degree of insulin antagonism is responsible for the improvement in tolerance after carbohydrate restriction in this group of diabetics. If antagonism to insulin had lessened then the levels of fasting insulin, as well as the levels after glucose, might have been expected to decline.

A possible explanation for these effects is that the lowering of blood glucose which follows dietary restriction may have allowed an improvement in the function of the beta cells. The studies of Dohan and Lukens (1948) have demonstrated the role of hyperglycaemia in causing islet-cell deterioration. Seltzer and Harris (1964) have also studied the effects of prolonged glucose infusion on blood insulin in normal people and diabetic patients. They have demonstrated the ease with which the insulin-secretory mechanism becomes exhausted in mild diabetics, when the islet cells are subjected to high blood-glucose levels for long periods of time. It is suggested that in the experiments reported in this paper the converse may have taken place, and that the lowering of blood glucose by diet has improved the ability of the pancreas to secrete insulin, which in turn has resulted in the improvement of glucose tolerance. Very occasionally similar remissions may follow treatment of severe diabetes with insulin (Taylor, 1960), and again one of the factors which make possible this type of improvement may be an increased secretion of insulin.

Weight reduction alone may not be the most important factor in the changes described in these obese patients. It will be seen from Table II that glucose tolerance and the blood-insulin response to glucose also improved in patients 6 to 7, neither of whom underwent significant weight reduction during the study. Moreover, the insulin response to glucose may also be improved after sulphonylurea therapy (Phear, 1962), suggesting that loss of weight is not an obligatory factor in the improvement.

Finally, these experiments give some support to the idea, particularly emphasized by Joslin *et al.* (1959), that energetic attempts to lower blood sugar are of cardinal importance in the early treatment of diabetes to prevent irreversible damage to islet cells.

Summary

Serial studies of the response of serum insulin to glucose ingestion have been made during a four-month period in a group of diabetic patients thought likely to respond to dietary restriction of carbohydrate.

In seven such patients, whose glucose tolerance improved on the diet, serum-insulin levels following glucose were higher after the diet, despite lower blood-glucose levels. Fasting serum-insulin levels were much higher in the diabetic group than in normal people and were unchanged after treatment.

It is suggested that these results are due to an improvement in the capacity of the pancreas to secrete insulin which follows the lowering of blood-glucose levels by dietary management.

We are indebted to Dr. Wilfrid Oakley and Dr. David Pyke, of the Diabetic Department, King's College Hospital, as well as to the hospital dietitians for many useful discussions and much valuable advice about the patients. We would also like to thank Dr. Clifford Hoyle for general help and encouragement, and Mr. D. G. Parry and Miss Marjorie Sandiford, who helped us at various times with the study.

This work was supported by grants from the Medical Research Council (to K. W. T.) and also by the British Diabetic Association and British Insulin Manufacturer. P. A. R. gratefully acknowledges support from a U.S. Public Health Service grant (1-F2-AH-19,337-01).

References

Berson, S. A., and Yalow, R. S. (1961). *Amer. J. Med.*, **31**, 874.
—— —— Bauman, A., Rothschild, M. A., and Newerly, K. (1956). *J. clin Invest.*, **35**, 170.
Bornstein, J., and Lawrence, R. D. (1951). *Brit. med. J.*, **1**, 732.
Bouchardat, A. (1875). *De la Glycosurie ou Diabète Sucre.* Germer-Baillière, Paris.
Dohan, F. C., and Lukens, F. D. W. (1948). *Endocrinology*, **42**, 244.
Ensinck, J., and Vallance-Owen, J. (1963). *Diabetes*, **12**, 353.
Hales, C. N. (1964). *Ciba Fdn Colloq. Endocr.*, **15**, 140.
—— and Randle, P. J. (1963a). *Lancet*, **1**, 790.
—— —— (1963b). *Biochem. J.*, **88**, 137.
Himsworth, H. P. (1949). *Lancet*, **1**, 465.
Huggett, A. St. G., and Nixon, D. A. (1957). Ibid., **2**, 368.
Joslin, E. P., Root, H. F., White, P., and Marble, A. (1959). *The Treatment of Diabetes Mellitus*, 10th ed. Kimpton, London.
Madison, L. L., Mebane, D., and Lochner, A. (1963). *J. clin. Invest.*, **42**, 955.
Naunyn, B. (1906). *Diabetes Mellitus*, 2nd ed. Holder, Vienna.
Newburgh, L. H., and Conn, J. W. (1939). *J. Amer. med. Ass.*, **112**, 7.
Phear, D. N. (1962). *Lancet*, **2**, 955.
Randle, P. J., Garland, P. B., Hales, C. N., and Newsholme, A. E. (1963). Ibid., **1**, 785.
Schalch, D. S., and Kipnis, D. M. (1964). *J. clin. Invest.*, **43**, 1283.
Seltzer, H. S., and Harris, V. L. (1964). *Diabetes*, **13**, 6.
—— and Smith, W. L. (1959). Ibid., **8**, 417.
Steinke, J., Soeldner, J. S., Camerini-Dávalos, R. A., and Renold, A. E. (1963). Ibid., **12**, 502.
Taylor, K. W. (1960). *Brit. med. J.*, **1**, 1853.
—— (1963). Ibid., **1**, 511.
Vallance-Owen, J., Hurlock, B., and Please, N. W. (1955). *Lancet*, **2**, 583.

Myxoedema After Deep *X*-ray Therapy to the Neck

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Brit. med. J., 1965, **1**, 1228–1230

External irradiation of the thyroid gland was at one time the standard treatment for thyrotoxicosis, and Groover *et al.* (1929) reported the incidence of severe hypothyroidism after radiotherapy to be 1.3% in a series of 305 cases. After treatment with radioiodine this complication is frequent, and was found by Green and Wilson (1964) to be 29% over a follow-up period of 10 years. They related its occurrence to the dose of radiation relative to the size of the gland, and not to an autoimmune reaction. As a complication of deep *x*-ray therapy to the neck in non-thyrotoxic patients, however, hypothyroidism would seem to be very rare, and we have been able to trace only one case in the literature, in which it appeared six years after treatment of carcinoma of the larynx (Félix *et al.*, 1961). We have recently encountered five patients who developed myxoedema after irradiation of the neck for reticuloses involving cervical lymph nodes, and for carcinoma of breast, oesophagus, and nasopharynx respectively. These cases are reported because of the rarity of this complication, and because of the interesting findings of thyroid auto-antibodies in all.

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Case 1

A woman aged 66 presented with gross enlargement of lymph nodes in both sides of the neck, and with a retropharyngeal mass which caused dysphagia. A biopsy specimen from the retropharyngeal tumour was reported as showing features compatible with either an anaplastic carcinoma or a reticulum-cell sarcoma. A course of radiotherapy was given from 30 October to 20 November 1961, using 250 kV *x* rays, half-value layer 2.6 mm. Cu, to a tumour dose of 2,625 rads, and the dose to the whole thyroid was calculated to be 2,625 rads. The masses subsequently regressed completely.

The patient remained well during the next three months, but on 12 March 1962 she complained of facial swelling, which began one month previously, accompanied by lassitude and sensitivity to cold. She exhibited gross periorbital swelling, dry coarse skin, hoarseness, and slow speech, and her appearance was typical of severe myxoedema. The thyroid gland was not palpable. The serum cholesterol was 455 mg./100 ml., the electrocardiogram showed shallow T waves in most of the chest leads, and the basal metabolic rate was 41% below normal. The thyroid complement-fixation test was positive to a titre of 1 in 240, and the tanned-red-cell agglutination and precipitin tests were negative.

She responded well to treatment with thyroxine, and by May 1963 was euthyroid. She died from spinal metastases six months later. Permission for necropsy was refused.

Case 2

Cervical and axillary lymph-node enlargement in a woman of 39 was shown histologically to be due to giant follicular lymphoma. Radiotherapy was applied to the left side of the neck in February 1958, using 250 kV *x* rays, half-value layer 2.6 mm. Cu, the incident dose being 2,500 r. She remained well until February 1961, when swelling in the right side of the neck, probably due to involvement of the right lobe of the thyroid, necessitated further radiotherapy, with subsequent complete regression of the swelling. The dose to the thyroid gland from both courses of radiotherapy was around 2,900 rads. In March 1962 she was readmitted to hospital complaining of extreme lethargy, sensitivity to cold, and huskiness of the voice. She was mentally slow, and appeared markedly myxoedematous. The thyroid gland was not palpable. The serum cholesterol was 171 mg./100 ml., the electrocardiogram showed complexes of very low voltage in most leads, and the basal metabolic rate was 20% below normal. The tanned-red-cell agglutination test was positive to a titre of 1 in 250, and the thyroid complement-fixation and precipitin tests were negative. On treatment with thyroxine she became euthyroid but died of her reticulosis on 21 June 1962. Permission for necropsy was refused.

Case 3

A woman aged 64 was admitted to hospital on 5 June 1962 suffering from carcinoma of the left breast with involvement of axillary lymph nodes. Simple mastectomy was followed by routine post-operative radiotherapy to the chest wall, axilla, supraclavicular region, and internal mammary chain of lymph nodes. The dose received by the left lobe of the thyroid was 3,650 rads. On 6 December she complained of swelling of the face and neck, of hoarseness, and of sensitivity to cold. There was swelling of the supraclavicular fossae, face, eyelids, arms, and hands, and the skin was dry and rough. The voice was hoarse and speech slow and the clinical picture was that of advanced myxoedema. The thyroid gland was not palpable.

The serum cholesterol was 252 mg./100 ml., the electrocardiogram showed reduction of the ventricular complexes in most leads, and the basal metabolic rate was 35% below normal. The thyroid complement-fixation test was positive to a titre of 1 in 30, and the tanned-red-cell agglutination and precipitin tests were both negative.

On treatment with thyroxine she improved rapidly, and in April 1963 was euthyroid. The thyroid complement-fixation test was still positive, but the titre had dropped to 1 in 10. She has remained well since then.

Case 4

A retropharyngeal tumour was found in a woman of 61 who sought medical advice because of an enlarged cervical lymph node. Biopsy of the tumour revealed a poorly differentiated squamous carcinoma. Treatment by radioactive cobalt was begun in December 1961, using 20 by 12 cm. parallel opposed fields extending from the base of the skull to the clavicles. These fields were later reduced to 12 by 8 cm. The tumour dose to the nasopharynx was 6,000 rads in six weeks, and the dose to the thyroid was estimated to be 3,000 to 4,000 rads. Treatment was followed by disappearance of the tumour. The patient remained well until January 1963, when on routine follow-up it was noted that her face was puffy and that her voice was deep and hoarse. She complained, moreover, of lethargy and of sensitivity to cold. The thyroid gland was not palpable.

Radioiodine uptake test: test dose 25 microcuries ^{131}I; gland uptake at five hours 16% dose, and at 48 hours 27% dose. Blood levels at 48 hours: total plasma ^{131}I 0.25% dose/litre, and protein-bound ^{131}I 0.23% dose/litre; urinary excretion at 0–8 hours 15% dose, at 8–24 hours 21% dose, at 24–48 hours 15% dose, and at 0–48 hours 74% dose. The serum cholesterol was 195 mg./100 ml. The tanned-red-cell agglutination test was positive to a titre of 1 in 250, and the thyroid complement-fixation and precipitin tests were negative.

Although the radioiodine test was not diagnostic, the clinical picture presented by the patient left no doubt that she was suffering from myxoedema, and treatment with thyroxine was started, reaching a daily maintenance dose of 0.3 mg. Subjective improvement was marked, and the facial appearance had returned to normal two months later. The patient has remained well.

Case 5

A woman aged 67 complained of dysphagia in July 1959. Oesophagoscopy demonstrated a post-cricoid tumour which biopsy showed to be a well-differentiated squamous carcinoma. A course of radiotherapy was started on 12 November 1959, using 250 kV *x* rays, half-value layer 2.6 mm. Cu, the tumour dose being 4,850 rads over a period of four weeks. The dose to the whole thyroid gland was estimated to be 4,850 rads. The patient remained well until November 1962, when she complained of extreme lethargy. Her facial features were coarse and puffy, her voice was deep and husky, and speech was slow, the clinical picture being that of typical myxoedema. The thyroid gland was not palpable.

The serum cholesterol was 600 mg./100 ml. Radioiodine studies: test dose 25 microcuries ^{131}I; gland uptake at 4 hours 8% dose, and at 48 hours 8% dose; blood levels at 48 hours: total plasma ^{131}I 0.18% dose/litre; urinary excretion at 0–8 hours 37% dose, at 8–24 hours 52% dose, at 24–48 hours 6% dose, and at 0–48 hours 95% dose. These findings, showing low thyroid uptake and high urinary excretion of ^{131}I, confirmed the clinical diagnosis of myxoedema. The tanned-red-cell agglutination, thyroid complement-fixation, and thyroid precipitin tests were negative, but antibody to the second antigen of the acinar colloid (Balfour *et al.*, 1961) was demonstrated in the serum by immunofluorescence.

Marked improvement followed treatment with thyroxine, and the patient has remained euthyroid.

Discussion

Four of the patients we have described showed well-marked clinical evidence of hypothyroidism from 4 to 12 months after completion of radiotherapy, and although in the fifth patient the interval was three years, in all cases the thyroid gland was directly irradiated. Malignant invasion of the gland seemed likely only in Case 2 and was confined clinically to one lobe. Coincidence cannot be excluded, but it seems to us much more likely that the development of myxoedema was related in some way to irradiation of the gland. The thyrotoxic gland is highly radiosensitive, and, using *x*-radiation for the treatment of thyrotoxicosis, Groover *et al.* (1929) found a dose of 1,500 to 2,000 r to be sufficient. None of our patients, however, was thyrotoxic. The normal thyroid, on the other hand, is very resistant to radiation (Warren, 1943), and, using ^{131}I in the treatment of angina pectoris, Goolden and Davey (1963) found that the minmum dose necessary for ablation of the gland was between 30,000 and 40,000 rads. A comparable dose delivered by external irradiation would cause severe soft-tissue damage. The amount of *x*-radiation received by the thyroid glands of our five patients ranged from 2,625 to 4,850 rads, and was therefore far

below that usually necessary to destroy the normal gland. If, therefore, myxoedema was related to radiotherapy, either the effect of irradiation was indirect or the thyroid glands were not normal initially.

That myxoedema was not a direct effect of irradiation is suggested by the finding of thyroid auto-antibodies in the serum of all five patients. Although only one antibody in low titre was found in each case, the serological findings were similar to those in "spontaneous" myxoedema, which is now generally believed to be of autoimmune origin (Owen and Smart, 1958; Roitt and Doniach, 1958; Doniach *et al.*, 1960). It is reasonable to speculate, therefore, whether irradiation was a factor in the induction of an autoimmune reaction in these patients. There is no serological evidence that radiation can initiate an autoimmune reaction in the normal thyroid gland, nor did Irvine *et al.* (1962) find any correlation between the presence of auto-antibodies and the subsequent development of myxoedema in their thyrotoxic patients treated with ^{131}I. On the other hand, Buchanan *et al.* (1962) found a higher incidence of microsomal antibody in patients treated with radioiodine than in those treated with antithyroid drugs, and Irvine (1963) and Doniach and Roitt (1963) found a frequent rise in the titre of thyroid antibodies during treatment with radioiodine.

Histological data on irradiated normal human thyroids are very scanty. Lindsay *et al.* (1954) found no evidence of Hashimoto's thyroiditis in five patients, four of whom were males, whose glands had been irradiated in the treatment of adjacent malignant disease, but obviously no conclusions can be drawn from such a small series. Although they found a high incidence of Hashimoto's thyroiditis in hyperplastic glands which had been treated with ^{131}I or with *x* rays, these changes may have preceded irradiation.

It may be that the thyroids of the five patients (Cases 1–5) were not normal healthy glands, and that the malignant disease from which they were suffering may have rendered them susceptible to damage by radiation. An autoimmune reaction may thus have been initiated by the damage to the thyroid epithelial cells. An alternative possibility is suggested by the experiments of Roitt *et al.* (1962), who showed that in rats mild trauma by radioiodine or *x* rays potentiated an inflammatory reaction to injected heterologous antithyroglobulin antibodies. Thus, if the thyroid glands in these patients were already the seat of focal thyroiditis, injury to the thyroid epithelial cells by radiation may have rendered them more susceptible to the action of thyroid auto-antibodies; or, alternatively, damage by antibodies may have sensitized the cells to the effect of radiation.

The apparent rarity of this complication may be explained by the greatly reduced life-span of patients suffering from diseases for which irradiation of the neck is required. Possibly minor damage to the thyroid may be more common than is realized, and screening of the glands, where appropriate, during deep *x*-ray therapy would be a simple and prudent precaution.

Summary

Five women suffering from malignant disease not arising from the thyroid gland developed myxoedema after therapeutic irradiation of the neck. The intervals between completion of radiotherapy and the diagnosis of myxoedema were 3 months, 5 months, 12 months (two patients), and 36 months respectively, and in all cases the thyroid gland was directly irradiated. The development of myxoedema, therefore, is believed to be related to radiotherapy.

The dose of radiation was far below that necessary to ablate the normal thyroid, and thyroid auto-antibodies in low titre were detected in all the patients. Myxoedema was unlikely, therefore, to have been a direct effect of radiation, and was probably mediated by an autoimmune reaction.

The possibility is discussed that the development of thyroid autoimmunity was related to irradiation of the gland.

We are indebted to Dr. M. A. C. Cowell and to Dr. E. R. Watson for referring Cases 4 and 5 to us, to Dr. J. B. Rennie for reading the script, and to Dr. J. M. Moore for performing the serological tests.

References

Balfour, B. M., Doniach, D., Roitt, I. M., and Couchman, K. G. (1961). *Brit. J. exp. Path.*, **42**, 307.
Buchanan, W. W., Koutras, D. A., Crooks, J., Alexander, W. D., Brass, W., Anderson, J. R., Goudie, R. B., and Gray, K. G. (1962). *J. Endocr.*, **24**, 115.
Doniach, D., Hudson, R. V., and Roitt, I. M. (1960). *Brit. med. J.*, **1**, 365
—— and Roitt, I. M. (1963). *Clinical Aspects of Immunology*, edited by P. G. H. Gell and R. A. Coombs, p. 626. Butterworth, London.
Félix, H., Dupré, N., Drape, M., and Court, L. (1961). *Lyon méd.*, **206**, 1043.
Goolden, A. W., and Davey, J. B. (1963). *Brit. J. Radiol.*, **36**, 340.
Green, M., and Wilson, G. M. (1964). *Brit. med. J.*, **1**, 1005.
Groover, T. A., Christie, A. C., Merritt, E. A., Coe, F. O., and McPeak, E. M. (1929). *J. Amer. med. Ass.*, **92**, 1730.
Irvine, W. J. (1963). *Symposium on the Thyroid and its Diseases.* Royal College of Physicians, London.
—— Macgregor, A. G., and Stuart, A. E. (1962). *Lancet*, **2**, 843.
Lindsay, S., Dailey, M. E., and Jones, M. D. (1954). *J. clin. Endocr.*, **14**, 1179.
Owen, S. G., and Smart, G. A. (1958). *Lancet*, **2**, 1034.
Roitt, I. M., and Doniach, D. (1958). Ibid., **2**, 1027.
—— Jones, H. E. H., and Doniach, D. (1962). *Reports of 2nd International Congress on Immunopathology, Kalamazoo 1961*, edited by P. Grabar and P. B. Miescher Schwabe, Basle.
Warren, S. (1943). *Arch. Path.*, **35**, 304.

Carbachol and Vitamin B_{12} Absorption

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Brit. med. J., 1965, 1, 1230–1231

Impaired absorption of vitamin B_{12} is known to occur in a considerable proportion of patients who have had partial gastrectomy (Adams, 1958; Deller, Richards, and Witts, 1962) and is almost always the result of deficiency of intrinsic factor (Herbert, 1959). The administration of carbachol has been found to increase vitamin-B_{12} absorption except in patients with pernicious anaemia (Baker and Mollin, 1955; Mollin, Booth, and Baker, 1957) and should therefore increase absorption in patients with partial gastrectomy unless there is complete atrophy of the gastric remnant or secretion is already maximally stimulated. However, Ardeman, Chanarin, and Doyle (1964) have been unable to demonstrate increase of intrinsic-factor secretion after administration of carbachol to eight "normal" subjects. Carbachol is, however, often used in tests of vitamin-B_{12} absorption in the belief that the test is then more

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