Thyroid disease following the administration of Thorotrast

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SYNOPSIS Four cases of thyrotoxicosis are reported among 35 patients who had been given Thorotrast during the investigation of intracranial haemorrhage. For the group as a whole Thorotrast had been given between 11 and 31 years (mean 23.4 years) before this study. Thyrotoxicosis occurred in four patients between six and 17 years (mean 11.8 years) after the injection of Thorotrast. The fact that thyrotoxicosis did not occur in a small control group of patients who had had a subarachnoid haemorrhage and in whom Thorotrast had not been used at angiography suggests that Thorotrast may be of aetiological significance. In view of the known association between thyrotoxicosis and changes in the lymphoreticular system it is possible that the irradiation of this system by retained thorium has resulted in an abnormality of function which renders these patients more liable to the development of thyrotoxicosis.

A fifth patient developed non-toxic thyroid enlargement 16 years after Thorotrast angiography.

Knowledge concerning the biological effects in man of small body burdens of radioactive material is limited, and is virtually confined to studies on persons, such as luminizers, who have ingested radium, or patients who have received Thorotrast during clinical investigation in the past. Thorotrast, a colloidal suspension of 232 thorium dioxide, was extensively used as a radiographic contrast medium between 1930 and 1947 when its use was largely abandoned following the report of the first malignancy attributable to this compound (MacMahon, Murphy, and Bates, 1947).

Many investigators have been concerned in assessing the risk of the development of malignant disease in internally irradiated populations. For example, it is now known that an increased incidence of osteogenic sarcoma is associated with body burdens of radium in excess of 0.4 μ c. (Dunham, 1958) and haemangioendothelioma of the liver is virtually a Thorotrast-specific tumour (Horta, Abbott, da Motta, and Roriz, 1965). In contrast, there is little or no information concerning the incidence of diseases, other than malignancies, in populations exposed to internal radiation. A reason for this may be that much of the research is concerned with the study of causes of death.

We have recently examined 35 patients who had

received intra-arterial Thorotrast. In this group of patients there was a higher incidence of thyroid disease than might have been expected by chance. The purpose of this paper is to draw attention to this finding and to give details of five cases.

MATERIAL

During investigation in the Department of Surgical Neurology, Edinburgh, 137 patients received intraarterial Thorotrast, usually in the course of carotid angiography. In 1966, 37 survivors were still residing in Edinburgh or nearby. Of these, 35 (18 men and 17 women) were interviewed.

Control information on the incidence of thyroid disease was obtained from the replies to a questionnaire sent to the general practitioners of patients who had not been exposed to Thorotrast.

RESULTS

Two men and two women developed thyrotoxicosis after the injection of Thorotrast. A third woman developed non-toxic thyroid enlargement.

These patients do not differ, with respect to diagnosis or the reason for angiography, from the remainder of the series. In over 80% of the cases angiography was carried out following a diagnosis of subarachnoid haemorrhage. In cases 1 to 4 the diagnosis of

subarachnoid haemorrhage was confirmed, either by the finding of bloodstained fluid on lumbar puncture or by the demonstration of a congenital arterial aneurysm following angiography. The diagnosis of subarachnoid haemorrhage in case 5 was presumptive.

No cases of thyrotoxicosis occurred among 10 men and 12 women in an average follow-up time of 14 years following subarachnoid haemorrhage and in whom angiography had been carried out using a contrast medium other than Thorotrast. In this control group one woman developed thyroid deficiency due to hypopituitarism following subarachnoid haemorrhage.

Apart from case 3 the amount of Thorotrast injected in the cases developing thyroid disease is not significantly different from the mean value of 25.5 ml. based on 30 cases where the dosage was accurately known.

The details of these cases are as follows.

CASE REPORTS

CASE 1 G.C., a man aged 55, at the age of 35 was investigated after a series of episodes with the characteristic symptoms of spontaneous intracranial haemorrhage into the subarachnoid space and into the left temporal lobe. A total of 36 ml. of Thorotrast was injected during bilateral carotid angiography. At craniotomy a large saccular aneurysm was found at the junction of the left internal carotid artery and the posterior communicating artery. This was dealt with by the application of clips to the neck of the aneurysm. No treatment was undertaken for a possible, second, small aneurysm at the junction of the right internal carotid artery and the ophthalmic artery. He made a good recovery apart from some residual dysphasia.

In 1963, following an attack resembling angina pectoris, the patient was treated with digoxin and potassium iodide. In June 1964 he was admitted to hospital complaining of increasing breathlessness, nausea, and abdominal discomfort, and was found to have a spontaneous pneumothorax. In addition, there was atrial fibrillation. The isthmus of the thyroid gland was enlarged.

Tests for thyroid antibodies were negative. The uptake of ^{131}I at four hours was 65%. The T_3 absorption test was in the hyperthyroid range. Liver function tests showed a consistent reversal of the A/G ratio (albumin 3.2 g.%, globulin 3.1 g.%). Alkaline phosphatase was 24 K.A. units, S.G.O.T. 29 units, S.G.P.T. 23 units.

The patient was treated with 6 mc. of ^{131}I and carbimazole and is now euthyroid.

CASE 2 J.S., a man aged 44, at the age of 18 had a spontaneous subarachnoid haemorrhage which produced a right hemiparesis. The diagnosis of subarachnoid haemorrhage was confirmed by lumbar puncture. There is no record of the amount of Thorotrast injected into the left carotid artery and no source of bleeding was visualized. He made a complete recovery and remained well

until March 1966, when he developed dyspnoea on exertion, palpitations, tremor of the hands, and weight loss.

On examination the thyroid was found to be generally enlarged but this was more marked on the left side. Protein-bound iodine measured 11.8 $\mu\text{g.}/100\text{ ml.}$ Following treatment with methylthiouracil and iodine, subtotal thyroidectomy was carried out. Histologically the diagnosis of hyperthyroidism was confirmed. He is now euthyroid.

CASE 3 C.McK., a woman aged 51, at the age of 30 was admitted to hospital, where a diagnosis of spontaneous subarachnoid haemorrhage was confirmed by lumbar puncture. No abnormality was detected following bilateral carotid and bilateral vertebral angiography, at which a total of 90 ml. of Thorotrast was injected.

She made a good recovery and remained well for five years when she developed exophthalmos, tiredness, irritability, palpitations, and weight loss, for which she was admitted to hospital.

Examination revealed a tense, nervous woman with marked exophthalmos. There was generalized enlargement of the thyroid gland. The basal metabolic rate was elevated (+45%). Following treatment with phenobarbitone and methylthiouracil she became euthyroid and has remained so.

CASE 4 L.G.H., a woman aged 61, at the age of 49 was investigated following two episodes suggestive of subarachnoid haemorrhage, after the second of which she developed a right third nerve paresis.

A total of 18 ml. of Thorotrast was injected during bilateral carotid angiography. Ligation of the right carotid artery in the neck was carried out following the demonstration of a saccular aneurysm at the junction of the right internal carotid artery and the posterior communicating artery.

She remained in good health for nine years, but in 1964 she was admitted to hospital complaining of nervousness, insomnia, and weight loss associated with increased appetite. A history of thyroid enlargement at the age of 16 was elicited.

On examination the thyroid gland was diffusely enlarged and nodular. The palpebral fissures were widened. The uptake of ^{131}I was 74% at four hours.

Following treatment with two doses of 5 mc. of ^{131}I she became euthyroid.

CASE 5 B.V., a woman aged 40, at the age of 16 was admitted to hospital for the investigation of localized epilepsy and left hemiparesis. At the age of 4, she was thought to have had meningitis but in retrospect this episode could have been due to a subarachnoid haemorrhage. An arteriovenous malformation in the right parietal region was demonstrated following right carotid angiography at which 20 ml. of Thorotrast was injected. The malformation was treated by x-ray therapy.

Sixteen years after angiography she was referred to hospital with symptomless thyroid enlargement which was more marked on the right side and had been present for one year. A diagnosis of non-toxic goitre was

TABLE I
DETAILS OF CASES DESCRIBED

Case	Sex	Age (yr.)	Details of Angiography			Details of Thyroid Disease			
			Reason for Investigation and Findings on Angiography	Site(s) of Injection	Amount of Thorotrast (ml.)	Age at Onset (yr.)	Diagnosis	Site of Enlargement	Interval from Thorotrast (yr.)
1	M	35	Subarachnoid haemorrhage Bilateral aneurysms	R. + L. carotid	36	53	Thyrotoxic heart disease	Isthmus	17
2	M	18	Subarachnoid haemorrhage No abnormality detected	L. carotid	?	44	Thyrotoxicosis	Diffuse L. > R.	16
3	F	30	Subarachnoid haemorrhage No abnormality detected	R. + L. carotid	90	35	Thyrotoxicosis	Diffuse	5
4	F	49	Subarachnoid haemorrhage Aneurysm R. int. carotid	R. + L. vertebral	18	59	Thyrotoxicosis	Diffuse nodular	9
5	F	16	Epilepsy L. hemiparesis Arteriovenous malformation	R. carotid	20	32	Non-toxic goitre	Diffuse nodular	16

confirmed at operation when partial thyroidectomy was carried out.

The left hemiparesis persists. Epilepsy is controlled by phenobarbitone. She is euthyroid.

The main features of these cases are summarized in Table 1.

DISCUSSION

We have been unable to obtain figures for the incidence of thyroid disease in Scotland. Logan and Cushion (1958) have reported the incidence of thyrotoxicosis in England and Wales to be 0.3 and 1.9 per 1,000 for males and females respectively. If one assumes that the corresponding figures for Scotland do not differ significantly from those given by Logan and Cushion the incidence of thyrotoxicosis in our cases is some 16 times greater than expected in males ($P < 0.005$), and some two and a half times greater in females.

There are several features common to the four cases developing thyrotoxicosis. Each suffered a spontaneous subarachnoid haemorrhage, in the course of investigation of which angiography, using Thorotrast, was carried out. No cause for the haemorrhage was demonstrated in two cases and no definitive treatment was undertaken. In the remaining two cases the haemorrhage occurred from an arterial aneurysm which was dealt with surgically.

Angiography, using Thorotrast, was carried out in a fifth patient who subsequently developed non-toxic thyroid enlargement. Although there is no definite history of subarachnoid haemorrhage in this patient an arteriovenous malformation was demonstrated, and was subsequently treated by x-ray therapy.

On the basis of four cases, and without fuller investigation, it is not possible to say whether the cases of thyrotoxicosis which developed in this series are aetiologically distinct, although an equal sex

ratio is in contrast to that normally found in large series where the incidence in females is some six times greater than in males (Logan and Cushion, 1958).

In the majority of cases of thyrotoxicosis occurring in this country, the gland shows diffuse hyperplasia. The cases which we are reporting did not differ in this respect. The gland was diffusely enlarged in three patients, two of whom had either exophthalmos or lid retraction. In the fourth patient, who presented with thyrotoxic heart disease, only the thyroid isthmus was palpably enlarged.

In common with the remaining cases in the series the patients who developed thyrotoxicosis had characteristic changes in the peripheral blood, consisting of a disturbance of red cell morphology and the presence of Howell-Jolly bodies in erythrocytes. These have been reported in detail by Langlands and Williamson (1967) who concluded that, as a result of radiation by the particles of thorium retained in reticulo-endothelial cells, there was a considerable disturbance of splenic function amounting to atrophy of that organ. Schur (1908) has also recorded the association of thyrotoxicosis and the presence of Howell-Jolly bodies in the erythrocytes of a patient in whom splenic atrophy was found at post-mortem examination.

More usually thyrotoxicosis is associated with splenomegaly, and, according to Williams (1962), this is but one aspect of a more generalized disturbance of the lymphoreticular system which occurs in a proportion of cases of thyrotoxicosis. This may be manifest as splenomegaly, generalized lymphadenopathy, thymic enlargement, or peripheral blood changes such as lymphocytosis or neutropenia. The association of thyrotoxicosis and lymphoreticular changes is an intriguing one. Autoantibodies occur in a proportion of cases of thyrotoxicosis and the long-acting thyroid stimulator (L.A.T.S.), for which a pathogenic role has been claimed, is an immuno-

globulin arising from cells of the lymphoreticular system (McKenzie, 1962).

In the cases which we report, following Thorotrast administration, the evidence for splenic atrophy is indirect and is inferred from peripheral blood changes. Thorotrast is retained by lymphoreticular cells and the possibility of abnormal function of these cells, as opposed to simple loss of function, is worth investigation.

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ADDENDUM

Since submission of the manuscript a further case of thyroid disease following Thorotrast administra-

tion has been seen in a woman of 55. In 1947, at the age of 35, she suffered a spontaneous subarachnoid haemorrhage, the diagnosis being confirmed by lumbar puncture. No source of bleeding was demonstrated following bilateral carotid angiography when 32 ml. of Thorotrast was injected. In 1953, during investigation in hospital for an iron-deficiency anaemia, asymptomatic enlargement of the thyroid gland was noted. When seen in 1967 the thyroid gland remained moderately enlarged, the enlargement affecting mainly the right lobe. Clinically she was euthyroid. The level of protein-bound iodine was $4.3 \mu\text{g}/100 \text{ ml}$. ^{131}I uptake was normal at four hours.

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