phosphate level during the glucose tolerance test, and concluded that glucose was being diverted away from the periphery. They also found a poor or no response to subcutaneous adrenaline despite significant quantities of glycogen in the tumour. The probable explanation is that the neoplastic tissue lacks glucose-6-phosphatase as was indeed demonstrated in our second patient.

In conclusion we believe that the hypoglycæmia in the present cases was of the same nature as that occurring in other non-pancreatic tumours and was not related to the abnormal steroid metabolism.

Acknowledgments.—I should like to thank the numerous people who have studied various aspects of these cases particularly Dr. T. Chalmers who looked after the first patient, Dr. P. Hugh-Jones, Dr. J. D. N. Nabarro, Dr. J. D. H. Slater and Drs. A. E. Kellie, A. P. Wade and E. R. Smith who performed more of the steroid assays.

REFERENCES

ANDERSON, H. B. (1930) *Amer. J. med. Sci.*, **180**, 71.
AUGUST, J., and HIATT, H. (1958) *New Engl. J. Med.*, **258**, 17.
BROSTER, L. R. and PATTERSON, J. (1948) *Brit. med. J.*, i, 781.
CONN, J. W., and SELTZER, H. S. (1955) *Amer. J. Med.*, **19**, 460.
EBERLEIN, W. R., and BONGIOVANNI, A. M. (1955) *J. clin. Endocrin.*, **15**, 1531.
GANDY, H. M., and KEUTMANN, E. H. (1958) *Amer. J. Dis. Child.*, **96**, 519.
HIATT, H. H. (1957) *Cancer Res.*, **17**, 240.
LAWRENCE, C. H. (1937) *Ann. intern. Med.*, **11**, 936.
MCFADZEAN, A. J., and YEUNG, T. T. (1956) *Arch. intern. Med.*, **98**, 720.
ROSSELET, J. P., *et al.* (1954) *Helv. chim. acta*, **37**, 1933.
STAFFIERI, J. J., CAMES, O., and CID, J. M. (1949) *J. clin. Endocrin.*, **9**, 255.
TOUCHSTONE, J. C., *et al.* (1957) *J. clin. Endocrin.*, **17**, 250.
WILKINS, L., *et al.* (1952) *J. clin. Endocrin.*, **12**, 1015.
WHITE, F. P., and SUTTON, L. E. (1951) *J. clin. Endocrin.*, **11**, 1395.

The following paper was also read:

Studies on Endemic Cretins in the Belgian Congo.—Professor P. A. BASTENIE, Dr. A. ERMANS, Dr. O. THYS, Professor M. DE VISSCHER and Dr. C. BECKERS (Brussels, Belgium).

Meeting
May 25, 1960

Stein-Leventhal Syndrome.—D. R. LONDON, B.M., M.R.C.P. (for F. T. G. PRUNTY, M.D., F.R.C.P.)

Mrs. V. S., aged 21, was referred as a possible case of Cushing's syndrome from another hospital where her 17-ketosteroids were estimated at 24·8 mg/24 hours and 17-ketogenic steroids 32·1 mg/24 hours. Her periods appeared when she was 13 and were normal until the age of 17, when she became pregnant. After a daughter had been born by Cæsarean section, the patient's periods became very scanty and irregular. Her weight, following the pregnancy, increased from 10 st. to 15 st. She had been hirsute since puberty.

On examination she was obese, had red striæ on her breasts, gross hirsuties of the face, limbs and abdomen, a male distribution of pubic hair, and acne on her face and back. There were no other physical abnormalities.

The blood picture and electrolytes were normal. The glucose tolerance test showed delayed absorption. The resting 17-ketosteroids were 12·3, 21·9 and 17·2 mg/24 hours rising, after stimulation with ACTH 20 units b.d. for four days, to 33 mg/24 hours. The control 17-ketogenic steroids were 11·1, 8·1 and 10·7 mg/24 hours, rising to 48 mg/24 hours after ACTH. Cortisol production was 31 mg/24 hours, based on urine tetrahydrocortisol and tetrahydrocortisone. Urine free cortisol was 20 μg/24 hours. Androgen production was 17·5 mg/24 hours based on urinary androsterone after intravenous injection of ^{14}C-androstenedione. On this day, the 17-ketosteroids were 17·2 mg. Twenty-four-hour excretion of gonadotrophins, estimated by mouse uterine weight, was 32·5 HMG/20A units per day. Radiography following pneumoperitoneum showed two grossly enlarged ovaries (Fig. 1), a finding confirmed at operation (Mr. G. W. Garland). Histology of the tissue removed at wedge resection demonstrated follicular and lutein cysts with marked mitotic activity in both granulosa cell and thecal layers (Fig. 2). There was more than one primordial ovum in the epithelial layers of some of the follicles.

The original diagnosis of Cushing's syndrome was excluded by the normal 17-ketosteroids and 17-ketogenic steroids, the normal urine free cortisol, and the cortisol production, which, although high, is below the level found in overt Cushing's syndrome (Brooks, 1960). The diagnosis of Stein-Leventhal syndrome was confirmed by the findings on radiology, at operation and by the histology of the operation specimen. The past history of a pregnancy was no bar to the diagnosis (Stein, 1958).

The only unusual feature was the solitary high gonadotrophin (Stein, 1959). This cannot be ascribed to ovulation as the patient was having a period at the time of the urine collection. The method used for this determination does not allow a distinction to be made between F.S.H.

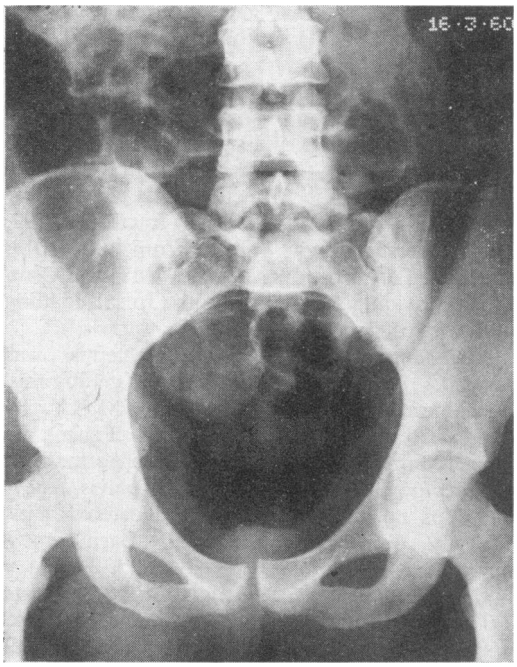

FIG. 1.—Radiograph showing bilateral enlargement of the ovaries.

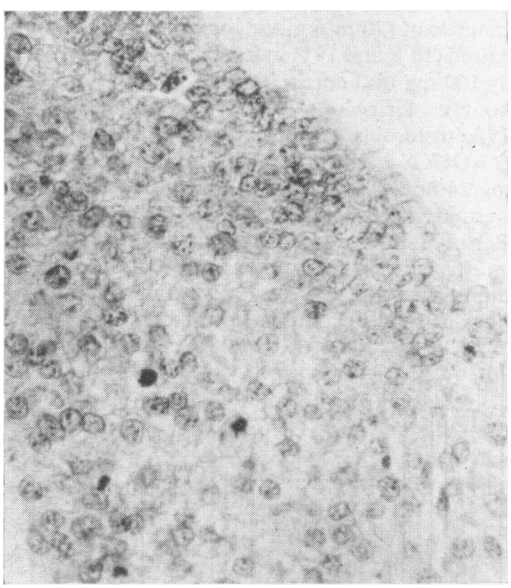

FIG. 2.—Lining of an ovarian follicle. The multiple mitotic figures are visible. ×230.

and L.H. Evidence has been offered that patients with the Stein-Leventhal syndrome produce excessive amounts of L.H. (Keettel *et al.*, 1957), but there are no data available to suggest an oversecretion of F.S.H. in this disorder.

That this patient was producing excessive androgens is suggested by the gross hirsuties and acne. Furthermore the androgen production is considered to be high, although confirmatory evidence on this point is limited. The excess androgen may be coming from either the ovary or from the adrenal. That the ovary is capable of producing androgen is well documented (Savard *et al.*, 1957; O'Donnell and McCaig, 1959; Mills *et al.*, 1959). Androstenedione and 17-hydroxy progesterone, but no œstrogen, were found in the follicular fluid of a case of Stein-Leventhal syndrome from our department (Short, 1960).

However, it is unlikely that in this case the ovary was the sole source of androgen, for the ketosteroid response to ACTH was normal. Thus it is probable that, in this patient, both the ovary and the adrenal were the sites of the excess androgen production.

REFERENCES

BROOKS, R. V. (1960) Unpublished.
KEETTEL, W. C., BRADBURY, J. T., and STODDARD, F. J. (1957) *Amer. J. Obstet. Gynec.*, **73**, 954.
MILLS, I. H., BROOKS, R. V., and PRUNTY, F. T. G. (1959) *Proc. R. Soc. Med.*, **52**, 1051.
O'DONNELL, V. J., and MCCAIG, J. G. (1959) *Biochem. J.*, **71**, 9P.
SAVARD, K., DORFMAN, R. I., GABRILOVE, J. L., and SOFFER, L. J. (1957) Proceedings of the Endocrine Society (Abstracts). New York; p. 89.
SHORT, R. V. (1960) Personal communication.
STEIN, I. F. (1958) *New Engl. J. Med.*, **259**, 420.
—— (1959) *Brit. med. J.*, ii, 301.

Stiff-man Syndrome with Atypical Hypopituitarism.—J. D. H. SLATER, M.B., M.R.C.P.

P. H., male, aged 64.

Progressive, persistent, painful stiffening of pelvic girdle and thigh muscles developed slowly during the autumn of 1957. By February 1958 he was unable to walk, the knees and hips being fixed in flexion. No other muscle groups involved. No generalized tetanic spasms but very painful localized spasms occurred on palpation of the affected muscles and also spontaneously on attempted movement.

On examination (June 1958).—Drawn and ill-looking with loss of skin elasticity and subcutaneous fat. Legs held flexed at about 90 degrees at hips and knees by persistent contraction of the flexor and extensor muscles of both joints. Coarse fasciculation of muscles present. Muscle stiffness only slightly diminished by Pentothal anæsthesia. Arm and ankle deep tendon reflexes present but sluggish. No myotonia. Plantar responses flexor. No sensory abnormalities. Visual fields normal. Body hair, body pigment and testicles probably normal for his age. Blood pressure 85/55–120/90 mm Hg. Jugular venous pressure normal. Generalized scaly skin rash (first appeared in 1956).

Investigations

Muscle. — Electromyography (Dr. A. T. Richardson): The affected muscles showed normal spontaneous motor unit activity in some areas with regions of electrical silence alongside. Lower motor neurons, peripheral sensory neurons and muscle fibres appeared intact.

Microscopy showed some variation in size of the muscle fibres with condensation and "lining up" of sarcolemmal nuclei. These changes were minimal and were present in both normal and stiff muscles. No change occurred following treatment.

Electrolyte composition (Professor J. N. Cumings): Both affected and unaffected muscles had normal content of Na, Mg and Cl on a dried weight basis. K content of stiff muscle normal (415 mEq/kg).

Sodium metabolism and body "space" measurements.—Persistent hyponatræmia (mean 122 mEq/l.) and hypochloræmia (mean 85 mEq/l.) were found with normal levels of serum K (4·0 mEq/l.), bicarbonate (26 mEq/l.) and blood urea (17–19 mg/100 ml). Plasma osmolarity 250 m.Osm/l. Total exchangeable Na was in the high normal range (53 mEq/kg), suggesting that the hyponatræmia was due to dilution and not to deficiency of sodium. Total exchangeable K normal (37 mEq/Kg). Total body water normal (33·5 l. with phenazone and 34·5 l. with urea; mean=64% of body weight) but the apparent extracellular fluid volume was greatly expanded (21·0 l. with ^{82}Br, 20·6 l. with inulin and 19·0 l. with NaCNS). Plasma volume also raised (74·2 ml/kg).

Rapid intravenous infusion of 431 mEq Na as 5% NaCl resulted in slight transient improvement of muscle pain and stiffness.

Renal function.—Glomerular filtration rate (inulin) 107 ml/min. Effective renal plasma flow (PAH) 544 ml/min; filtration fraction 0·197. Urine specific gravity ranged from 1001–1018. Calculated urine osmolarity exceeded 600 m.Osm/l. on occasion. Normal response to salt loading and salt restriction.

Hæmatology. — An apparent anæmia was present. Hæmoglobin 61% (9·0 g/100 ml), hæmatocrit 30%, M.C.H.C. 29%, M.C.V. 89 c.mm. Red cell fragility reduced. Plasma Fe 32µg/100 ml; vitamin-B_{12} absorption normal.

Radiology.—Skull, chest, spine, pelvis, knees and hips normal except for mild osteoarthritic changes. Pituitary fossa normal. Barium meal normal.

Calcium.—Serum Ca 9·3 mg/100 ml, phosphate 3·0 mg/100 ml and alkaline phosphatase 6·6 K.A. units/100 ml. Urine calcium output (on normal ward diet) 220 mg/24 hours.

Glucose tolerance.—Normal. No fall in plasma phosphate or serum K. No glycosuria.

Endocrine glands.—Adrenals: Excretion of water load (20 ml/kg body weight) markedly impaired (15% and 19% in four hours) but corrected by 100 mg oral cortisone (65% and 94% in four hours). Urine total 17-OH corticosteroids, and 17-ketosteroids in normal or low normal range (17-OHCS 5·2–11·6 mg/24 hours; 17-KS 4·5–11·2 mg/24 hours). Plasma Porter-Silber chromogen normal (free 8, conjugated 6 µg/100 ml) (Dr. D. N. Baron). Brisk response to corticotrophin.

Thyroid: ^{131}I neck uptake at twenty-four hours diminished (8%, 9% and 16% of dose) and 0–48 hour urine ^{131}I excretion elevated (74%, 75% and

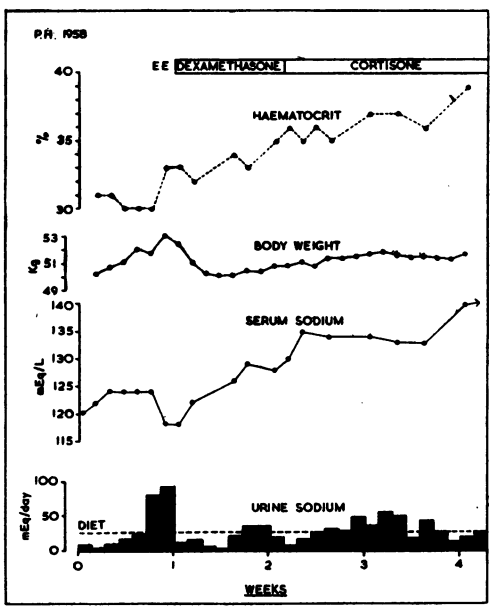

FIG. 1.—Rise of serum sodium concentration and hæmatocrit without significant change of body weight or sodium balance when treated with dexamethasone (0·5 mg b.d.) and then cortisone (12·5 mg t.d.s.).

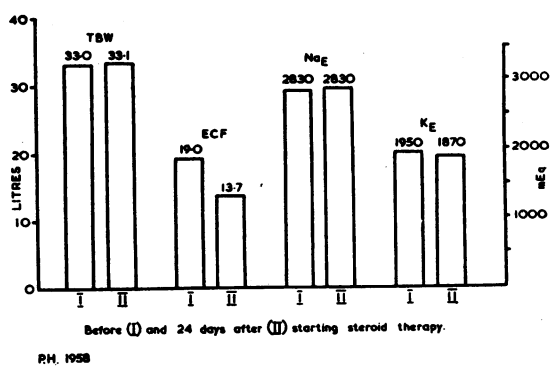

FIG. 2.—Total body water—TBW (phenazone space), extracellular fluid volume—ECF (thiocyanate space) and total exchangeable sodium—Na_E—and potassium—K_E—before and after steroid therapy.

72% of dose). B.M.R. +3%. After T.S.H. ^{131}I neck uptake rose to 47% of the dose in 24 hours.

Pituitary: Urine follicle stimulating hormone output less than 4 mouse-units per twenty-four hours. No rise of urine 17-OHCS output when given an 11-β-hydroxylase inhibitor (SU 4885), suggesting limitation of corticotrophin reserve.

Electrocardiography showed low voltage complexes with flat T-waves which became normal after treatment.

Progress.—Because there was some evidence of impaired pituitary function he was given dexamethasone in physiological doses (0·5 mg b.d.). Within seven days, most of his muscle stiffness had disappeared. The serum sodium concentration and hæmatocrit became normal. The extracellular fluid volume fell considerably within four weeks without measurable change of total body water, body weight, sodium balance and total exchangeable sodium or potassium (Figs. 1 and 2).

Since December 1958 he has been taking prednisone 2·5 mg t.d.s. and L-thyroxine 0·1 mg t.d.s. and has remained symptom free except for some slight residual flexion deformity due to fibrosis around the hip and knee joints.

Comments.—The clinical picture of slowly progressive painful muscle stiffness without any other demonstrable clinical abnormality was described by Moersch and Woltman (1956) under the heading "stiff-man syndrome". Our patient closely resembles many of theirs, but differs from the two patients reported by Asher (1958) and Price and Allott (1958) in that he never developed generalized tetanic convulsions (although painful localized spasms were very troublesome), there were no periods of remission and his mental state has always been normal.

Impairment of anterior pituitary function was not suspected clinically but was suggested by the metabolic studies undertaken to elucidate the nature of the persistent hyponatræmia. However, the fact that a water load could only be excreted normally in the presence of steroids, the low ^{131}I neck uptake (repeated ×3) which was corrected by T.S.H., the low follicle-stimulating hormone output and the restoration of the electrocardiogram to normal following treatment all provide reasonably convincing evidence of partial hypopituitarism.

Tendon contractures of the lower limbs without demonstrable abnormality of the muscles has been described in 5 patients with Addison's disease treated with deoxycortone (DOCA) (Thorn, 1951; Aubertin and Bergouignan, 1951; Adams *et al.*, 1953). The condition is relieved by the administration of cortisone or adrenocortical extract. Recently Wisenbaugh and Heller (1960) have described a patient with classical Addison's disease who developed flexion contractures before any treatment had been given. In all these cases there was undoubtedly a profound disturbance of sodium and potassium metabolism. In our patient, however, the only metabolic abnormality found was in water distribution within the body which implied considerable diminution in the intracellular fluid volume.

A similar abnormality of water distribution is also seen in other conditions, particularly severe malnutrition (Medical Research Council, 1951) and infusion of hypertonic saline did not exacerbate the muscle stiffness in our patient. Therefore cell-shrinkage *per se* is unlikely to be the cause of the muscle spasm. The evidence strongly suggests, however, that our patient's muscle stiffness and partial hypopituitarism are causally related. The mechanism remains obscure.

REFERENCES

ADAMS, R. D., DENNY-BROWN, D., and PEARSON, C. M. (1953) Diseases of Muscle. New York; p. 477.
ASHER, R. (1958) *Brit. med. J.*, i, 265.
AUBERTIN, E., and BERGOUIGNAN, M. (1951) *Ann. Endocr., Paris*, **12**, 888.
MOERSCH, F. P., and WOLTMAN, H. W. (1956) *Proc. Mayo Clinic*, **31**, 421.
PRICE, T. M. L., and ALLOTT, E. N. (1958) *Brit. med. J.*, i, 682.
Medical Research Council (1951) *Spec. Rep. Ser., med. Res. Coun., Lond.*, No. 275.
THORN, G. W. (1951) The Diagnosis and Treatment of Adrenal Insufficiency. 2nd ed. Springfield, Ill.; p. 150.
WISENBAUGH, P. E., and HELLER, H. M. (1960) *J. clin. Endocrin.*, **20**, 792.

Acromegaly Treated by Needle-Implantation of ^{198}Au seeds into the Pituitary Gland, showing changes in growth, carbohydrate and calcium metabolism. — M. T. HARRISON, M.D., M.R.C.P., G. F. JOPLIN, M.R.C.P., M. HARTOG, M.R.C.P., and RUSSELL FRASER, M.D., F.R.C.P.

S. R., male, aged 39.

History.—Acromegaly diagnosed elsewhere in 1956, and first treated early in 1959 with external irradiation 3,500 rad. This caused no regression of acromegalic appearance, nor of the headache; mild diabetes mellitus then developed. Patient first seen at Hammersmith Hospital, July 1959.

On examination (July 1959).—Gross acromegalic appearance; tongue, hands and feet conspicuously enlarged. Thyroid impalpable. Clinically euthyroid. No visual defect.

Investigations (*see* Table I) confirmed activity of acromegaly. Lateral skull film showed a greatly enlarged pituitary fossa of 210 sq mm (normal <130 sq mm), with undercutting of the anterior clinoids and thinning of the dorsum sellæ.

TABLE I.—SUMMARY OF INVESTIGATIONS

	Pre-implant (Oct. 1959)	Three months Post-implant (Jan. 1960)
Hand volumes (right/left : ml) ..	653/605	550/500
Insulin tolerance test: (11·1 units S.I./sq.m). Sum of blood sugars at 60, 90 and 120 min. (n<135)	189 Abnormally =Resistant	68 Abnormally =Sensitive
Prednisone load test: change in overnight urinary sugar after 20 mg at noon, 4 p.m., 8 p.m. (n<50 mg/h)	29——→366	27——→39
Urinary calcium (mg/24 h) on 550 mg/day intake (n<200)	300	160
Sr. test for exchangeable calcium (n=8–18 plasma units) ..	17·3	18·9
Daily deposition of calcium (n=1·0–2·0 plasma units) ..	2·4	1·9
Plasma citrate (mg%) (n=1·5–3·0)	5·50	2·15
UR. 17-KS mg/24 h	8, 13, 18, 22	3, 2, 4, 6
UR. 17-KGS mg/24 h	5, 9, 6, 7	1, 1, 1, 0
Cortisol production rate (Dr. C. Cope, ^{14}C cortisol test) in mg/24 h (n=6–20)	(not done)	2·5
^{131}I test: 48-hour neck uptake% (and T) .. (n=25–50); [T(n=3–13)]	55 (6)	37 (3·7)
Water diuresis test (1 litre) % diuresis in 4 hours	59, 43, 52	14
Growth hormone assay (serum) .. .. (n=80–240 μg/l)	461	at 3/12 261 at 6/12 295

Treatment (13.10.59).—*Transethmoid implantation* of two seeds of ^{198}Au into pituitary tumour. (13·3 mc each.) Dosimetry calculations from the post-implant X-rays showed that 45% of the gland received >20,000 rads (60%>10,000 rads), and that the peak dose to the diaphragma sellæ (assuming normal position) was 8,000 rads. For a short period after the implant there were signs of pituitary infection which subsided with antibiotics. A small maintenance dose of cortisone became necessary.

Clinically the acromegalic features clearly regressed by six weeks, and headache ceased altogether.

Test evidence of improvement (Table I).—(1) *Soft tissue changes:* Measurement of hand volume by displacement of water (Falta, 1915) showed a significant decrease of 16% after therapy, the error of the method being not greater than 5%.

(2) *Carbohydrate metabolism:* (*a*) In order to detect abnormal resistance to insulin, as occurs in acromegaly or Cushing's syndrome, we have found it of value to carry out an insulin tolerance test using a larger dose of insulin than in the conventional test. After 11·1 units/sq.m, the rate of return of blood sugar levels to normal is observed (Fig. 1). In normal subjects the sum of the blood sugar levels at 60, 90 and 120 min. after injection

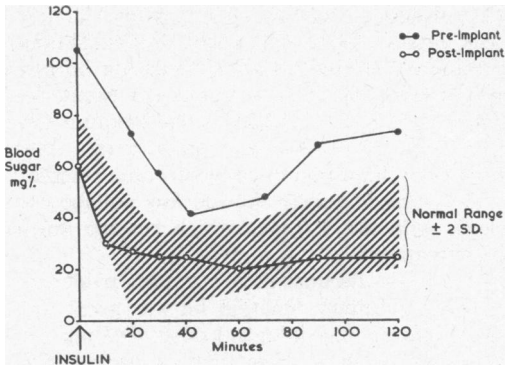

FIG. 1.—Insulin tolerance tests.

of this dose of insulin is less than 135 mg%. Thus he was clearly resistant before treatment, and became sensitive after. (*b*) Prednisone test: Measurement of the overnight urinary excretion of glucose following 3 doses of prednisone four-hourly permits separation of prediabetic from normal subjects (Joplin *et al.*, 1960). Glycosuria is normally slight, not exceeding 50 mg/hour. Table I shows the responses of our patient before and after treatment, and indicates that this diabetic tendency has disappeared.

(3) *Calcium metabolism:* Fig. 2 shows the

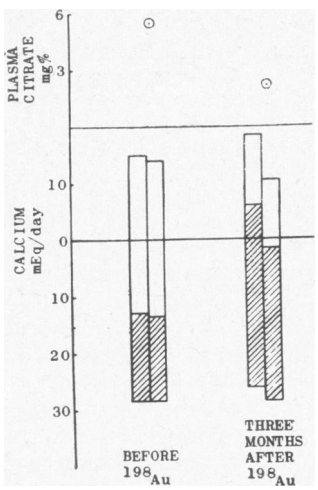

FIG. 2.

calcium balances before and after treatment. initially there was an excessive calcium loss in the urine, together with a low fæcal output. Both these features disappeared after treatment, although the net balance remained about the same. It is of interest that his plasma citrate levels were initially high (Fig. 2) and fell to normal.

A negative calcium balance in acromegaly has been recognized for some years (Bauer and Aub, 1941) and may be the cause of the osteoporosis which sometimes develops. The cause of this and of the hypercalciuria is unknown, but the finding here of a high plasma citrate level is probably relevant. This change may be related to increased parathyroid function, since the parathyroid glands are enlarged and often adenomatous in acromegaly (Cushing and Davidoff, 1929) and we have shown that growth hormone has a parathyrotrophic action in rats (Fraser and Harrison, 1960). The increased rate of bone formation in our patient, shown by the strontium tracer test (Fraser *et al.*, 1960) is also suggestive of hyperparathyroidism.

(4) *Growth hormone assay:* Levels of growth hormone in the serum were assayed by an immunological technique with tanned red cells. The level was abnormally high before therapy and fell significantly afterwards.

These newer tests appear to be of value both in the diagnosis of acromegaly, and in the assessment of effects of therapy.

REFERENCES

BAUER, W., and AUB, J. C. (1941) *J. clin. Invest.*, **20**, 295.

CUSHING, H., and DAVIDOFF, L. M. (1927) *Monogr. Rockefeller Inst. med. Res.*, No. 22.

FALTA, W. (1915) Ductless Glandular Diseases. Philadelphia.

FRASER, R., and HARRISON, M. T. (1960) *Ciba Found. Coll. Endocrin.*, **13**, 135.

——, ——, and IBBERTSON, H. K. (1960) *Quart. J. Med.*, **29**, 85.

JOPLIN, G. F., FRASER, R., and KEELEY, K. J. (1960) To be published.

Hashimoto's Disease with Complement-fixing Antibodies to Several Human Organs.—DEBORAH DONIACH, M.D. (for R. VAUGHAN HUDSON, F.R.C.S.).

J. L., male, aged 64. The patient, a dental surgeon, was in good health and quite unaware of having a goitre, which was first noted in February 1959 when he attended hospital for laryngitis and smoker's cough. The thyroid was found to be very firm, diffusely enlarged to an estimated 60 g with no thrill or bruit, quite painless and larger on the right so that carcinoma of the thyroid was suspected. The patient was euthyroid, looked young for his age and had normal skin and hair. He denied feeling cold or tired and had no choking sensation. Bowels regular, pulse 72 regular, blood pressure 140/80. No eye signs and no evidence of pretibial myxœdema. Liver and spleen not palpable, no œdema. No albuminuria or glycosuria.

Past illnesses.—Always healthy except for fairly frequent attacks of tonsillitis and laryngitis, and chronic cough (25–30 cigarettes daily). Typhus fever in 1914 war, left inguinal herniorrhaphy in 1948 and again in 1956. Infected parotid duct 1954. No thyroid swelling had been noted on 3 previous admissions to the Middlesex Hospital. However, on the first admission in 1948 the trachea was noted to be central while in 1956 it showed "slight deviation to the right" and the ESR was 21 mm in one hour (Wintrobe, normal 0–15) which suggests that the thyroid condition may have developed between these two dates. His weight was 10 st 8 lb on the first admission and has not changed in the last twelve years. No history could be elicited of any episode suggestive of past hyperthyroidism and there was no history of past jaundice, rheumatic fever or any allergic manifestations or skin rashes.

Family history.—Patient's sister has had thyrotoxicosis with fairly severe exophthalmos and ocular pareses for some years, treated with antithyroid drugs and radioiodine since 1956, and subsequently required permanent thyroid replacement. Mother, father and 6 other siblings had no thyroid disease.

Investigations.—B.M.R. = +15% (Robertson-Reid standard, normal −15 to +15), serum cholesterol 240 mg%, ^{131}I uptake 29%/24 hours, urinary excretion 48%/24 hours. Forty eight-hour plasma radioactivity 0·7% with protein-bound fraction of 0·6%/litre. Scintigram showed a uniform thyroid-shaped uptake pattern with higher counts over the larger right lobe. Triiodothyronine (T_3) given in doses of 120μg daily for eight days (Werner's test) suppressed the thyroid uptake to 2%/24 hours and the total forty eight-hour plasma level to 0·04%/litre. Seroflocculation tests gave normal results with thymol turbidity of 3 units, zinc sulphate turbidity 10 units, colloidal gold 1 unit. However, electrophoretic strip showed raised gamma globulins, and serum protein estimation gave a reversed A/G ratio: total proteins 6·9, A 3·7, G 3·2 g%. Serum bilirubin 0·6 mg%, alkaline phosphatase 9·5 K.-A. units. Immunological tests: tanned cell hæmagglutination test positive to a titre of 250,000, thyroglobulin precipitin in agar gel positive up to 1/8 serum dilution (weak), complement-fixation test (C.F.T.) with whole thyrotoxic thyroid homogenate positive to 1/128 serum dilutions. C.F.T. also positive with other human organs including liver, kidney and suprarenal. In view of this, further studies were undertaken using subcellular fractions of human liver and thyroid obtained by differential centrifugation in a Spinco ultracentrifuge (Roitt *et al.*, 1960) with the following results:

Cell fraction used as antigen	*C.F.T. titre (patient's serum)*
Liver nuclear fraction	64
Liver mitochondria	<512
Liver "microsomes"	256
Liver souble antigens (supernatent fraction)	16
Thyrotoxic thyroid "microsomes"	16

The L–E cell test proved negative but Coons' fluorescent antibody method showed staining of the nuclei in a thyroid section suggesting the presence of antinuclear factors in the patient's serum. The patient's serum also proved cytotoxic to thyroid cells in tissue culture (*see* Pulvertaft *et al.*, 1959).

Follow-up.—On administration of L-thyroxine 0·3 mg daily the goitre gradually decreased in size to an estimated weight of 35 g in 1 year, and became softer. The patient felt no different and continued in perfect health so that in February 1960 he decided to try doing without tablets and stopped taking thyroxine of his own accord. He felt no worse and slept rather better, his smoker's cough troubled him less. In May 1960, the goitre was again very firm, tense and about 80–100 g in size, still not producing pressure symptoms, while the patient remained euthyroid and full of energy. Antibody tests repeated at intervals during the sixteen months' follow-up showed persistently high tanned cell titres with positive precipitin reactions, while the C.F.T. titres fluctuated somewhat. The patient was advised to resume thyroxine therapy in order to reduce the size of his goitre and to avoid any risk of malignant transformation which might be encouraged by the continuous TSH overstimulation and lymphoid hyperplasia obviously going on in his thyroid gland.

Comment.—Hashimoto's disease is rare in men and a recent survey of 303 cases investigated immunologically in our laboratory showed a sex ratio of 12 F/1 M, which agrees with figures published from other parts of the world (Woolner *et al.*, 1959). The finding of thyrotoxicosis in a close relative is not uncommon and suggests that an abnormality of the thyroid might have preceded the auto-immunizing thyroiditis in the patient. No evidence of underlying thyrotoxicosis could be demonstrated in our case on present investigation as shown by the complete suppression of ^{131}I uptake obtained with T_3. Overt hyperthyroidism does not appear to have existed at any time in this man but one cannot exclude an abnormality which, although clinically silent, might have provided the continuous immunological stimulus necessary for progressive auto-sensitization. We have not yet had an opportunity of testing the patient's sister for auto-antibodies but the fact that she became hypothyroid soon after ^{131}I therapy suggests that she may also have some thyroiditis.

As a rule auto-antibodies are strictly organ-specific to the thyroid gland in Hashimoto's disease but about 10% of patients give positive complement-fixation reactions with other human organs (Roitt and Doniach, 1958) particularly liver and kidney, and this does not appear to be necessarily associated with any clinical disturbance in these organs. This phenomenon was studied in hospital patients with various diseases by Mackay and Gajdusek (1958) and other workers (Hackett *et al.*, 1960). It is not yet known to what extent these non-specific reactions can be considered as true auto-antibodies although they certainly occur much more frequently in patients suffering from systemic lupus erythematosus (S.L.E.), in whom a general disturbance of immunological tolerance appears to exist. From a practical point of view it is important to control positive thyroid CFT reactions obtained in goitre patients with tests done concurrently using human liver as an antigen to avoid mistakes in diagnosis due to non-organ-specific reactions. In the present patient only a fraction of the C.F.T. titre could be attributed to specific thyroid "microsome" antibodies.

Hashimoto's disease and primary myxœdema sometimes occur in association with S.L.E. or with allied conditions such as lupoid hepatitis and rheumatoid arthritis. In these cases the patients have high titre thyroid antibodies as well as L.E. cells and/or positive Waaler-Rose tests. A small number of patients with uncomplicated Hashimoto's disease also have antinuclear factors in their serum but hardly ever in amounts sufficient to produce a positive L.E. cell test. In these cases the antinuclear reaction can only be demonstrated by the sensitive fluorescent antibody technique (White, 1959) and it is unlikely that the patients will ever develop clinical manifestations of S.L.E. The theoretical implications of these relationships between thyroid auto-immunity and more widespread diseases of the immune mechanisms are at present under study (Hijmans *et al.*, 1960).

REFERENCES

Hackett, E., Beech, M., and Forbes, I. J. (1960) *Brit. med. J.*, ii, 17.

Hijmans, W., Doniach, D., Roitt, I. M., and Holborow, J. (1960) In Preparation.

Mackay, I. R., and Gajdusek, C. D. (1958) *Arch. intern. Med.*, **101**, 30.

Pulvertaft, R. J. V., Doniach, D., Roitt, I. M., and Hudson, R. V. (1959) *Lancet*, ii, 214.

Roitt, I. M., and Doniach, D. (1958) *Lancet*, ii, 1027.

——, ——, and Couchman, K. (1960) In: Mechanism of Antibody Formation. Prague symposium, Czechoslovak Academy Press; p. 70.

White, R. G. (1959) *Exp. Cell. Res.*, Suppl. 7, p. 263.

Woolner, L. B., McConahey, W. M., and Beahrs, O. H. (1959) *J. clin. Endocrin.*, **19**, 53.

(*Meeting to be continued*)