Since we adopted this method of access to the circulation for haemodialysis, the morale of each patient has changed considerably. Patients no longer live with their fears of an artificial Teflon shunt with its possible hazards and complications. They can rehabilitate themselves more easily and their lost working hours have decreased considerably. Similarly, life for members of the staff is no longer punctuated by frustrating crises of clotted shunts and infection.

We have not observed any evidence of cardiac embarrassment in spite of the alteration in circulatory dynamics produced by the introduction of the arteriovenous fistula.

We would like to suggest that this technique might be of value in circumstances other than haemodialysis where repeated access to the circulation is required—for example, repeated transfusions in aplastic anaemia. In this regard Williams *et al.* (1967) and Anderson *et al.* (1967) have reported on the successful use of the conventional type of Quinton–Scribner Teflon shunt in a total of three patients with aplastic anaemia requiring regular transfusions. It is noted, however, that in two cases the problem of clotting occurred. From our experience we would suggest that a permanent surgically created arteriovenous fistula as described here would be a less troublesome method of obtaining access to the circulation when repeated transfusions are required.

Summary

An arteriovenous fistula was created surgically in 14 patients on regular dialysis treatment in order to provide repeated access to the circulation. In 11 patients the initial arteriovenous fistula functioned satisfactorily and without complica-

tions. In two patients in whom the initial fistula failed to function, success was achieved in the opposite forearm. In one patient in whom the procedure failed initially a second attempt to create a fistula has been postponed owing to the poor calibre of her veins and the urgency of maintaining adequate haemodialysis.

ADDENDUM.—Since this communication was submitted for publication two further patients have had successful arteriovenous fistulas established. In addition one patient (Case 9) in whom arteriovenous fistula formation on 31 January 1967 was unsuccessful and in whom a Quinton shunt was replaced has recently had a functioning fistula established by use of her remaining ulnar artery. In September 1967 the total number of patients with successful fistulas was therefore 16.

REFERENCES

- Anderson, D. C., Emslie-Smith, D., Macgregor, A. M. C., and Stewart, W. K. (1967). *Lancet*, 1, 509.
 Brescia, M. J., Cimino, J. E., Appel, K., and Hurwich, B. J. (1966). *New Engl. J. Med.*, 275, 1089.
 Carmody, M. (1964). *Proceedings of European Dialysis and Transplant Association*, No. 1.
 Hegstrom, R. M., Quinton, W. E., Dillard, D. H., Cole, J. J., and Scribner, B. H. (1961). *Trans. Amer. Soc. artif. intern. Organs.*, 7, 47.
 Murray, J. S., Pendras, J. P., Lindholm, D. D., and Erickson, R. V. (1964). *Ibid.*, 10, 191.
 Pendras, J. P., and Smith, M. P. (1966). *Ibid.*, 12, 222.
 Quinton, W. E., Dillard, D. H., Cole, J. J., and Scribner, B. H. (1962). *Ibid.*, 8, 236.
 ——— and Scribner, B. H. (1960). *Ibid.*, 6, 104.
 Williams, B. T., Blainey, J. D., Dawson-Edwards, P., Hilton, D. D., and Simpson, K. M. (1967). *Brit. med. J.*, 2, 484.

Thyrocalcitonin Deficiency after Treatment of Thyroid Disorders by Surgery or Radioiodine

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The isolation of thyrocalcitonin from human thyroid tissue (Hirsch, Voelkel, and Munson, 1964; Milhaud, Moukhtar, Bourichon, and Perault, 1965; Smith, Laljee, and Dorrington, 1966; Aliapoulos, Voelkel, and Munson, 1966; Tashjian, Frantz, and Lee, 1966; Mazzuoli, Coen, and Baschieri, 1966; Laljee, Smith, and Dorrington, 1967) and the demonstration of its hypocalcaemic action in man (Foster, Joblin, MacIntyre, Melvin, and Slack, 1966; Bell, Barrett, and Patterson, 1966) have stimulated interest in the importance of this hormone in human physiology.

High serum calcium levels stimulate the release of thyrocalcitonin (Foster, Baghdiantz, Kumar, Slack, Soliman, and MacIntyre, 1964; Care, 1965). If the calcium-lowering effect of this hormone was absent the serum calcium might rise higher and fall more slowly after an intravenous calcium load in comparison with a normal response. Deficiency of thyrocalcitonin might occur after removal or destruction of most of the thyroid gland, as may occur after surgery or radioiodine therapy. This possibility has been investigated by studying the response of patients to an intravenous calcium infusion (Smith and Laljee, 1967).

Patients and Methods

Subtotal Thyroidectomy Group.—Patients received intravenous calcium infusions two or three days before and at the same interval after subtotal thyroidectomy for thyrotoxicosis (five) or non-toxic goitre (four); thus each patient acted as his own control. Antithyroid drugs and potassium iodide were given preoperatively to patients with thyrotoxicosis.

Radioiodine Therapy Group.—Our studies included 24 patients who had been treated with radioiodine for thyrotoxicosis from 2 to 15 years previously and a group of seven patients of similar age without any evidence of thyroid disorder who agreed to help in this investigation after its value had been fully explained to them.

Technique.—The intravenous infusion of calcium was given at a constant rate over four hours by means of a D.C.L. micro-pump type T (Messrs. F. A. Hughes & Co. Limited). The dose of elemental calcium was 15 mg./kg. body weight given as a calcium gluconate solution (15 mg. of calcium per 5 ml.). Blood samples were taken before (0 hours) and immediately after the infusion (4 hours), and subsequently at 8, 12, and 24 hours. The serum calcium was estimated by an edetic acid titration with calchichrome as indicator and a manual titrator (Messrs. Evans Electroselenium Ltd.). The rise in serum calcium and elevation above pre-infusion level was plotted at four-

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hourly intervals up to 12 hours. The area beneath the graph was calculated, and it represented the response to the calcium infusion (Fig. 1).

FIG. 1.—Representation of response to four-hour calcium infusion and calculation of the area below the curve of serum calcium values.

Results

Subtotal Thyroidectomy.—There was no significant difference between the preoperative and postoperative responses to the calcium infusion in nine patients (Fig. 2). No difference was apparent between the patients with thyrotoxicosis and those

FIG. 2.—Responses to calcium infusion. O = Euthyroid patients. ● = Hypothyroid patients on thyroxine. ▲ = Mean value of each group. H = Hypothyroidism developed six months later.

Details of Patients and the Response After Intravenous Calcium Infusion

Groups	No. Studied	Mean Age ± S.D.	Mean Serum Calcium Values (mg./100ml.) ± S.E.		Mean Area of Graph ± S.E.
			Before Infusion (0 hours)	Rise After Infusion (4 hours)	
Subtotal thyroidectomy:					
1. Thyrotoxicosis:					
Before operation	5	37 ± 5	9.84 ± 0.24	4.59 ± 0.44	27.65 ± 1.56
After operation			9.44 ± 0.20	4.59 ± 0.55	28.75 ± 3.8
2. Simple goitre:					
Before operation	4	46 ± 5	9.85 ± 0.09	4.46 ± 0.51	28.08 ± 3.52
After operation			9.05 ± 0.12	3.92 ± 0.61	28.55 ± 5.6
Radioiodine therapy:					
1. Euthyroid	8	62 ± 7	10.49 ± 0.12	6.54 ± 0.36	43.17 ± 2.05
2. Hypothyroid on thyroxine	16	59 ± 7	9.96 ± 0.15	5.61 ± 0.37	38.80 ± 2.71
Control	7	55 ± 5	9.77 ± 0.34	4.58 ± 0.73	30.13 ± 4.28

with non-toxic goitres (see Table). Three patients had higher calcium levels postoperatively after the infusion compared with their preoperative values. Two became hypothyroid six months after the operation (indicated by H in Fig. 2); the other had a large multinodular goitre. The small portion left appeared grossly disorganized, and accordingly the patient was started on thyroxine immediately after operation.

Radioiodine Therapy.—The response to calcium infusions in 24 patients after radioiodine therapy (Fig. 2) differed significantly from both the preoperative and postoperative surgical groups ($P < 0.005$) and the control group of similar age ($P < 0.05$). There was a positive correlation ($r = +0.50$, $P < 0.02$) between the response to the calcium load and the time interval since the irradiation of the thyroid (Fig. 3). No correlation was apparent in the radioiodine group when the results were plotted in relation to the age of the patients or the total dose of calcium administered.

Discussion

Intravenous calcium infusions were used to assess thyrocalcitonin secretory capacity because the release of this hormone is stimulated by high serum calcium levels and its calcium-lowering action corrects experimental hypercalcaemia (Foster *et al.*, 1964). It does not influence renal excretion of calcium directly but acts by inhibiting the resorption of bone (Friedman and Raisz, 1965; Milhaud *et al.*, 1965; Aliapoulos and Munson, 1965; Gaillard, 1966; Foster *et al.*, 1966; Johnston and Deiss, 1966). The most sensitive measurement of its action is the serum calcium level. The greater rise of

FIG. 3.—Correlation of response to calcium infusion represented by area below serum calcium curve and time interval (months) since radioiodine therapy ($r = +0.50$, $P < 0.02$).

serum calcium and the persistence of elevated readings after intravenous calcium loading are consistent with a deficiency of thyrocalcitonin.

Surgical and radioiodine treatment of thyrotoxicosis may damage the parathyroids (Adams and Chalmers, 1965), but there was no clinical or biochemical evidence of this in our patients. In fact, parathyroid damage would not influence the speed of recovery from hypercalcaemia after calcium loading (Hahnemann and Friis, 1965). Hypothyroidism will alter the response to a calcium infusion (Krane, Brownell, Stanbury, and Corrigan, 1956; Lowe, Bird, and Thomas, 1962). Our patients were all euthyroid, including those with post- ^{131}I hypothyroidism who were on adequate replacement doses of thyroxine.

The effect of subtotal thyroidectomy on the response to an intravenous calcium load was insignificant in most cases. These

patients were left with an amount of thyroid tissue thought to be sufficient to keep them euthyroid. However, two patients who became hypothyroid six months later did not lower the calcium level so efficiently as others in this group. The other patient with a defective response had a radical excision of a multinodular gland, and the tissue left was severely deranged. In these three patients little or no active thyroid tissue was left in the body. In pigs and in rats similar results were found after total thyroidectomy (Care, Duncan, and Webster, 1967; Gittes and Irvin, 1965). Similar calcium infusion studies on 14 patients who had subtotal thyroidectomies have shown defective handling of the calcium load in five (Hahnemann and Friis, 1965). In other infusion studies four out of seven hypothyroid patients receiving thyroxine had delay in return to preinfusion calcium levels (Williams, Hargis, Galloway, and Henderson, 1966). Finally, Ibbertson, Roche, and Pybus (1967) have shown failure to lower promptly the serum calcium after an infusion of calcium in patients with spontaneous hypothyroidism when on thyroxine.

Antithyroid medication has been reported to reduce the release of thyrocalcitonin in pigs (Duncan and Care, 1967), and the glands have a higher thyrocalcitonin content (Care, Duncan, and Webster, 1966). Our studies showed no difference in the response of patients with thyrotoxicosis, who had antithyroid drugs, and patients with non-toxic goitres or those who had no thyroid disorders. Our patients did not have high doses of antithyroid drugs, whereas the pigs had relatively large doses, resulting in considerable gland hyperplasia and hypothyroidism. The latter can produce an abnormal response to a calcium load. Parallel studies of thyroid tissue from patients treated preoperatively with antithyroid drugs in doses sufficient to control their symptoms have not shown any increase in the thyrocalcitonin content of these glands compared with tissue from patients with non-toxic goitres and necropsy thyroid tissue (Laljee *et al.*, 1967). It seems unlikely, therefore, that thyrocalcitonin release was inhibited by the doses of antithyroid drugs given to our patients, and this medication would still be effective two to three days after the operation.

Radioiodine therapy damages thyroid tissue extensively, leading to progressive loss of function due to impairment of cell division. Experience has shown that in many patients hypothyroidism develops insidiously many years after radioiodine therapy (Beling and Einhorn, 1961; Green and Wilson, 1964; Dunn and Chapman, 1964; Nofal, Beierwaltes, and Patno, 1966). Thyrocalcitonin production may similarly fail after thyroid irradiation, and our results suggest that this is also time-dependent. The defective response was independent of the age of the patient.

It is probable that thyrocalcitonin production is deficient in some patients after thyroid surgery or radioiodine therapy owing to factors which are similar to those that result in hypothyroidism. The evidence presented suggests that thyrocalcitonin deficiency can be demonstrated by challenging the thyroid with a calcium load before hypothyroidism is manifest. Furthermore, in patients treated with radioiodine thyrocalcitonin deficiency is time-dependent, but it may precede or follow the onset of hypothyroidism.

Summary

Intravenous calcium infusions were administered to patients treated by surgery or radioiodine for thyroid disorders in order

to assess whether these radical procedures had resulted in a deficiency of thyrocalcitonin.

A defective response to a calcium load was observed in three out of nine patients after thyroid surgery; they had suffered extensive removal of thyroid tissue. In 24 patients treated for thyrotoxicosis by radioiodine a progressive decrease was demonstrated in the response to a calcium load with the passage of time after irradiation. The failure to handle the calcium load efficiently in these patients who have had extensive removal of or damage to the thyroid tissue has been interpreted as evidence of thyrocalcitonin deficiency.

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REFERENCES

- Adams, P. H., and Chalmers, T. M. (1965). *Clin. Sci.*, **29**, 391.
- Aliapoulos, M. A., and Munson, P. L. (1965). *Surg. Forum*, **16**, 55.
- Voelkel, E. F., and Munson, P. L. (1966). *J. clin. Endocr.*, **26**, 897.
- Beling, U., and Einhorn, J. (1961). *Acta radiol. (Stockh.)*, **56**, 275.
- Bell, N. H., Barrett, R. J., and Patterson, R. (1966). *Proc. Soc. exp. Biol. (N.Y.)*, **123**, 114.
- Care, A. D. (1965). *Nature (Lond.)*, **205**, 1289.
- Duncan, T., and Webster, D. (1966). *J. Endocr.*, **35**, XXVII.
- — (1967). *Ibid.*, **37**, 155.
- Duncan, T., and Care, A. D. (1967). *Brit. J. Surg.*, **54**, 196.
- Dunn, J. T., and Chapman, E. M. (1964). *New Engl. J. Med.*, **271**, 1037.
- Foster, G. V., Baghdiantz, A., Kumar, M. A., Slack, E., Soliman, H. A., and MacIntyre, I. (1964). *Nature (Lond.)*, **202**, 1303.
- Joplin, G. F., MacIntyre, I., Melvin, K. E. W., and Slack, E. (1966). *Lancet*, **1**, 107.
- Friedman, J., and Raisz, L. G. (1965). *Science*, **150**, 1465.
- Gaillard, P. J. (1966). *J. Bone Jt Surg.*, **48B**, 386.
- Gittes, R. F., and Irvin, G. L. (1965). *Science*, **148**, 1737.
- Green, M., and Wilson, G. M. (1964). *Brit. med. J.*, **1**, 1005.
- Hahnemann, S., and Friis, Th. (1965). *Acta med. scand.*, **177**, 587.
- Hirsch, P. F., Voelkel, E. F., and Munson, P. L. (1964). *Science*, **146**, 412.
- Ibbertson, H. K., Roche, A. H. G., and Pybus, J. (1967). *Aust. Ann. Med.*, **16**, 121.
- Johnston, C. C., jun., and Deiss, W. P., jun. (1966). *Endocrinology*, **78**, 1139.
- Krane, S. M., Brownell, G. L., Stanbury, J. B., and Corrigan, H. (1956). *J. clin. Invest.*, **35**, 874.
- Laljee, H. C. K., Smith, R. N., and Dorrington, K. J. (1967). *J. Endocr.*, **39**, 507-516.
- Lowe, C. E., Bird, E. D., and Thomas, W. C., jun. (1962). *J. clin. Endocr.*, **22**, 261.
- Mazzuoli, G. F., Coen, G., and Baschieri, L. (1966). *Lancet*, **2**, 1192.
- Milhaud, G., Moukhtar, M. S., Bourichon, J., and Pérault, A.-M. (1965). *C.R. Acad. Sci. (Paris)*, **261**, 4513.
- Nofal, M. N., Beierwaltes, W. H., and Patno, M. E. (1966). *J. Amer. med. Ass.*, **197**, 605.
- Smith, R. N., and Laljee, H. C. K. (1967). In *Symposium on Thyrotoxicosis*, p. 186, edited by W. J. Irvine. Edinburgh.
- — and Dorrington, K. J. (1966). *J. Bone Jt Surg.*, **48B**, 388.
- Tashjian, A. H., Frantz, A. G., and Lee, J. B. (1966). *Proc. nat. Acad. Sci. (Wash.)*, **59**, 1138.
- Williams, G. A., Hargis, G. K., Galloway, W. B., and Henderson, W. J. (1966). *Proc. Soc. exp. Biol. (N.Y.)*, **122**, 1273.