respectively. Eight days after the operation the bone marrow contained a few myelocytes and normoblasts; on day 12 granulocytes reappeared in the blood stream and by day 18 the bone marrow showed definite signs of regeneration.

The success of the graft was monitored by chromosomal and serological analysis. No dividing cells could be found in a pretransplantation sample of bone marrow. A postoperative sample (20 August) yielded eight dividing cells, all of which were female. The donor was group O and the patient was group A, other red cell antigens being obscured by previous transfusions. Analysis (6 November) three months after grafting showed that 80-90% of the patient's red cells were group O; by 131 days (11 December) no A cells could be found. There was also evidence of donor takeover in the lymphoid system. Lymphocyte cultures (10 August) stimulated with PHA yielded 24 dividing cells in which the sex could be determined; 21 were female and 3 were male. Lymphocyte cultures stimulated by pokeweed on the same day yielded two cells, one of each sex. By 17 September all cells in division after stimulation with PHA were female.

His subsequent progress was uneventful. His hair was rapidly regrowing and he was ready to resume a normal life, though for the coming winter at least he had to be protected from casual infections by viruses. His experience, including six weeks in isolation, seemed to have had no adverse effects; on the contrary, his mother said "it has brought him out—he is really articulate."

Discussion

The technique used to secure a permanent bone marrow graft in this case was developed by Thomas and his colleagues in Seattle (Thomas and Storb, 1970; Storb *et al.*, 1974). In a series reported by Storb *et al.* (1974) 24 patients received grafts for hypoplasia of the bone marrow; 21 grafts, all from histocompatible siblings, were established but subsequent graft rejection or graft-against-host reaction reduced the survivors to 11. In this instance we were fortunate that graft-against-host reaction was totally averted and that no treatment except the scheduled methotrexate was needed.

In four of the Seattle patients bone marrow aplasia had developed after infectious hepatitis and in one of these the bone marrow graft effected a long-term restoration of function. To this may be added another case of post-hepatitis aplasia in which transplantation was performed successfully by Camitta *et al.*

(1974), who also reviewed the literature on this relatively rare condition. Out of 76 patients only five spontaneously attained a complete remission and two others obtained a partial remission. Thus the mortality is about 90%, so that the chance of recovery with a histocompatible graft (three out of six so far) represents an advance.

Thomas has stressed the importance of averting presensitization to minor histocompatibility antigens by previous blood transfusion, especially with blood from donors who are related to the patient. Thus, once a diagnosis of severe aplastic anaemia has been made, an immediate priority is to discover whether there is a histocompatible sibling and to plan the treatment accordingly. In Britain the size of families is such that less than half of all patients will have such a sibling and, as yet, the prospects for using bone marrow from unrelated donors are not known. Secondly, if the existence of a histocompatible donor does encourage the attempt to graft it is vital to ensure that adequate supportive therapy, especially platelet transfusions and measures to guard against infection—isolation, granulocyte transfusions, or preferably both—can be provided.

Finally, there remains an ethical problem. Though the discomfort for the donor is slight and transient there is a risk, which is that of a general anaesthetic. With the whole family encamped nearby it was possible to explain the situation at leisure during the days while the mixed lymphocytes in culture were failing to react. In fact, our donor never hesitated and we felt that it was right to proceed, but it is a problem which will recur and has no simple solution.

We are indebted to Dr. H. Everley Jones for referring this case, to Dr. R. Storb for advice and encouragement, and, not least, to the marrow donor.

The report was drafted by Dr. H. E. M. Kay. Requests for reprints should be sent to him at the Royal Marsden Hospital, Fulham Road, London SW3 6JJ.

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MEDICAL MEMORANDA

Apathetic T-3 Toxicosis

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Thyrotoxicosis may be clinically occult and may even present with apathy, in contrast to the more usual hyperdynamic syndrome (Lahey, 1931 a, 1931 b, 1932). "Triiodothyronine (T-3) toxicosis" is a biochemically occult form of hyperthyroidism in which the simple tests of thyroid function give normal results. We present a case of both clinically and biochemically "hidden hyperthyroidism" due to apathetic T-3 toxicosis.

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Case Report

A 43-year-old woman of Swiss-Italian origin was first seen at St. Bartholomew's Hospital in 1969 because of a nodule in the left lobe of the thyroid gland. In 1958 she had developed a diffuse goitre and heat intolerance and had lost weight. She was treated medically in Italy with apparent success. Her mother, who was from Interlaken, and three maternal aunts had required thyroidectomy for thyrotoxicosis. The patient complained of tiredness and malaise. On examination she had a puffy face, appeared slow and apathetic, and was thought to be clinically hypothyroid. P.B.I. was 5 µg/100 ml (normal range 4-8 µg/100 ml). Radioiodine studies: scan showed single area of functioning thyroid tissue to the left of the midline; uptake was 22% of the administered dose at six hours, 32% at 24 hours, and 29% at 48 hours (normal maximum uptake 50%). She was then lost to follow-up.

In 1971 she was again referred because of the thyroid nodule. She complained of tiredness and menorrhagia. Her physical appearance had not changed. Her pulse was 70/min and the ankle jerk relaxation time was clinically normal. Two out of three clinicians who saw her thought that she was hypothyroid; the third refused to commit himself. She was given thyroxine 300 µg daily on clinical grounds and to suppress the goitre. After two months on thyroxine she had lost 4 kg in weight and was hyperactive,

nervous, and intolerant of heat. The nodule in the thyroid did not change. After stopping thyroxine she gained weight and lapsed again into lethargy.

Investigations (1971) before thyroxine treatment were: P.B.I. 5.3 $\mu\text{g}/100\text{ ml}$, T-3 resin uptake 123% (normal range 108-122%), free thyroxine index 4.3 (normal range 4-8). Radioiodine studies: scan unchanged; uptake 33% at 24 hours, 28% at 48 hours. Anti-thyroglobulin titre 1/80; immunofluorescent thyroid epithelial cell antibodies weakly positive.

Changes found during TRH test in thyroid disease (Ormston *et al.*, 1971). ▲ - ▲ = Initial, preoperative response (1971). ● - ● = Postoperative response (1973).

Technetium scan after two months on thyroxine showed no suppression of uptake of radioisotope by the left-sided nodule. Technetium scan after thyroid-stimulating hormone (TSH) 10 units intramuscularly daily for three days showed diffuse uptake in both lobes of the thyroid.

Serum TSH levels in the thyrotrophin-releasing hormone (TRH) test (Ormston *et al.*, 1971) (see chart) were: basal 0.8 $\mu\text{U}/\text{ml}$, at 20 minutes 1.0 $\mu\text{U}/\text{ml}$, at 60 minutes 0.9 $\mu\text{U}/\text{ml}$ —that is, absent response, suggesting thyrotoxicosis.

In view of the results of the TRH test, suggesting thyrotoxicosis in the presence of a normal P.B.I. and radioiodine uptake, T-3 toxicosis was considered. The serum T-3 was 455 ng/100 ml (normal range 130-300 ng/100 ml), as measured by a modification of the method of Sterling (*et al.*, 1969), kindly arranged by Dr. R. Hoffenberg, Northwick Park Hospital.

Treatment.—Carbimazole 10 mg thrice daily was given with symptomatic improvement in lethargy and return of the menses to normal. When judged to be euthyroid she underwent partial thyroidectomy. A nodular thyroid gland was found. Histological examination showed focal thyroiditis affecting the whole gland and the presence of a solitary benign colloid nodule in the left lobe.

Postoperative Course and Investigation.—The patient became clinically and biochemically euthyroid. The lethargy lessened and the menses became normal. P.B.I. 7.4 $\mu\text{g}/100\text{ ml}$, T-3 resin uptake 113%, free thyroxine index 7.2, serum T-3 130 ng/100 ml. Technetium scan showed equal uptake in two small thyroid lobes.

Serum TSH levels on the TRH test were basal 9.6 $\mu\text{U}/\text{ml}$, at 20 minutes 73 $\mu\text{U}/\text{ml}$, at 60 minutes 48 $\mu\text{U}/\text{ml}$ —excessive response compatible with post-thyroidectomy status (Odell *et al.*, 1967; Hedley *et al.*, 1971) (see chart).

Comment

A series of papers in the American literature of the 1930s (Lahey, 1931 a, 1931 b, 1932) first drew attention to cases of thyrotoxicosis presenting in an atypical fashion with profound apathy rather than the more classical hyperdynamic state. Lahey described such patients as sluggish and apathetic, with cool, dry, wrinkled, and pigmented skin. They tended to have the disease in non-activated form for many years and sometimes progressed, particularly postoperatively, into stupor, coma, and even to death without ever passing through an activated phase. There is even yet relatively little in the literature on the presentation of thyrotoxicosis with apathy, testifying to the difficulty of diagnosis and perhaps to the lack of general awareness of the possibility of an apathetic presentation. These patients usually have results typical of hyperthyroidism in conventional thyroid function tests (Lahey 1931 a, 1931 b, 1932; McGee *et al.*, 1959), and so once thyroid disease is suspected the diagnosis is relatively simple to make.

The present case is of special interest in that not only was the clinical diagnosis masked but also the simple conventional thyroid function tests gave normal results. The diagnosis of thyrotoxicosis was suspected clinically when the patient became overtly thyrotoxic on a normal replacement dose of thyroxine. This was substantiated by the failure of suppression of uptake of isotope by the thyroid nodule while she was taking thyroxine and by the absent TSH response to TRH. The final diagnosis was confirmed by the raised serum T-3 level.

This case is also interesting because of the patient's typical "activated" thyrotoxicosis in earlier life, followed some 10 years later by apathetic thyrotoxicosis while producing T-3 in excess, which was apparently converted to typical "activated" thyrotoxicosis on administration of thyroxine.

It is tempting to speculate that these phenomena may be explained by a difference in the tissue response to thyroxine and T-3.

Requests for reprints should be sent to Dr. G. M. Besser.

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