though—as with other penicillins so far tested—hypersensitivity to penicillin G means hypersensitivity also to this derivative. Drug-resistance can be induced easily *in vitro* but did not account for relapses *in vivo*, though there was evidence in two cases that it could occur in minor degree.

In our present series we have deliberately excluded some respiratory infections in which a clinical response was observed; the bacteriology of such cases is often obscure and we are in these trials guided by the belief that two criteria are essential: disappearance of the target pathogens in cases and carriers, and parallel clinical improvement in cases. Without these criteria a therapeutic trial on an antibacterial agent is questionable. On this basis, we consider that the results reported here indicate a place for penbritin as a non-toxic penicillin of high bactericidal broad-spectrum activity in the oral treatment of urinary and possibly in systemic infections due to pyogenic cocci and sensitive Gram-negative bacilli. It warrants trial also in infections of the biliary tract and in some alimentary infections, peritonitis, and pre-operative intestinal surgery; it cannot at present be recommended for the treatment of intestinal carriers of salmonellae, despite the high sensitivity of these organisms *in vitro*. In view of the variation in sensitivity of typical coliforms toward the drug, its use in urinary and abdominal infections should be contingent upon adequate bacteriological control, which should include tests at concentrations attainable in the affected tissue.

In assessing the novel features of this new compound we should not forget the fact that penicillin G itself has an inhibitory effect upon many coliforms (Abraham *et al.*, 1941; Schwartzman, 1946), sometimes bactericidal and strong enough to enable it to be used therapeutically (Helmholtz and Sung, 1944; Stewart, 1945). Methicillin, phenethicillin, and phenoxypentylpenicillin lack such activity toward coliforms, so that penbritin represents a valuable chemical advance in thus enhancing a specific property within the penicillin family of substances.

Summary

"Penbritin" has a bactericidal action, comparable to that of penicillin G upon pyogenic cocci, upon a wide range of coccal and bacillary pathogens.

It is affected by penicillinase and is therefore inactive against penicillinase-forming strains of *Staph. aureus* and certain coliforms.

Given orally in doses of 50–100 mg./kg./day, the new compound is freely absorbed and maintains a bactericidal level in the plasma for four hours or more. It is rapidly excreted, in very high concentration, in the urine.

Apart from transient rashes in three carriers of salmonellae, no toxic effects were observed in 28 patients who received the drug for five days or more.

Eight children with severe urinary infection due to coliforms and/or streptococci responded rapidly to treatment, as did six children with other infections; six carriers of *Salm. typhi-murium* and two of *E. coli* serotypes were not cleared of infection.

Penbritin warrants further trial as a bactericidal penicillin-like drug with the antibacterial range of the tetracyclines.

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DIURETIC RESPONSE TO CHLORTHALIDONE

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Chlorthalidone ("hygroton") is a new diuretic introduced in Switzerland in 1959 and in this country in 1960. It is a sulphamyl benzophenone derivative (see Formula) synthesized in the Geigy Laboratories (Graf *et al.*, 1959). Pharmacological studies on laboratory animals have been reported (Stenger, 1959; Stenger *et al.*, 1959; Pulver *et al.*, 1959). The drug is only slightly soluble in water; absorption from the gut is

therefore slow, but it is said to be almost complete. After intravenous administration the drug is rapidly removed from the plasma and taken up by the tissues. Kidney takes up more, weight for weight, than any other organ and retains it longer. This presumably accounts for the prolonged diuretic action, which continues when the drug can no longer be detected in the plasma. There is little breakdown in the body, and 90% of an intravenous dose is recovered unchanged in the urine over 24 hours.

Chlorthalidone is an *in vitro* inhibitor of carbonic anhydrase, but this property probably accounts for only a small part of its diuretic action. Sodium excretion parallels chloride rather than bicarbonate excretion. The rates of excretion of sodium and chloride are not affected by acidosis and alkalosis. In these respects the drug resembles chlorothiazide, but it is not yet known whether it inhibits the same reabsorptive mechanisms. The action of chlorthalidone is much more prolonged—over 24 hours in most animal and human studies; the manufacturers therefore recommend its use two to four times a week rather than daily. The dose has varied from 600 mg. (Reutter and Schaub, 1959) to 50 mg. (Ford, 1960) in a day.

Since powerful oral diuretics of low toxicity are already available, any drug which is to replace them must have virtually no serious side-effects and a better mode of action. Chlorthalidone has now been in widespread use in Europe and America for over a year and no serious idiosyncrasies have so far been reported. A steady prolonged diuresis is nearer the physiological state than rapid intermittent diuresis. We therefore regard chlorthalidone as worthy of serious study, and have carried out preliminary trials to determine the ideal dose and the pattern of diuresis in normal and oedematous subjects.

Methods

Dose-response Curves

Dose-response curves were constructed for nine normal males (staff and students) aged 20–34 years. A preliminary experiment was carried out on two men. Diet was restricted to 200 ml. of water and a constant portion of food, every two hours for 24 hours; urine was collected every two hours, and volume and sodium content were measured. The routine was followed on a control day and two widely separated treatment days, when 50 and 600 mg. of chlorthalidone respectively were administered. The duration of activity was 18 hours at both dose levels, and peak diuresis was achieved within the first six hours. The proportion of the extra sodium excretion which occurred within the first six hours was similar (60% and 67%) for the two doses. Similar results were reported by Veyrat, Arnold, and Duckert (1959). Six-hourly collections of urine were therefore employed for the dose-response curve; this permitted closer control of intake and activity than is

possible with longer collection periods in ambulant subjects.

Urine was collected from 7 a.m. to 1 p.m., and a constant breakfast was taken at the same time on each of three control and six treatment days. All subjects had an adequate night's sleep before the tests, and similar routine activities were followed on each occasion. At least three clear days were allowed between treatment days. Urine was preserved with saturated thymol-chloroform and stored at -20°C . pending analysis. Sodium and potassium were estimated by flame photometry, chloride was measured potentiometrically, pH by pH meter, bicarbonate by the Technicon autoanalyser, and hydrogen-ion excretion as titratable acidity by back titration with sodium hydroxide to pH 7.4, using bromothymol blue as indicator. Plasma sodium, potassium, chloride, bicarbonate, urea, and uric acid were estimated before and 24 hours after the 400-mg. dose.

Studies on Oedematous Subjects

Chlorthalidone was administered to eight in-patients (Table I) with fluid retention due to cardiac or hepatic

TABLE I.—*Patients with Fluid Retention Treated with Chlorthalidone*

Patient	Sex and Age	Diagnosis	Site of Fluid Retention	Daily Intake			
				Water (ml.)	Protein (g.)	Sodium (mEq)	Potassium (mEq)
1	F 55	Polycythaemia vera. Hepatic vein thrombosis	Ascites	2,000	40	22	120
2	F 40	Hepatic cirrhosis	Ascites. Peripheral oedema	2,000	40	24	38
3	F 64	" "	Ascites	1,500	40	22	40
4	F 76	" "	"	1,500	40	22	40
5	M 44	" "	"	1,500	40	22	80
6	F 60	Myocardial ischaemia. Congestive heart failure	Peripheral oedema	2,000	UR	22	45
7	F 54	Cardiomyopathy. Congestive heart failure	"	1,500	UR	22	38
8	F 76	Myocardial ischaemia. Congestive heart failure	"	1,500	UR	22	38 and 98

UR = Unrestricted.

disease. They were confined to bed except for toilet purposes, on a diet of constant sodium, potassium, and water content. At least four days were allowed for equilibration before the diuretic was given. Plasma electrolytes, urea, and (in six patients) uric acid were estimated immediately before, and 24 and 48 hours after, each dose of chlorthalidone. Urine was collected in 24-hour periods and preserved and analysed as above.

A further 20 patients with oedema or hypertension were treated with chlorthalidone in the ward or as out-patients without urinary-excretion studies. Plasma electrolytes, urea, and uric acid were estimated at frequent intervals.

TABLE II.—*Dose-response Curve to Chlorthalidone. Six-hour Urinary Excretion in Nine Normal Subjects (Mean $\pm$ S.E.)*

Dose (mg.)	pH	Volume (ml.)	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Bicarbonate (mEq)	Titrateable Acidity (mEq)
Control	6.2 $\pm$ 0.6	243 $\pm$ 30	33 $\pm$ 4	19 $\pm$ 1	41 $\pm$ 5	1.9 $\pm$ 0.5	2.8 $\pm$ 0.6
12.5	6.8 $\pm$ 0.2	426 $\pm$ 27	80 $\pm$ 8	27 $\pm$ 3	97 $\pm$ 11	2.5 $\pm$ 0.7	2.7 $\pm$ 0.8
25	6.4 $\pm$ 0.3	588 $\pm$ 77	94 $\pm$ 9	34 $\pm$ 3	127 $\pm$ 11	2.8 $\pm$ 1.0	4.2 $\pm$ 1.2
50	6.8 $\pm$ 0.2	497 $\pm$ 20	115 $\pm$ 11	29 $\pm$ 2	116 $\pm$ 12	3.2 $\pm$ 0.6	2.5 $\pm$ 1.0
100	7.1 $\pm$ 0.1	574 $\pm$ 73	118 $\pm$ 13	31 $\pm$ 2	124 $\pm$ 8	5.5 $\pm$ 1.0	0.7 $\pm$ 0.5
200	7.2 $\pm$ 0.3	653 $\pm$ 95	131 $\pm$ 15	30 $\pm$ 6	129 $\pm$ 15	15.2 $\pm$ 3.4	1.0 $\pm$ 0.7
400	7.4 $\pm$ 0.2	725 $\pm$ 114	163 $\pm$ 18	37 $\pm$ 6	159 $\pm$ 18	17.0 $\pm$ 3.5	0.4 $\pm$ 0.4

Results in Normal Subjects

The dose-response curves for volume, sodium, potassium, chloride, bicarbonate, and hydrogen-ion excretion and urinary pH are shown in Table II. The same data are presented in less familiar form in Table III; for each dose the *extra* volume passed (compared with the control day) is shown, and the *extra*

TABLE III.—*Urinary Increment in Normal Subjects Treated with Diuretics (Mean ± S.E.)*

Diuretic	Dose in mg.	Sodium (mEq/l.)	Potassium (mEq/l.)	Chloride (mEq/l.)	Bicarbonate (mEq/l.)	Volume (ml.)
Chlorthalidone*	12.5	267 ± 34	39 ± 18	310 ± 41	1 ± 4	187 ± 30
	25	217 ± 38	42 ± 14	281 ± 25	0 ± 4	369 ± 81
	50	362 ± 57	42 ± 10	307 ± 21	8 ± 5	283 ± 44
	100	298 ± 39	38 ± 11	282 ± 29	12 ± 5	331 ± 58
	200	274 ± 32	40 ± 8	237 ± 32	35 ± 10	410 ± 90
	400	304 ± 32	40 ± 11	272 ± 32	27 ± 5	506 ± 103
Hydroflumethiazide†	100	193	24	220	2	596
Hydrochlorothiazide†	100	289	17	318	16	449
Chlorothiazide†	1,000	183	35	145	54	504

* 6-hour urine collections. Present data.

† 10-hour urine collection (Edmonds and Wilson, 1959).

electrolytes excreted are expressed as a concentration in the extra volume. The patient is pictured as passing his normal urine for the day plus an increment due to the diuretic; the volume and composition of this increment for each dose are shown in Table III. For this calculation it is assumed that the subject would have passed urine identical to that secreted on the control day if no diuretic had been given. This is only an approximation to the truth, since patients on constant diet and activity still display some unexplained variation in urinary output (Baldwin *et al.*, 1960); the standard errors of the results shown in Table III are therefore high. The urinary increments produced by therapeutic doses of three thiazide diuretics (derived from the data of Edmonds and Wilson, 1959) are shown for comparison.

Only random non-significant changes in sodium, potassium, and chloride concentration in the urinary increment take place with alteration in dose, but the bicarbonate concentration increases significantly with increasing dose. The pH of the increment cannot be calculated, but it must also rise with the dose, since the pH of the total output increases.

From Tables II and III it is clear that the maximum salt-and-water elimination per mg. of chlorthalidone—that is, the cheapest diuresis—can be achieved by giving small doses (12.5 or 25 mg.) at frequent intervals such as once every one or two days.

In the treatment of oedematous patients a more important consideration is the prevention of electrolyte disturbance during diuresis. This object can be achieved if the urinary increment closely resembles extracellular fluid in electrolyte composition. The dose of chlorthalidone which produces an increment most closely resembling extracellular fluid is 100–200 mg.; we have therefore used 100 or 200 mg. at intervals of several days when treating patients for oedema. Even at this dose chlorthalidone, like the thiazides, produces an increment with too high a concentration of sodium, chloride, and potassium. Depletion of these elements during rapid diuresis is therefore a possibility with chlorthalidone, as with the thiazides, but at the correct dose level chlorthalidone should be less likely to cause disturbance of acid-base balance.

No significant alteration in plasma electrolytes, urea, or uric acid occurred in the normal subjects after a single 400-mg. dose of chlorthalidone.

Results in Oedematous Subjects

All the eight patients studied in hospital on constant diet showed a diuretic response to single doses of 100 or 200 mg. of chlorthalidone. In all eight, diuresis or saluresis continued for more than 24 hours, in four for over 48 hours. In six the pattern of diuresis differed from that in normal subjects; little or no bicarbonate was excreted; urinary pH failed to rise in three and fell in two others; potassium excretion was excessive in three.

Second courses of chlorthalidone were given to seven of the patients during treatment with spironolactone (an aldosterone inhibitor) 200-mg. eight-hourly. Spironolactone was given for at least 24 hours before the diuretic in view of its slow onset of activity (Shaldon *et al.*, 1960). The results are summarized in Table IV. In four

TABLE IV.—*Response to Chlorthalidone With and Without Spironolactone in Patients Listed in Table I*

Patient	Treatment	Urinary Excretion: Mean of at Least Two Control Days and of First and Second Day after Each Dose of Diuretic				
		Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Bicarbonate (mEq)	Volume (ml.)
1	A	2	76	35	7	890
	B*	43	130	178	0	1,730
	C*	186	49	202	7	2,170
2	A	55	30	51	4	910
	B	202	53	190	10	1,670
	C	360	23	274	45	2,380
3	A	7	17	20	0	1,190
	B	194	48	246	0	2,190
	C	120	18	101	23	1,250
4	A	22	12	21	0	380
	B*	126	24	174	0	920
	C*	217	29	120	54	1,940
5	A	6	2	12	0	470
	B	74	37	113	4	1,370
	C	199	39	194	26	2,290
6	A	7	19	13	2	1,150
	B	44	24	62	0	1,430
	C	105	24	76	11	2,400
7	A	22	20	41	0	670
	B	49	24	73	0	860
	C	55	13	52	6	830
8	A	8	10	10	—	440
	B	82	13	65	—	640
	D	158	15	110	—	1,040

A=Control. B=Chlorthalidone. C=Chlorthalidone and spironolactone. D=Chlorthalidone and potassium chloride.

* Dose of chlorthalidone 200 mg. Other patients received 100 mg. chlorthalidone on each occasion.

cases urinary potassium excretion fell to control levels or below during the second diuresis, and in every case bicarbonate excretion and urinary pH rose. Four of the patients with ascites excreted more water, sodium, and chloride after the second dose of chlorthalidone, in spite of having less oedema by this time.

Patient 8, who had a low serum potassium (2.7 mEq/l.) was given a second dose of chlorthalidone during treatment with oral potassium chloride 6 g. a day. There was a greater diuretic response.

In two of the patients successive doses of chlorthalidone with spironolactone produced a diminishing response which was not explained by changes in plasma electrolytes or urea or by complete absence of oedema.

The only significant ($P < 0.05$) changes in plasma electrolytes and urea during this study were a mean fall in plasma chloride of 4 mEq/l. and in plasma potassium of 0.7 mEq/l. after chlorthalidone alone. Plasma potassium rose by an average of 0.2 mEq/l. after

chlorthalidone with spironolactone, but the rise was not significant. Plasma uric acid was studied in six patients; changes occurred gradually during the stay in hospital, and may have been unrelated to treatment; in the three patients with cirrhosis there was a rise (mean 2.9 to 4.6 mg./100 ml.) and in the three with heart failure a fall (mean 6.3 to 4.9 mg./100 ml.).

Early in our experience with the drug, doses that would now be regarded as excessive (100–200 mg. daily for 4–14 days) were given to four oedematous patients, one of whom had known renal disease. In three there was a rise in blood urea to over 100 mg./100 ml. with return to control levels over the following week, when the drug had been withdrawn. One patient with cirrhosis (Patient 3, Table I) was treated as an out-patient with chlorthalidone 100 mg. once a week, potassium chloride, and spironolactone; she remained free of oedema. After one month her blood urea had risen to 71 mg./100 ml.; it fell to 40 mg./100 ml. over the five days after withdrawal of all therapy. She subsequently developed uraemia on other diuretic regimes. No consistent changes in plasma urea or electrolytes occurred in the remaining patients. Plasma uric acid rose in the majority, but the change was not significant.

Toxicity

Urine specimens taken during a diuresis in the normal subjects showed no albuminuria or microscopical abnormality. No urinary abnormality was detected during treatment of the ward patients. The only complaints made by patients or normals were of tiredness after diuresis and generalized headache in a few subjects, most of whom were subject to migraine attacks.

Discussion

These results and other published studies on patients (Veyrat, Arnold, and Duckert, 1959; Veyrat, Arnold, and Muller, 1959; Reutter and Schaub, 1959; Ford, 1960; Fuchs *et al.*, 1960) show that it is an extremely effective diuretic, with few side-effects, and of comparable potency to injected mercurials. Its action has many similarities to that of chlorothiazide, including predominant sodium and chloride excretion, and less prominent increase in urinary potassium, bicarbonate, and pH. Its duration of action, after an oral dose, is much longer—about 18 hours in normal subjects and up to 72 hours in patients with oedema.

The pattern of excretion is altered in some patients with oedema, the urinary potassium increasing and the sodium, bicarbonate, and pH falling. These changes are similar to those produced when aldosterone is administered to normal subjects (August *et al.*, 1958), and they have been correlated with high excretion of aldosterone in patients receiving chlorthalidone (Veyrat, Arnold, and Muller, 1959). The correction of this abnormal diuretic pattern by simultaneous administration of spironolactone is further suggestive evidence that hypersecretion of aldosterone is the cause of the abnormality. Similar results have been obtained with the thiazides and acetazolamide (Liddle, 1958; Edmonds and Wilson, 1960; Farrelly *et al.*, 1960; Shaldon *et al.*, 1960). The use of such combined therapy is becoming the rule in the treatment of ascites, and is often required in patients with cardiac failure. It is worth noting, however, that similar results can sometimes be obtained by the less expensive simultaneous administration of oral potassium chloride.

The main problem we have encountered in the use of chlorthalidone in the control of oedema has been a rise in the blood urea in a few patients who have been treated with large doses or in whom therapy has been continued after oedema has disappeared. This is a well-recognized complication of treatment with other diuretics. In two patients there was a simultaneous fall in plasma sodium and chloride, suggesting that the excessive excretion of sodium and chloride in relation to water was at least a partial cause. A logical treatment of this complication of diuretic therapy is the administration of a drug such as prednisone or an osmotic diuretic to increase water excretion (Shaldon *et al.*, 1960). Our experience with both prednisone and mannitol, used in combination with chlorthalidone or other diuretics, has been uniformly disappointing, and we now prefer to relax dietary sodium restriction.

In the short-term studies described here there was no consistent effect on uric acid metabolism, but a rise in serum uric acid was noted by Ford (1960).

Diuretics are now well established as sole or adjuvant therapy in hypertension (Megibow *et al.*, 1948; Hall and Owen, 1959; Dustan *et al.*, 1959; Dollery *et al.*, 1959), and for this purpose excretion of sodium and chloride (Farnsworth, 1946) appears to be of prime importance. Since acute changes in blood volume cause rapid alteration in responsiveness to other antihypertensive drugs (Dustan *et al.*, 1959; Dollery *et al.*, 1959), intermittent diuresis is undesirable. By virtue of its prolonged powerful saluretic action, chlorthalidone should be ideally suited to this function. We suggest the use of small doses (12.5–25 mg.) daily, to minimize diuretic “peaks.” This is also the most economical dosage in non-oedematous subjects. Our preliminary experience with chlorthalidone in antihypertensive therapy confirms its potency.

Summary

Chlorthalidone has been administered to nine normal subjects and 28 patients. It is a powerful diuretic with a duration of action of 24–72 hours in patients with oedema. The dose-response curve in normal subjects and the pattern of diuresis in normal and oedematous subjects are described.

An improvement in diuresis and a reduction in potassium loss have been achieved in some patients by simultaneous administration of spironolactone.

The recommended doses are 100–200 mg. once or twice a week for the treatment of oedema, and 12.5–25 mg. every day as adjuvant therapy in hypertension.

There have been few side-effects. Hypokalaemia can be prevented by administration of potassium chloride or spironolactone. A reversible rise in blood urea has sometimes followed over-vigorous use of the diuretic.

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BLOOD RADIATION DOSE AFTER ¹³¹I THERAPY OF THYROTOXICOSIS

CALCULATIONS WITH REFERENCE TO LEUKAEMIA

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Although ¹³¹I has been extensively used for the treatment of thyrotoxicosis there is occasionally some hesitation in choosing this form of treatment. Possible hazards that come to mind are the induction of neoplastic changes and genetic damage.

Carcinoma of the thyroid may be induced by exposure of the gland to ionizing radiations in infancy or childhood (Duffy and Fitzgerald, 1950; Simpson *et al.*, 1955; Clark, 1955; Fetterman, 1956; Simpson and Hempelmann, 1957; Wilson *et al.*, 1958), and neoplasms of the thyroid have been reported after the use of ¹³¹I therapy for thyrotoxicosis in childhood (Sheline *et al.*, 1959). However, ¹³¹I therapy should certainly not be used for the treatment of juvenile thyrotoxicosis. Thyroid carcinoma has rarely been reported to follow the use of x-rays for the treatment of thyrotoxicosis (Quimby and Werner, 1949; Wilson *et al.*, 1958; Goolden, 1958; Willis, 1959), and so far no cases have been attributed to ¹³¹I therapy in adults.

The possibility that ¹³¹I therapy may predispose to the development of leukaemia has until recently not been so fully considered. However, there is a known

association between exposure to ionizing radiations and the subsequent development of leukaemia (Court Brown and Doll, 1957). Our own interest was stimulated by the occurrence of acute monocytic leukaemia in a patient treated for thyrotoxicosis with ¹³¹I one and a half years previously (Blomfield *et al.*, 1959). This case is now reported in detail, and further investigations have been made in an attempt to measure the radiation dose to the blood and bone-marrow resulting from ¹³¹I therapy of thyrotoxicosis and to relate this to work on the development of leukaemia after irradiation.

Case Report

A married woman aged 60 complained of nervousness, palpitations, heat intolerance, and excessive sweating during the previous three years. Her weight had decreased by 12 kg. When she first attended hospital on February 13, 1957, she was emaciated and hyperkinetic, and had bilateral exophthalmos, lid lag, and lid retraction. The thyroid was slightly enlarged and irregular. Although the skin was warm and moist, finger tremor was not present. There was a regular tachycardia of 100 a minute. No other abnormal physical signs were observed. The blood film was normal, the haemoglobin being 17.1 g./100 ml., white-cell count 4,000/c.mm. (50% neutrophils, 4% eosinophils, 38% lymphocytes, 8% monocytes). The serum cholesterol was 195 mg./100 ml. There was no radiological evidence of tracheal compression or abnormality of the chest. A radioactive iodine tracer test showed a four-hour uptake of 58% and a 48-hour uptake of 69%. The 48-hour plasma-protein-bound ¹³¹I was 0.74% dose per litre.

A diagnosis of thyrotoxicosis was made, and on April 10 a therapeutic dose of 4.9 mc of ¹³¹I was given to produce an estimated dose of 7,000 rads to the thyroid. Subsequent measurements showed that the uptake of the therapeutic dose was slightly higher than that of the preliminary tracer dose, so that the dose to the thyroid was about 8,200 rads.

When seen on May 16 the patient was thought to be euthyroid, but by September she had gained 10 kg., and complained of intense cold and drowsiness. She presented the typical appearance of myxoedema. Her face was swollen, the features coarse, the skin rough, and the voice deep. The pulse rate was 76 a minute with sinus rhythm. There were no enlarged lymph nodes and the liver and spleen were not palpable. A radioactive iodine tracer test showed no significant thyroïdal uptake and a urinary T index of 1.1 (Fraser *et al.*, 1953). The serum cholesterol was 390 mg./100 ml. and the basal metabolic rate minus 17%. Although the patient was not anaemic, the following investigations were carried out as part of a study of the blood in patients with hypothyroidism (Tudhope and Wilson, 1960). Haemoglobin was 15.4 g./100 ml., white-cell count 7,000/c.mm. (68% neutrophils, 1% eosinophils, 23% lymphocytes, 8% monocytes), and blood film normal. The platelet count was 216,000/c.mm. Sternal bone-marrow was normal. The preparations were retained and subsequent examination confirmed the normal appearance. The total red-cell volume using ⁵¹Cr (30 µc) was 1.71 litres. The red-cell utilization of iron using ⁵⁹Fe (1 µc) was within the normal range.

Treatment with L-thyroxine sodium 0.1 mg. daily was started on October 30, and after increasing to 0.15 mg. daily a month later, she was judged to be euthyroid by February, 1958. On April 2 the haemoglobin was 14.8 g./100 ml., and the blood film normal. On April 11 the total red-cell volume using 42 µc of ⁵¹Cr was 1.86 litres. The total blood-irradiation dose contributed by the ⁵¹Cr and ⁵⁹Fe studies was calculated as 0.24 rad. During April, 1958, she complained of a burning sensation at the tip of the tongue, for which she was advised to stop smoking. She failed to do so and successive courses of treatment with riboflavin and vitamin B₁₂ failed to relieve the symptom. At this time she