improved. Imipramine appeared to be most effective in recurrent depression.

Straker (1959) treated with imipramine 26 patients from his private practice mostly suffering from endogenous depression: 80% recovered or were "vastly improved."

Sloane *et al.* (1959) selected 30 patients—the majority suffering from endogenous depression—who would otherwise have been given E.C.T.: 80% recovered, and the authors felt that the results were comparable to or even somewhat better than those of E.C.T. An abortive attempt to carry out a controlled trial on 12 patients was made, but it was terminated after two weeks and no useful conclusions could be drawn.

Mann (1959) gave imipramine to 70 cases of depression of various types and found that 63% recovered or were much improved: 40 cases were described as suffering from "neurotic depression," but this group included many involuntal cases.