- Lander, H. (1955). *J. Path. Bact.*, **70**, 157.
 Ligterink, J. A. T. (1951). *Ned. T. Geneesk.*, **95**, 3490.
 McAlpine, D. (1931). *Lancet*, **1**, 846.
 Malamud, N. (1939). *Arch. Neurol. Psychiat.* (Chicago), **41**, 943.
 Marshall, A. H. E., and White, R. G. (1950). *Brit. J. exp. Path.*, **31**, 157.
 Miller, H. G. (1953a). *A.M.A. Arch. Neurol. Psychiat.*, **69**, 695.
 — (1953b). *British Medical Journal*, **1**, 177.
 — and Evans, M. J. (1953). *Quart. J. Med.*, **22**, 347.
 — and Gibbons, J. L. (1953). *British Medical Journal*, **2**, 1345.
 — (1954). *Ann. Intern. Med.*, **40**, 755.
 — and Stanton, J. B. (1954a). *Quart. J. Med.*, **23**, 1.
 — (1954b). *Nervenarzt*, **25**, 118.
 — and Gibbons, J. L. (1956). *Quart. J. Med.*, **25**, 427.
 Moyer, A. W., Jarvis, G. A., Black, J., Koprowski, H., and Cox, H. R. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, **75**, 387.
 Russell, D. S. (1937). *J. Path. Bact.*, **45**, 357.
 — (1955). *Brain*, **78**, 369.
 Sellings, B., and Meilman, E. (1955). *New Engl. J. Med.*, **253**, 275.
 Shallard, B., and Latham, O. (1945). *Med. J. Aust.*, **1**, 145.
 Stanton, J. B., Miller, H. G., and Gibbons, J. L. (1953). *Rev. Neurol. Psychiat.*, **89**, 46.
 Van Bogaert, L. (1949). *Acta neurol. psychiat. belg.*, **49**, 811.
 Waksman, B. H., and Adams, R. D. (1955). *J. exp. Med.*, **102**, 213.
 Wolf, A. (1952). *1st int. Congr. Neuropath. Rome, 1952*, **1**, 121.

LYMPHADENOID GOITRE (HASHIMOTO'S DISEASE)

DIAGNOSTIC AND BIOCHEMICAL ASPECTS

BY

DEBORAH DONIACH, M.D.

Thyroid Research Assistant, Institute of Clinical Research

AND

R. VAUGHAN HUDSON, F.R.C.S.

Middlesex Hospital, London, W.1

In most cases the diagnosis of lymphadenoid goitre is first made by the pathologist after thyroidectomy (Statland *et al.*, 1951; Lindsay *et al.*, 1952). Clinically, this type of goitre may be confused with "simple" non-toxic goitre; but thyroid carcinoma is often suspected because of the firm texture of the gland, leading the surgeon to undertake total thyroidectomy, with the attendant risk of post-operative tetany and vocal-cord paralysis. Since lymphadenoid goitres are non-malignant and many respond to thyroxine administration, it is important to establish the diagnosis pre-operatively.

The clinical picture has already been fully described (Joll, 1939; Schilling, 1945; Statland *et al.*, 1951; Lindsay *et al.*, 1952; Blake and Sturgeon, 1953). In diagnosis much help can be obtained with radioactive iodine (^{131}I) tracer tests combined with basal metabolic rate (B.M.R.) and serum cholesterol estimation; the changes in serum protein pattern which occur are also of diagnostic value.

We report here various tests with ^{131}I on 28 patients with Hashimoto's disease, and biochemical studies in which the serum protein abnormalities before and after treatment with thyroid hormones were observed and correlated with the state of thyroid activity in 11 of the patients (Table I). Serum protein studies were also made in 25 cases previously subjected to thyroidectomy for Hashimoto's struma, and in two control series consisting of 25 patients with other types of goitre and 8 myxoedematous patients without goitre.

Clinical Features

The group tested with ^{131}I consisted of 26 women and two men aged 28–68 (mean 52 years) who had noticed the goitre a few weeks to 15 years previously. There was a history of thyrotoxicosis in one case, but most patients presented with a feeling of pressure in the neck and symptoms suggesting hypothyroidism (17 of the 28). Thyroid pain was present in four cases. All the goitres were firm, of uniform consistency, and involved the entire gland, the enlargement

being mostly symmetrical and thyroid-shaped with well-delineated upper poles and pyramidal lobe; but in five cases the swelling was predominantly unilateral, and in three others the gland had a nodular surface. Histological proof of lymphadenoid goitre is available in 12 cases, the diagnosis in the remainder being based on clinical findings and investigations and the subsequent shrinkage of the goitre on administration of thyroid hormones.

Five cases are described, two to illustrate atypical clinical features suggestive of subacute thyroiditis, and the other three for the detailed investigations.

Illustrative Cases

Case 1

E. M., housewife aged 43. May, 1953, rapid swelling of thyroid, with increasing tenderness and throbbing, four weeks after onset of stomatitis and gingivitis associated with removal of septic teeth, symptoms reaching a maximum within next two months, with general lassitude and pain radiating to ears and back of head, accompanied by feeling of pressure in neck. September, 1953, thyroid estimated three to four times normal size, right lobe large, firm, and tender, left lobe softer and smaller. Gingivitis still present, with enlarged, tender lymph nodes in neck. Skin cool, no tremor. T. 98° F. (36.7° C.), P.R. 70, B.P. 140/65 mm. Hg. W.B.C. 5,300 per c.mm. E.S.R. 49 mm. (Wintrobe). ^{131}I uptake 72% in 24 hours, with thyroid-shaped distribution showing uptake over area of maximum swelling and pain. Swelling gradually subsided without thyroid medication, reaching almost normal size in December, 1953, though gland still firm and tender. Repeat ^{131}I uptake 69%; E.S.R. 48 mm.; B.M.R. –26%. Partial thyroidectomy performed in view of persistent pain and pressure symptoms; weight of gland 20 g. Histology, lymphadenoid goitre.

Case 2

Y. C., housewife aged 56. On admission: three weeks' painful, firm thyroid swelling, more marked on right, with feeling of pressure. B.M.R. –10%. Serum cholesterol 233 mg. per 100 ml. E.S.R. 77 mm. (Westergren). Plasma proteins: total 8.25 g. per 100 ml. (albumin 4.45 g., globulin 3.8 g., gamma globulin 2.3 g.). Thymol turbidity 15 units; alkaline phosphatase 4.2 units; bilirubin 0.12 mg. per 100 ml. ^{131}I uptake 65%, urine excretion 13%, in 24 hours. Topography showed bilateral uptake with maximum over tender right lobe. Within two weeks pain subsided and swelling diminished. ^{131}I uptake three months later, 52% in 24 hours. Owing to persistent discomfort and patient's fear of cancer, subtotal thyroidectomy performed five months after onset of goitre; weight of gland 42 g. Histology, lymphadenoid goitre.

Comment.—Clinically, Cases 1 and 2 suggested either haemorrhage into a thyroid cyst or subacute thyroiditis. The tender, firm goitre and the raised E.S.R. were thought to indicate thyroiditis (Blake and Sturgeon, 1953). Iodine uptake is usually completely suppressed in the acute stage of de Quervain's thyroiditis (McConahey and Keating, 1951; Crile, 1952; Fraser and Harrison, 1952), but a raised uptake has been reported in the recovery stage (Freedberg *et al.*, 1952; Trunnell, 1955) and is thought to be a rebound phenomenon. Our patients were tested some time after the onset of illness, and this delay was thought to explain their high iodine uptake. The distribution of ^{131}I was unlike that in thyroid cyst or carcinoma. The other atypical feature was the fairly rapid onset and the subsequent recession of the goitre without treatment.

Case 3

J. C., housewife aged 38. Goitre since 1947, with attacks of neck pain since 1948 and increasing lassitude since 1950. When seen in 1953 there was a large, firm, horseshoe-shaped goitre. B.M.R. –18%. ^{131}I uptake 66% in 24 hours, with symmetrical distribution. Treated with thyroid, 2–3 gr. (0.13–0.2 g.) daily, with return of normal energy and reduction in size of goitre to less than half. Twice stopped taking

thyroid for two to four months, with prompt return of symptoms and increase in goitre. Results of serum protein estimations are shown in Table I. In February, 1956, following exacerbation of neck pain with enlargement of goitre in spite of continuous thyroid medication, operation decided on to establish diagnosis with more certainty. Tracer tests repeated pre-operatively showed neck uptake of ^{131}I 20%

FIG. 1.—Case 3: Cut surface of thyroid gland.

FIG. 2.—Case 3: Contact autoradiograph from 10 μ section of gland.

FIG. 3.—Case 3: Histological autoradiograph (S. R. Pelc) showing uptake of ^{131}I in colloid of scattered thyroid follicles.

in 24 hours (thyroxine suppression), biological half-life (B.H.L.) 2.8 days; 48-hour plasma ^{131}I 0.41% of dose per litre; protein-bound fraction 72% of total. B.M.R. —26%. Weight of thyroid removed, 80 g. Histology, lymphadenoid goitre. (Figs 1–3.)

Comment.—Pain is uncommon in Hashimoto's disease, and all four cases in which it was present had a greater iodine uptake than is usual, yet were indistinguishable histologically from cases without this symptom. We have noticed that patients often complain of aching in the thyroid after T.S.H. injections, and that tenderness also occurs in thyrotoxic patients overtreated with antithyroid drugs and whose goitre has enlarged owing to endogenous T.S.H. overproduction; medicinal goitres in which the enlargement is equally due to T.S.H. overproduction have also been reported to be occasionally painful (Breidahl and Fraser, 1955). In view of the evidence of T.S.H. overstimulation in Hashimoto goitres, it is conceivable that pain may be connected with a rapid hypertrophy of glandular elements and lymphoid invasion with resulting intracapsular tension in these firm glands.

Case 4

G. L., housewife aged 59. Two years' painless goitre with 6–12 months' slowing down, hoarseness, paraesthesiae of hands, puffiness of face. Clinically hypothyroid with large, firm, symmetrical goitre showing prominent pyramidal lobe. B.M.R. —8%. Serum cholesterol 380 mg. per 100 ml. ^{131}I uptake 63%. Plasma clearance rate at one hour, 29 ml. per minute. 48-hour plasma ^{131}I , 0.32% of dose per litre; B.H.L. 8.5 days. Potassium perchlorate, given one hour

FIG. 4.—Case 4: Electrophoretic pattern of serum proteins, obtained by scanning of paper strip. A, Initial pattern before operation, showed raised gamma-globulin fraction. B, Four and a half months after operation, showing return of protein pattern to normal after removal of thyroid.

after a dose of ^{131}I to test protein-binding capacity of gland, produced a fall in neck uptake from 32% to 25%. Serum protein estimations are shown in Table I. Treated with thyroid, 2 gr. (0.13 g.) daily, but, as goitre was no smaller after two months, operation undertaken for pressure symptoms. Thyroid weight 165 g. Histology, lymphadenoid goitre with marked fibrosis. Four and a half months after operation serum protein pattern and flocculation tests returned to normal values.

Case 5

N. E., housekeeper aged 60. Eighteen months' increasing myxoedema; goitre noticed last three months. Firm, rubbery, diffuse enlargement of thyroid, estimated $2\frac{1}{2}$ times normal size. B.M.R. —22%. Serum cholesterol 170 mg. per 100 ml. ^{131}I uptake 44%, excretion 32%, in 24 hours. Plasma clearance rate, 25 ml. per minute; 48-hour plasma activity, 0.4% per litre; protein-bound fraction, 65% of total. B.H.L. 12 days. No increase in iodine uptake after 5 units of T.S.H., suggesting impaired thyroid reserve. Goitre decreased on thyroid medication.

TABLE I—Differential Serum Protein Estimations and Liver Function Tests in Hashimoto's Disease

Patient	Sex and Age	Duration of Thyroid Treatment (2-3 gr. Daily) (Months)	Serum Cholesterol (mg. per 100 ml.)	E.S.R. (Wintrobe) Cor. to P.C.V. of 45% (mm. in 1 Hour)	Serum Proteins*										Liver Function Tests					Clinical Details and Thyroid Function
					Total Proteins (g. per 100 ml.)	Albumin (g. per 100 ml.)	Globulins				Alpha ₁ (g. per 100 ml.)	Alpha ₂ (g. per 100 ml.)	Beta (g. per 100 ml.)	Gamma (g. per 100 ml.)	Colloidal Gold (Units)	Thymol Turbidity (Units)	Zinc Sulphate (Units)	Cephalin-Cholesterol (Units)	Alkaline Phosphate (Units)	Serum Bilirubin (mg. per 100 ml.)
							%	%	%	%	%	%	%	%						
J. C. (Case 3)	F 38	20	—	34	6.9	2.95	42.6	0.14	2.0	0.69	10.0	0.83	12.0	2.30	2	9	—	3	5.2	<0.4
		30	—	42	6.9	2.35	34.0	0.21	2.9	1.06	15.3	1.28	18.5	2.90	3	15	—	3	6.5	<0.4
		31	—	39	6.9	2.95	42.6	0.17	2.6	0.72	10.3	0.76	11.0	2.30	5	8	—	3	—	—
		2½ post-op.	190	28	7.9	3.73	47.1	0.14	1.8	0.77	9.8	1.00	12.7	2.26	2	7	15	3	5.6	<0.4
G. L. (Case 4)	F 59	8 post-op.	—	16	6.5	3.03	46.6	0.04	0.7	0.68	10.6	1.20	18.3	1.55	1	3	10	—	—	—
		0	380	40	8.2	3.80	46.5	0.12	1.5	0.76	9.3	0.73	8.7	2.80	5	14	—	4	4.2	<0.4
		2	220	37	7.7	2.32	32.7	0.13	1.7	1.32	17.1	1.23	16.0	3.50	4	17	—	3	3.4	—
		1½ post-op.	500	32	7.1	2.63	32.1	0.17	2.4	1.00	14.0	1.15	16.2	2.15	3	10	12	2	—	—
D. L.	M 68	3 post-op.	250	18	7.2	4.00	62.2	0.13	2.0	0.65	10.2	0.84	13.2	0.78	1	7	15	3	5.4	<0.4
		4 post-op.	200	16	6.4	—	—	—	—	—	—	—	—	—	—	3	12	—	—	—
		0	300	36	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
		3	140	40	7.5	2.98	39.6	0.19	2.1	0.64	8.5	0.59	7.9	3.10	—	30	—	—	5.8	<0.4
D. G.	F 43	13	—	25	—	—	42.0	—	2.4	Test unsuccessful	12.2	—	—	29.6	5	30	—	4	—	<0.4
		16	160	28	—	—	—	—	—	—	—	—	—	—	2	9	14	3	15.3	<0.4
		20	210	30	6.8	3.04	44.6	0.13	1.9	0.88	13.0	0.94	13.9	1.81	4	8	14	4	4.9	<0.6
		0	380	33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C. F.	F 52	6	290	28	6.4	2.70	43.4	0.32	5.2	0.72	11.7	0.90	14.6	1.56	—	—	—	—	6.3	<0.4
		11	280	21	6.2	3.10	48.3	0.17	2.9	0.69	10.8	0.74	17.3	2.51	1	5	—	3	9.8	<0.4
		15	—	18	6.9	3.14	45.2	0.22	3.2	0.91	13.2	1.17	17.0	1.46	3	6	12	3	—	<0.4
		18	—	29	7.9	3.38	42.8	0.36	4.6	1.16	14.7	1.30	16.4	1.70	1	4	13	3	—	<0.4
E. N.	F 50	0	470	—	6.5	3.39	52.0	0.09	1.4	0.19	3.1	0.68	10.5	2.15	Not done	8	10	—	Normal	—
		19	292	—	—	—	—	—	—	—	—	—	—	33.0	3	6	13	4	—	—
F. S.	F 38	0	400	24	8.9	3.97	44.6	0.16	1.8	0.56	6.3	1.10	12.3	3.11	5	20	44	4	3.3	<0.4
		0	140	14	6.4	3.33	52.0	0.21	3.1	0.57	9.0	0.72	11.3	1.57	3	7	14	3	3.0	—
L. S.	F 45	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
		3	220	32	6.3	2.58	41.0	0.25	4.0	0.75	12.0	0.72	11.5	2.00	—	—	—	—	—	—
		4	290	37	7.7	2.50	32.1	0.30	4.1	0.97	12.8	1.16	15.0	2.77	5	14	—	3	3.7	<0.4
		9	—	38	6.3	2.57	40.8	0.21	3.4	0.86	13.7	0.64	10.1	2.02	4	9	—	3	3.4	<0.4
L. L.	F 64	12	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
		15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
		18	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
		21	—	—	7.2	3.07	42.7	0.21	3.0	0.75	10.4	1.00	13.9	2.17	5	10	22	4	2.6	—
L. L.	F 64	4	—	30	6.7	2.70	42.0	0.17	2.4	0.62	9.3	0.95	14.2	2.26	3	9	—	3	13.1	<0.4
		12	—	18	—	—	45.4	0.12	2.5	0.86	12.8	—	17.4	—	3	6	—	2	12.1	<0.4
		15	—	19	6.7	2.97	44.2	0.12	1.8	0.86	12.8	1.07	16.1	1.68	3	6	—	2	—	—
		21	—	—	7.2	3.07	42.7	0.21	3.0	0.75	10.4	1.00	13.9	2.17	4	7	13	3	—	—

TABLE I—continued

Patient	Sex and Age	Duration of Thyroid Treatment (2-3 gr. Daily) (Months)	Serum Cholesterol (mg. per 100 ml.)	E.S.R. (Wintrobe) (mm. in 1 Hour)	Serum Proteins*										Liver Function Tests					Clinical Details and Thyroid Function		
					Total Proteins (g. per 100 ml.)	Albumin		Globulins						Thymol Turbidity (Units)	Zinc Sulphate (Units)	Cephalin-Cholesterol (Units)	Alkaline Phosphatase (Units)	Serum Bilirubin (mg. per 100 ml.)				
								Alpha ₁			Alpha ₂		Beta						Gamma			
								g. per 100 ml.	%	g. per 100 ml.	%	g. per 100 ml.	%						g. per 100 ml.		%	
I. R.	F 52	1 10	190 —	17 23 —	6.7 — 7.2	2.54 —	37.8 45.7	0.30 —	4.1 2.8	0.86 —	12.4 13.5	1.00 —	15.6 15.0	2.00 —	29.7 22.5	2 2 2	— — 13	1 3 4	12.2	0.4	Goitre and slowing down B.M.R. +1. 131I uptake 37%. Firm, uniform goitre about 40-50 g. Improved on thyroid	
I. S.	F 49	24 30	— —	38 27	7.7 6.7	2.70 2.83	35.1 42.2	0.25 0.35	3.3 5.2	0.89 0.79	11.6 11.8	1.49 1.07	19.3 16.1	2.37 1.66	30.7 24.7	2	—	3	—	—	Goitre since Jan., 1951. Lost 1 lb. weight. B.M.R. +33. 131I uptake 41%. Goitre decreased with thyroid gr. 2 daily	

* The serum proteins were fractionated by paper electrophoresis after the method of Flynn and de Mayo; the strips were stained with azocarmine B and graphs made with a recording reflectance scanner (Joyce and Loebel). The patterns obtained were cut up into their five component peaks and the area of paper corresponding to each was weighed to 0.1 mg. and expressed as a percentage of the total area. The total serum proteins were estimated by the biuret method; from this and the percentages obtained by scanning, the protein fractions were calculated in g. per 100 ml. Electrophoretic strips and flocculation tests were carried out in the routine laboratory of the Courtauld Institute.

TABLE II—Average Values and Range of Serum Protein Fractions and Liver Function Tests

Serum Proteins (Paper electrophoresis)										Liver Function Tests†						
Groups	Total Proteins (g. per 100 ml. Biuret Method)	Albumin		Globulins						Colloidal Gold (Units) Normal <2	Thymol Turbidity (Units) Normal <5	Zinc Sulphate Turbidity (Units) Normal <12	Cephalin-cholesterol (Units) Normal <3	Alkaline Phosphatase (Units) Normal <15	Serum Bilirubin (mg. per 100 ml.) Normal <0.4	
		g. per 100 ml.	%	Alpha ₁		Alpha ₂		Beta								Gamma
				g. per 100 ml.	%	g. per 100 ml.	%	g. per 100 ml.	%							
Hashimoto goitre* (11 cases; av. age 50.1 years)	7.0 (6.2-8.9)	3.01 (2.35-3.97)	42 (32.1-52.0)	0.2 (0.09-0.36)	2.8 (1.4-5.2)	0.79 (0.2-1.3)	11.5 (3.1-17.1)	0.96 (0.59-1.49)	14.3 (7.9-17.4)	2.13 (1.46-3.11)	29.3 (21.1-41.4)	15.9 (10-44)	3 (1-4)	6.7 (2.6-15.3)	<0.4 (highest 1.0)	
Hashimoto goitre: post-thyroidectomy (25 cases; av. age 55.1 years)	6.8 (5.6-8.7)	3.33 (1.85-4.4)	48.7 (33.1-62.2)	0.21 (0.08-0.3)	2.6 (1.2-4.7)	0.95 (0.3-1.94)	12.8 (3.8-28.5)	1.08 (0.65-1.77)	15.8 (10.0-26.4)	1.5 (0.78-2.97)	21.8 (12.2-35.2)	9.5 (2-29)	2.2 (1-4)	5.8 (2.5-16)	<0.4 (highest 0.9)	
Controls: Euthyroid and hyperthyroid (25 cases; av. age 40.4 years)	6.55 (5.2-7.6)	3.39 (2.3-5.2)	51.1 (37.7-70.0)	0.17 (0.08-0.39)	2.6 (1.2-5.4)	0.73 (0.34-1.49)	11.4 (1.8-22.5)	1.01 (0.48-1.7)	15.5 (8.4-23.6)	1.22 (0.67-1.56)	19.1 (10.9-24.4)	5.5 (3-11)	2 (1-4)	4.1 (2.5-6.3)	<0.4 (highest 0.8)	
Myxoedematous (8 cases; av. age 55 years; av. B.M.R. -30%)	6.9 (6.2-8.1)	3.2 (2.61-4.18)	44.7 (34.0-56.6)	0.26 (0.18-0.55)	3.6 (2.3-7.7)	0.83 (0.61-1.34)	12.5 (9.1-18.6)	1.18 (0.85-1.46)	17.9 (12.2-23.5)	1.4 (1.11-1.83)	21.1 (16.8-27.0)	7.5 (5-10)	2.4 (1-3)	—	—	

* Results in this group represent the average of 26 tests done on 11 patients.

† Results of flocculation tests are not usually expressed in fractions of units; these averages were calculated for comparison of the four groups.

‡ Zinc sulphate test carried out on only 14 patients and alkaline phosphatase on 16 patients in the control group.

Results of Radioactive Iodine Tests

Fig. 5 shows the thyroid ^{131}I uptake and B.M.R. in the 28 patients tested; 24-hour uptake varied between 19% and 73% and B.M.R. between -29% and +3%, the mean being -16% as compared with -5% in normal subjects (Aub du Bois, normal range -20 to 0).

FIG. 5.—Twenty-four-hour neck uptake of ^{131}I and B.M.R. in 28 patients with untreated lymphadenoid goitre.

B.M.R. with the size of the goitre in our patients. Isotope distribution was invariably uniform and followed the outline of the goitre, the uptake being greater on the side of the larger lobe in asymmetric goitres.

In patients investigated more fully the results illustrate the functional behaviour of the thyroid in this condition. The biological half-life was short and varied between 2.8 and 12 days; 48-hour plasma activity was 0.39%, 0.41%, 0.32%, and 0.4% of the dose per litre in four patients tested, 65–75% of the total being protein-bound. These results are high, especially in view of the low B.M.R.s in these cases. Five units of T.S.H. had no effect on iodine uptake in a case of Hashimoto's disease, whereas the same dose in normal subjects increased the three- and six-hour readings two- to three-fold. Potassium perchlorate, 400 mg., caused the neck uptake to fall by 22% in 30 minutes, the drug having no effect in normal or thyrotoxic patients under the same conditions.

In Case 3, in which 800 microcuries of ^{131}I had been given 48 hours pre-operatively, direct analysis of the extirpated gland, using combined isotope and chromatography techniques (Mrs. R. Pitt-Rivers), showed only 12% of the total iodine stored as thyroxine, whereas a normal gland analysed by the same method contained 24.3% of thyroxine iodine. Figs. 2 and 3 show the macroscopic and histological autoradiographs of this gland; the isotope was taken up in fairly evenly scattered small foci, which explains why topographical surveys *in vivo* produce isocount pictures which follow the outline of the palpable goitre in Hashimoto's disease. The histological autoradiograph shows protein-bound iodine in the colloid of some follicles, none being present in the many clumps of epithelial cells devoid of colloid.

Biochemical Results

Serum protein studies were first undertaken to explain the consistently raised E.S.R. in Hashimoto's disease; a rise in gamma globulins was found, though total and differential serum proteins appeared normal in most cases when estimated by the conventional biuret method. Results of flocculation tests of liver function which depend on the relative concentrations of globulins and albumin were also abnormal, though none of the patients had a history or symptoms of liver disease. Since these studies were started, other reports of similar findings in lymphadenoid goitre have appeared. Table I shows the results in 11 cases of Hashimoto's disease; the rise in gamma globulins is still present after 2½ years of thyroid medication in some cases, but returned

to normal 4½ months after removal of the goitre in one case (Fig. 5) and after 8 months in another. The mean value for gamma globulins in these 11 cases was 2.13 g. per 100 ml. (29.3% of total protein). Table II shows the corresponding figures in the other three groups of patients tested.

The two control groups consisted of (1) 25 euthyroid and hyperthyroid patients, 21 with "simple" non-toxic goitre, and 4 with untreated Graves's disease; and (2) 8 cases of primary or secondary myxoedema, in view of the possible influence of thyroid deficiency on the gamma globulins. In the first group the average gamma globulin level was 1.22 g. per 100 ml. (19.1%). Results of flocculation tests were: colloidal gold "negative" in 19 patients, 1 unit in four, and 2 units in two patients. For thymol turbidity the highest value obtained was 4 units (5 cases); zinc sulphate turbidity ranged between 3 and 11 units. Group 2 had an average gamma globulin level of 1.4 g. per 100 ml. (21.1%) and normal flocculation values, except for one patient who had a thymol turbidity of 7 units with a colloidal gold of 2 units.

The post-operative group consisted of 25 proved cases of Hashimoto's disease thyroidectomized 6 months to 22 years previously, collected from the records of the Middlesex Hospital. The mean value for gamma globulins in this group was 1.5 g. per 100 ml. (21.8%). The colloidal gold test was "negative" in 15 cases, 1 unit in five, 2 units in one, 3 units in two, and 4 and 5 units in one case each. All the patients with negative colloidal gold results and five with colloidal gold of 1–3 units also had normal values for the other flocculation tests, except one with a thymol turbidity of 7 units, a zinc sulphate of 14 units, and gamma globulin 1.9 g. per 100 ml. This patient had had a hemithyroidectomy two years previously and still had an enlarged left thyroid lobe. Three other patients in this group had markedly raised gamma globulins and flocculation results, one of them (Case 2 described above) having gamma globulins 2.97 g. per 100 ml., colloid gold 5 units, thymol turbidity 12 units, and zinc sulphate turbidity 29 units, three years after partial thyroidectomy.

Table II further shows that the other globulin fractions do not differ significantly in the four groups, and that the gamma globulins appear to be raised at the expense of the albumin fraction in cases of Hashimoto's disease.

Discussion

Radio-iodine Studies

The ^{131}I studies in patients with lymphadenoid goitre show a normal or high thyroid uptake, even in the presence of clinical myxoedema and a low B.M.R., and a uniform distribution of iodine which follows the outline of the palpable swelling. These characteristics help to distinguish lymphadenoid goitre from non-toxic nodular and from malignant goitres. In non-toxic nodular goitre the ^{131}I distribution is uneven and the isocount picture rarely portrays the shape and extent of the goitre. In malignant goitres and thyroid cysts the uptake is usually diminished or absent over the affected side, and the over-all uptake is never high unless the patient also shows signs of hyperthyroidism.

The more detailed studies carried out in four clinically subthyroid patients show a relatively high 48-hour plasma activity and a short B.H.L. compared with the normal, which was 55 to 106 days in four subjects studied by Hickey and Brownell (1954) and varied between 30 and 180 days in ten cases of non-toxic colloid goitre studied by us. These results suggest that in lymphadenoid goitre there is a small thyroidal iodine pool with a high specific activity. The same feature is often found in carcinoma of the thyroid, but here the isotope is localized to a small remnant of normal but overstimulated tissue (Rotblat and Owen, 1954). The lack of response to T.S.H. has also been reported by other workers (Levy *et al.*, 1955; Skillern *et al.*, 1956), and supports the histological evidence of T.S.H. overstimulation of the gland in Hashimoto's disease: the small number of intact follicles work at full capacity and cannot be further

stimulated. Protein-binding of iodine does not appear to proceed at a normal rate as shown by the perchlorate test. Dr. W. R. Trotter (personal communication), who suggested the test to us, has obtained similar results in other cases of lymphadenoid goitre. In health and in thyrotoxicosis protein-binding is so rapid and complete that no unbound iodide can be released, and neck readings continue to rise after giving perchlorate (Berson and Yalow, 1955). Direct analysis of the gland indicates that thyroxine storage is defective in Hashimoto's disease, since the percentage of thyroxine iodine was only half the normal in our patient.

Biochemical Studies

The first report of the occurrence of raised gamma globulins in Hashimoto's disease appeared in 1953, when Fromm *et al.* published differential protein estimations in four cases of this disease and one case each of de Quervain's and Riedel's thyroiditis. In three of their cases of Hashimoto's disease the gamma globulins were over 2 g. and in the other cases between 1.66 and 1.83 g. per 100 ml. Cooke and his colleagues (Cooke and Wilder, 1954; Cooke and Luxton, 1955; Luxton and Cooke, 1956) have reported abnormal colloidal gold curves in Hashimoto's disease. Observing patients on prolonged thyroid medication, they found that with adequate dosage the liver-function tests tended to return to normal, though the reversal was usually slow and took up to 29 months. At their suggestion an extensive study was made at the Cleveland Clinic, and the results (Skillern *et al.*, 1956) confirm and extend previous observations.

Our findings similarly show the presence of raised gamma globulins and flocculation values in untreated lymphadenoid goitre, and it appears that the larger goitres were associated with the most striking changes in electrophoretic pattern, though the flocculation tests were also abnormal in patients with small lymphadenoid goitres whose gamma globulins were still within the normal range.

The thymol, colloidal gold, and zinc tests usually gave concordant results, though in a few instances the colloidal gold results disagreed with the other flocculation reactions and with the electrophoretic strip. The cephalin-cholesterol test proved least useful and gave the same results in simple goitre, thyrotoxicosis, myxoedema, and Hashimoto's disease, which was to be expected, since the test is more influenced by the beta-globulins than by those in the gamma fraction. The E.S.R. was always raised in Hashimoto's disease, but is so unspecific (Meyers *et al.*, 1953) that it was not infrequently raised in the control groups when all other tests were normal. In three cases of thyroid carcinoma so far tested we have found normal gamma globulins and flocculation tests. In one of the cases the goitre was uniform, the B.M.R. in the hypothyroid range, and the E.S.R. very high. Normal serum protein values and a unilateral iodine uptake decided in favour of thyroid carcinoma, and this was proved at operation.

Myxoedema is often associated with a raised E.S.R. (McAlpine, 1955) and sometimes with a rise in total serum proteins. The electrophoretic pattern did not show increased gamma globulins in our myxoedematous controls, though some had a raised beta fraction, as expected in the presence of high serum lipids.

Our post-operative survey shows that serum proteins are normal in most cases of Hashimoto's disease after removal of the goitre, and in two cases we have actual proof of this change from high pre-operative gamma globulins to normal values after operation. There was a lag of several months before this reversal took place, for three patients tested 10 days, 2½ months, and 3½ months post-operatively still had abnormal results.

It appears, therefore, that the abnormal gamma globulins are closely associated with the presence of the goitre, and we are unable to agree with Skillern *et al.* that they are entirely due to thyroid deficiency, since abnormal results were seen in patients who were euthyroid and had received more than physiological doses of thyroxine for over two years.

It is well known that gamma globulins are the serum protein fraction mainly associated with antibodies; moreover, the thyroid is grossly infiltrated with lymphoid tissue and plasma cells in Hashimoto's disease, and these cells have been shown to produce gamma-globulin antibodies elsewhere in the body (Harris and Harris, 1956). It is possible that a qualitative alteration of thyroid proteins or other special circumstances could provoke the formation of auto-antibodies. The presence of an antigen in the thyroid would explain the accumulation of antibody-producing cells in the gland and the enlargement of surrounding lymph nodes. If the antigenic protein escaped from the gland by breakdown of follicles, antibody production could also occur at other sites, which would account for the large quantity of gamma globulin produced and for the lag period in their disappearance after operation, since when the source of antigen is removed at thyroidectomy there might be some delay in the cessation of antibody production by the reticulo-endothelial system.

Summary

The pre-operative diagnosis of lymphadenoid goitre can now be made by a combination of ¹³¹I tracer tests with the older tests of thyroid function and the addition of serum protein tests made available by the recent finding of increased gamma globulins in the serum in Hashimoto's disease, which, in the absence of liver disease, give rise to abnormal results of flocculation tests.

Five cases of lymphadenoid goitre are described, two which were clinically atypical and suggested subacute thyroiditis, and three studied in some detail with ¹³¹I and biochemically.

¹³¹I tests in 28 cases of Hashimoto's disease showed normal or high uptakes even in the presence of myxoedema, and a uniform distribution of isotope corresponding with the outline of the goitre. Short biological half-life and high plasma activity suggest a small thyroidal iodine pool, other tests providing further evidence of deficient protein-binding and thyroxine storage in this type of goitre.

Liver function tests and differential serum protein estimations were carried out in 11 cases of Hashimoto's disease with 25 cases of other goitres and 8 of myxoedema as controls, and a post-operative group of 25 cases of Hashimoto's disease tested in order to study the effect of removal of the goitre on the serum proteins. The findings suggest that paper electrophoresis in combination with flocculation tests provide diagnostic help and distinguish lymphadenoid goitre from simple non-toxic goitre and from carcinoma of the thyroid. Results obtained in the post-operative survey suggest that removal of the goitre is associated with a return to normal of the gamma globulins.

It is put forward as a working hypothesis that the raised serum gamma globulins represent an immune response to an antigen released by the goitre.

This investigation was in part supported by a grant from the Clinical Research Fund of the Middlesex Hospital.

We are grateful to Professor Sir Charles Dodds and his staff at the Courtauld Institute of Biochemistry for their untiring co-operation in these investigations, and to Professor J. E. Roberts and his staff for the isotope tests. Fourteen of the isotope tests were carried out by one of us during tenure of a research scholarship at the Royal Free Hospital. Our thanks are due to Miss G. Barry, senior surgeon, and to Mr. H. S. Williams, hospital physicist; to the surgeons of the Middlesex Hospital who allowed us to test the post-operative patients; to Dr. R. P. K. Coe for permission to quote case C.F., and Dr. W. R. Trotter for case E.N.; to Mrs. R. Pitt-Rivers for her analyses; and to Dr. S. Pelc for the histological autoradiographs. We are particularly

grateful to Dr. E. T. Knudsen and Mr. C. F. M. Rose for their help and advice, and to Dr. K. M. Jones for his interest, co-operation, and assistance in the analysis of the radio-iodine tests.

ADDENDUM

Since this paper was submitted, immunological studies have shown that the serum of patients with Hashimoto's disease contains a precipitating auto-antibody which reacts specifically with human thyroglobulin. A preliminary communication of this work has appeared (Roitt *et al.*, 1956). The thyroglobulin precipitin test was positive in all the patients listed in Table I and in several from the post-operative group where only part of the thyroid had been removed; Case 3 and Case 4 still show the precipitin nine and twelve months after subtotal thyroidectomy, though results of serum protein tests are now normal. Case 5 has failed to show precipitins by the method used after 3 years of thyroid administration. Full results will be published elsewhere.

REFERENCES

- Berson, S. A., and Yalow, R. S. (1955). *J. clin. Invest.*, **34**, 186.
 Blake, K. W., and Sturgeon, C. T. (1953). *Surg. Gynec. Obstet.*, **97**, 312.
 Breidahl, H., and Fraser, R. (1955). *Proc. roy. Soc. Med.*, **48**, 1026.
 Cooke, R. T., and Luxton, R. W. (1955). *Lancet*, **1**, 968.
 — and Wilder, E. (1954). *Ibid.*, **1**, 984.
 Crile, G., jun. (1952). *Ann. intern. Med.*, **37**, 519.
 Fraser, R., and Harrison, R. J. (1952). *Lancet*, **1**, 382.
 Freedberg, A. S., Chamovitz, D. L., and Kurland, G. S. (1952). *Metabolism*, **1**, 36.
 Fromm, G. A., Lascano, E. F., Bur, G. E., and Escalante, D. (1953). *Rev. Asoc. méd. argent.*, **67**, 162.
 Harris, T. N., and Harris, S. (1956). *Amer. J. Med.*, **20**, 114.
 Hickey, F. C., and Brownell, G. L. (1954). *J. clin. Endocr.*, **14**, 1423.
 Joll, C. A. (1939). *Brit. J. Surg.*, **27**, 351.
 Levy, R. P., Kelly, L. W., and Jeffries, W. McK. (1955). *Amer. J. med. Sci.*, **231**, 61.
 Lindsay, S., Dailey, M. E., Friedlander, J., Yee, G., and Soley, M. H. (1952). *J. clin. Endocr.*, **12**, 1578.
 Luxton, R. W., and Cooke, R. T. (1956). *Lancet*, **2**, 105.
 McAlpine, S. G. (1955). *Ibid.*, **2**, 58.
 McConahey, W. M., and Keating, F. R. (1951). *J. clin. Endocr.*, **11**, 1116.
 Meyers, A. J., Trevorow, V., Washburn, A. H., and Mugrage, E. R. (1953). *Blood*, **8**, 893.
 Roitt, I. M., Doniach, D., Campbell, P. N., and Hudson, R. V. (1956). *Lancet*, **2**, 820.
 Rotblat, J., and Owen, G. M. (1954). Radioisotope Conference. Vol. I, page 68.
 Schilling, J. A. (1945). *Surg. Gynec. Obstet.*, **81**, 533.
 Skillern, P. G., Crile, G., McCullagh, E. P., Hazard, J. B., Lewis, L. A., and Brown, H. (1956). *J. clin. Endocr.*, **16**, 35.
 Statland, H., Wasserman, M., and Vickery, A. L. (1951). *Arch. intern. Med.*, **88**, 659.
 Trunnell, J. B. (1955). *Trans. Amer. Goiter Ass.*, p. 453.

VISCERAL LESIONS IN HERPES ZOSTER

BY

R. WYBURN-MASON, M.A., M.D.

The peripheral nerves and posterior and trigeminal sensory nerve roots contain not only various sizes of myelinated, but also unmyelinated "afferent" fibres. Distally the afferent unmyelinated fibres originate (or end) as free nerve endings not only in the epidermis or dermis, but also between the deeper tissues, including muscles, periosteum, joints, and fascia (Ranson and Davenport, 1931; Feindel, Weddell, and Sinclair, 1948). They also arise (or end) on the blood-vessel walls. Some of them are visceral in origin (Kuntz and Hamilton, 1938). All the evidence suggests that in the somatic tissues these fibres conduct impulses which give rise to diffuse, radiating, compelling burning pain (see Fulton, 1949).

In the posterior nerve roots all the afferent unmyelinated fibres of the peripheral nerves, whether they originate in the skin, deep somatic tissues, blood vessels, or viscera, are grouped together laterally. Division of the lateral part of these roots cuts the unmyelinated fibres, and now on stimulation of the peripheral nerve

distal to the section no autonomic reflex changes occur as they do in intact animals (Ranson and Davenport, 1931; Clark, Hughes, and Gasser, 1935).

Mode of Production of Lesions of Herpes Zoster

The skin lesions of herpes zoster lie in the area of sensory supply of the posterior and trigeminal nerve roots. They manifest themselves firstly as a reddening of the skin followed by oedema and blister formation—that is, the appearance of fluid between the epidermal layers. Typical inflammatory changes are found in the skin papillae, in the deeper parts of the corium, and in the hair follicles. Subcutaneous fat may also contain knots of inflammatory cells. Lewis (1927), in his classical researches, showed that irritation of sensory nerves and the posterior nerve roots results in vasodilatation and the release of a vasodilator substance (H-substance), probably histamine, in the skin. He further demonstrated that in cases of herpes zoster the same substance was released in the affected tissues and that "herpetic and herpetiform eruptions occur as sequels to lesions of the sensory nerve tracts; not only do they follow irritative lesions of the (root) ganglion, but they are produced also by lesions of those tracts distal to the ganglia themselves." It seems probable that the unmyelinated fibres of the posterior roots with free nerve endings in the skin and other tissues and on the blood vessels are those concerned.

Herpes Zoster and Lesions of Deep Somatic Tissues

When zoster is of gangrenous type the lesions extend deeply and lead to much scarring. Glandular swelling and inflammation in the region of the affected skin lesions is usual and may precede the latter (Bichelon, 1907; Lebel, 1920; Ramond, 1923), so that they cannot be due to secondary infection of the skin. The subcutaneous tissues, fat, and muscles may contain painful and swollen areas identical in character with "fibrositis" and "myositis" (see Brain, 1931; Wilson, 1940; Ford, 1946). Synovial effusions occur in the affected areas and the joints may become ankylosed with fibrous tissue. The pericapsular joint tissues are often swollen and painful, and, when the hand is affected, this gives appearances indistinguishable from those of rheumatoid arthritis, so-called "periartthritis chronica rheumatica" (Guillain and Pernet, 1910; Guillain and Rouvillier, 1913). The affected limb may exhibit oedema and cyanosis. When the lower limb is involved, permanent pitting oedema may remain (Wilson, 1940). The muscles sometimes waste either immediately or after a variable period. When a limb is affected, its bones may become osteoporotic (see Schönfeld, 1929), or show Sudeck's atrophy (Sudeck, 1910). Schleicher (1949) describes chronic inflammatory changes in the marrow of the affected bones. Pleural reactions and haemorrhagic pleural effusions may appear beneath zoster of the chest wall (Curtin, 1902; Mann, 1931) or there may be symptoms and signs of irritation of the parietal peritoneum (Ford, 1946).

In cases of ophthalmic herpes sterile inflammatory changes often occur in the eye, resulting in a panophthalmitis and not infrequently in the appearance of haemorrhages and thromboses in the retinal vessels. Afterwards the eyelids may remain permanently oedematous. It is reasonable to suppose that these manifestations in the deeper somatic tissues are produced in a manner analogous to those in the skin—namely, by disturbance in the unmyelinated fibres of the posterior spinal and trigeminal sensory nerve roots.

Herpes Zoster Accompanied by Visceral Lesions

Unmyelinated afferent fibres with their cell bodies in the posterior root ganglia run from the viscera uninterruptedly through the autonomic ganglia and white rami communicantes to enter the posterior nerve roots with those from somatic tissues. The posterior nerve roots through which