limb following radical mastectomy: two such patients have been treated in this way with initial improvement, but too recently for inclusion in this report.

Summary

A new "physiological" operation for the treatment of chronic lymphoedema of the lower limb is reported which involves the transposition of subcutaneous lymphatics into the deep (subfascial) compartment of the limb by means of a buried "shaved" skin-flap. In this way the internal drainage of lymph from the lymphoedematous subcutaneous compartment into the deep lymphatics—or, more probably, the muscle venules—is attempted.

Three illustrative case reports are submitted after follow-up for periods of from one to two and a half years. Two patients with obstructive lymphoedema have yielded good results, with considerable reduction in size of the limb and restoration to normal activity. One patient with primary lymphoedema due to lymphatic hypoplasia has been improved.

The operation would appear to have its principal indication in the treatment of limbs presenting appreciable enlargement from readily pitting lymphoedema, in the presence of valved superficial lymphatics. There is evidence, however, that subcutaneous fibrosis may undergo resolution after the operation.

In the patient with obstructive lymphoedema first treated the clinical response to burying the "shaved" skin-flaps in varying directions at separate operations demonstrated the advisability of burying the flaps in the direction of superficial lymph flow. Further experience is necessary fully to assess the value of the method in treating cases of primary lymphoedema; particularly in the presence of the hyperplastic type of developmental abnormality, re-orientation of the flaps may prove necessary to drain the dilated and valveless subcutaneous lymphatic channels, often associated with dermal backflow, demonstrable by radiographic lymphangiography.

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EFFECT OF DESFERRIOXAMINE AND D.T.P.A. IN IRON OVERLOAD

BY

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Accumulation of excess iron in the body is associated with such complications as cirrhosis of the liver, diabetes mellitus, and heart failure. Patients suffering from idiopathic haemochromatosis may be improved by repeated venesections, which remove the excess iron (Finch and Finch, 1955), but in patients with haemosiderosis following repeated transfusions for various types of refractory anaemia venesection is obviously not feasible, and such subjects—for example, children with thalassaemia major—may be kept alive by transfusion, only to die later from intractable cardiac failure associated with iron deposition in the heart muscle (Smith *et al.*, 1960).

The therapeutic use of chelating agents led to the hope that one might be found which would have a high specificity for iron. Although the earlier developed agents dimercaprol and ethylenediamine-tetra-acetate (E.D.T.A.) will both remove some iron from the body (Ohlsson *et al.*, 1953; Seven *et al.*, 1954) neither is quantitatively very effective. Diethylenetriamine-penta-acetate (D.T.P.A.), another substance related to E.D.T.A., has been shown to remove significant quantities of iron in iron-storage disease (Fahey *et al.*, 1961). Bickel *et al.* (1960) have described a different type

of iron-chelate, ferrioxamine, which was isolated from *Streptomyces pilosus* during the investigation of iron-containing metabolites with growth-stimulating properties for a number of micro-organisms. Ferrioxamine is a brownish-red complex from which the trivalent iron may be removed by chemical methods to give the corresponding iron-free compound desferrioxamine (Fig. 1).

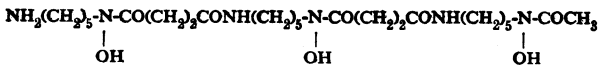

FIG. 1.—Chemical formula for desferrioxamine B.

Desferrioxamine B, which is the chief product of Ciba's streptomyces strain, will theoretically take up 9.3 parts of trivalent iron for every 100 parts by weight (Vischer, 1961). The stability of ferrioxamine is remarkably high at neutral *p*H, and desferrioxamine has a high degree of specificity for trivalent iron. *In-vitro* experiments show that it will remove iron from the main protein complexes, transferrin, haemosiderin, and ferritin (Wöhler, 1961). Both ferrioxamine and desferrioxamine are very readily soluble in water.

Desferrioxamine B appears to offer several advantages over other chelating agents, and this paper reports our observations on the effect of this substance in normal subjects and in patients with iron overload. It includes, for comparison, one patient treated with D.T.P.A.

Materials and Methods

Complete 24-hour collections of urine in iron-free glassware were made before, during, and after courses of chelate treatment in 10 subjects. Three were men with supposedly normal iron stores and the rest were patients with various degrees of iron overload.

The iron in the urine was estimated by a modification of the method of Bothwell and Mallett (1955). All estimations were done in duplicate. Preliminary investigations showed that results by this method compared well with parallel determinations made after wet ashing of urine samples with sulphuric and nitric acids, and with independent analyses carried out in the Research Department of Ciba Limited, Basle (Peters, personal communication).

In one subject the fate of an intravenous injection of ^{59}Fe-ferrioxamine was studied by estimation of radioactivity in the plasma, whole blood, and urine, and by *in-vivo* counting over sacrum, heart, liver, and spleen.

Results

Normal Subjects

Three male subjects (Cases 1 to 3) who were normal from the haematological standpoint (two with hypertension and one convalescing from a myocardial infarction) were each given three injections of 200 mg. of desferrioxamine intramuscularly during a 24-hour period. All showed an increase of about 1 to 1.5 mg. of urinary iron excretion above the baseline values (Table I).

TABLE I.—*Effect of 600 mg. Desferrioxamine (D.F.) on Urinary Iron Excretion in Three Men with Normal Iron Stores*

Case	Day	Treatment	24-hour Urinary Fe (mg.)
1	1	—	0·02
	2	600 mg. D.F.	0·94
	3	—	0·31
	4	—	0·16
2	1	—	0·69
	2	600 mg. D.F.	1·64
	3	—	0·77
3	1	—	0·32
	2	600 mg. D.F.	1·75
	3	—	0·79

Transfusion Siderosis

Two patients with aplastic anaemia were studied.

Case 4.—The patient was diagnosed as suffering from aplastic anaemia in 1955 at the age of 50. He has since required transfusion at approximately six-week intervals. In 1961 he developed diabetes mellitus while receiving A.C.T.H. and he also showed some signs of cardiac failure. At the time of study he had received 322 bottles of blood. He was deeply pigmented, showed heavy deposits of iron in bone-marrow and liver biopsy, and his serum iron was 280 μg./100 ml.

This man was given an intravenous infusion of D.T.P.A. (2 g. in 500 ml. of 5% glucose in 0.18% sodium chloride over six hours) at the end of a blood transfusion. Next day he received two intramuscular injections of 1 g. of D.T.P.A. The intravenous infusion was well tolerated, but the intramuscular injections caused great pain, which persisted for several days. The total amount of iron excreted after these injections was 51.2 mg. (Table II).

Case 5.—A married woman developed aplastic anaemia in 1954 when aged 39. At the time of study in 1962 she had received 274 bottles of blood by transfusion and showed marked pigmentation of transfusion siderosis. Liver biopsy revealed a heavy deposition of iron.

This patient was given initially a single intravenous infusion of 600 mg. of desferrioxamine in 1,500 ml. of 0.9% sodium chloride over nine hours. She developed a fever, but this was associated with typical influenzal symptoms and similar intercurrent illness was very prevalent in the ward at the time. Several days later, when she had recovered from this intercurrent episode, she was given 200 mg. of desferrioxamine by intramuscular injection three times a day for one week. The amount of iron excreted in the urine was 7.78 mg. after the intravenous dose and approximately 59 mg. after the intramuscular injections.

TABLE II.—*Effect of D.T.P.A. and Desferrioxamine (D.F.) on Urinary Excretion of Iron in Subjects with Iron Overload*

Case No.	Diagnosis	Treatment			Iron Excretion in Urine (mg.)			
		Route	Chelate	Total (G.)	Baseline per Day	Total with Treatment	Estimated Excess Excreted	(mg) Fe/G. Chelate
4	Transfusion siderosis ..	I.V. and I.M.	D.T.P.A.	4·0	0·63	51·2	48·7	12·2
5	,, ,,	I.V.	D.F.	0·6	0·70	7·78	6·4	10·7
		I.M.	D.F.	4·2	0·70	59·54	53·2	12·7
		Oral	D.F.	1·8	0·54	2·34	0·7	0·4
		I.M.	D.F.	2·4	0·54	34·19	28·8	12·0
6	Sideroblastic anaemia ..	I.M.	D.F.	6·0	0·63	105·0	98·1	16·4
7	Refractory ,, ..	I.M.	D.F.	0·6	0·02	5·74	5·7	9·5
8	Haemochromatosis ..	I.M.	D.E.	6·0	1·20	179·3	164·9	27·5
9	,,	Oral	D.F.	1·8	1·10	4·6	1·3	0·7
		I.M.	D.F.	2·4	1·10	85·9	79·3	33·0
10	Haemochromatosis (partially treated)	Oral	D.F.	1·8	0·36	3·67	2·1	1·2
		I.M.	D.F.	2·4	0·40	21·10	19·1	8·0

On a subsequent admission this patient was given 200 mg. of desferrioxamine by mouth three times a day for three days. This produced a doubtful slight increase in iron excretion. A second course of intramuscular desferrioxamine (200 mg. t.d.s. for four days) resulted in the excretion of 34 mg. of iron in the urine (Table II, Fig. 2).

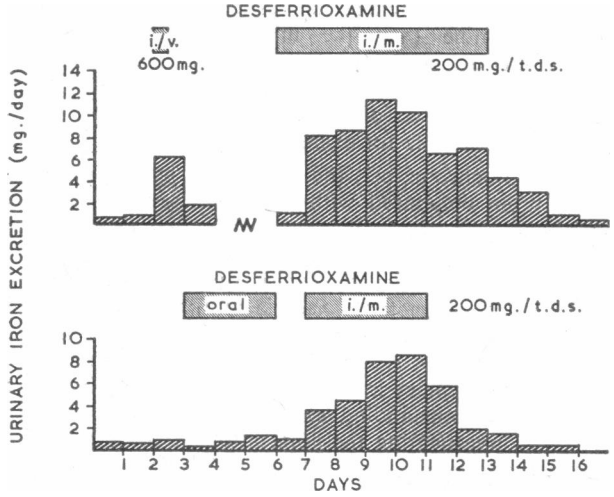

FIG. 2.—Case 5. Excretion of iron in urine of patient with transfusion siderosis treated with desferrioxamine.

Refractory Sideroblastic Anaemia

Case 6.—A married woman was diagnosed in 1958 at the age of 68 as a case of refractory sideroblastic anaemia. She was treated with pyridoxine both orally and parenterally with no definite benefit and had required transfusion at intervals. At the time of study she had received a total of 37 bottles of blood. Her serum iron was 216 μg./100 ml. She was not notably pigmented.

She was given 10 days' treatment with desferrioxamine (200 mg. three times a day by the intramuscular route). This resulted in an excretion of 105 mg. of iron in her urine (Table II, Fig. 3).

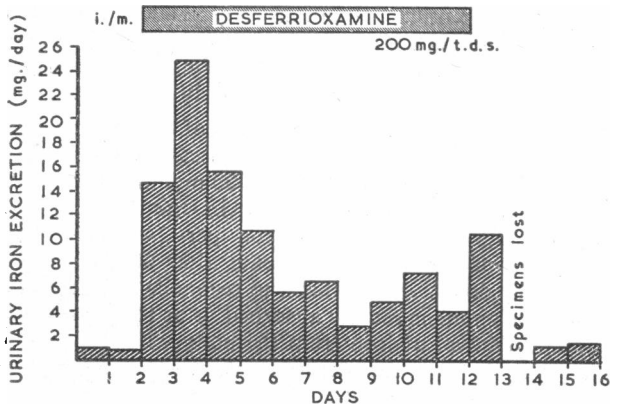

FIG. 3.—Case 6. Excretion of iron in urine of patient with refractory sideroblastic anaemia treated with desferrioxamine.

Refractory Anaemia. ? Reticulosis

Case 7.—A 52-year-old man suffered from a refractory anaemia the cause of which was probably a reticulosis. He had received approximately 15 bottles of blood during the course of his illness and some parenteral iron. He was observed to have excess iron in the bone-marrow but had no other evidence of iron-storage disease.

Three injections of 200 mg. of desferrioxamine resulted in an increase in urinary iron excretion of some 5 mg. above the baseline value (Table II).

Idiopathic Haemochromatosis

Three male patients with classical idiopathic haemochromatosis were studied.

Case 8.—This patient presented as an emergency admission with diabetic ketosis at the age of 60. In addition to the clinical features of haemochromatosis, biopsies showed excessive iron deposits in bone-marrow, gastric mucosa, and liver. The serum iron was high (200 to 280 μg./100 ml.). His iron absorption, tested with 5 mg. of ^{59}Fe given as labelled haemoglobin (Callender *et al.*, 1957) was high for an iron-laden subject (23%) and the utilization was low (1.7%).

A course of 200 mg. of desferrioxamine intramuscularly three times a day for 10 days resulted in a total iron excretion of 179.3 mg. (Table II, Fig. 4).

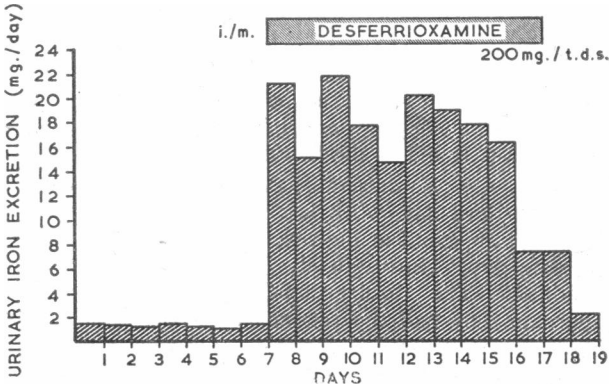

FIG. 4.—Case 8. Excretion of iron in urine of patient with haemochromatosis treated with desferrioxamine intramuscularly.

Case 9.—This patient was diagnosed in 1956 as having cirrhosis of the liver. In 1962 at the age of 59 he developed the full clinical picture of haemochromatosis with pigmentation, cirrhosis, diabetes, and gonadal atrophy. Liver biopsy showed a characteristic picture with heavy iron deposition, and the serum iron was 295 μg./100 ml.

A short oral course of desferrioxamine (200 mg. three times a day for three days) was accompanied by a slight increase in iron excretion, but by the intramuscular route 200 mg. given three times a day for four days produced an excretion of 85.9 mg. of iron in the urine (Table II).

Case 10.—This man of 59 had been diagnosed as suffering from haemochromatosis in 1961. He had diabetes, and liver biopsy had shown characteristic fibrosis and heavy iron deposition. At the time of study he had been partially treated by venesection (total 38 pints; 21.6 litres) but was still pigmented and his serum iron was high (264 μg./100 ml.).

He received 200 mg. of desferrioxamine by mouth three times a day for three days with little effect. Four days' intramuscular injections of 200 mg. three times a day resulted in a total iron excretion of 21 mg. (Table II).

Intravenous Injection of ^{59}Fe-ferrioxamine

One normal subject was given intravenously 200 μg. of desferrioxamine labelled with 12 μg. of $^{59}Fe^{+++}$—that is, an excess of desferrioxamine so that all the labelled iron was presumed to be bound. The disappearance of ^{59}Fe from the plasma, the excretion in the urine, and the pattern of *in-vivo* counting were studied.

In contrast to the clearance curve seen when ^{59}Fe is given to normal subjects as labelled plasma (Huff *et al.*, 1950), the disappearance of ^{59}Fe-ferrioxamine does not follow a simple exponential curve (Fig. 5). The picture is complicated, for not only is ^{59}Fe removed from the

plasma to tissues but at the same time a large proportion of the dose is excreted in the urine. Plasma activity

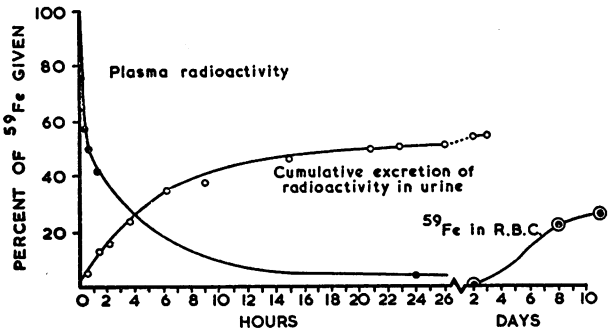

FIG. 5.—Results obtained on giving ^{59}Fe-ferrioxamine intravenously.

dropped to half the initial value after 40 minutes, but 4% was still detectable at 24 hours. A total of 37.8% of the dose was excreted in the urine over the first nine hours and 55% by the end of three days. Negligible activity was found in the faeces during this time.

No activity was detectable in circulating erythrocytes until the third day, when less than 1% had appeared; 22% had appeared at the seventh day and 26% on the eleventh day. Unfortunately further samples were not obtained. The results indicated that at 11 days approximately half the retained radioactivity had been utilized in red-cell formation. Surface counting suggested that the remainder was retained in the liver and spleen.

Discussion

Desferrioxamine promises to be the most useful chelating agent for iron yet available. Its marked specificity for iron as opposed to other metals or the alkaline earths makes it improbable that, even with long-term treatment, it will deplete the body of other important substances. In our experience repeated intramuscular injections have been well tolerated and are not painful.

Our normal male subjects excreted significantly increased amounts of iron after parenteral desferrioxamine. This is in agreement with Wöhler's (1961) findings and reflects the remarkable avidity of desferrioxamine for iron. Such an increase was not observed by Fahey *et al.* (1961) in normal subjects after D.T.P.A.

The patients with iron overload showed considerable increase in iron excretion whether the desferrioxamine was given by the intravenous or the intramuscular route. Wöhler (1961) has suggested that intravenous infusion is more effective, but other workers have not confirmed this (Pitcher, 1961; Maier, 1961).

The amount of iron removed per gramme of desferrioxamine given parenterally to subjects with iron overload varied from 8 to 33 mg. It was of the same order in the patient treated with D.T.P.A. and similar figures are reported by Fahey *et al.* (1961).

As other workers have observed with both D.T.P.A. and desferrioxamine, excretion of iron tends to be maximal at the beginning of treatment. This suggests that only the readily mobilizable iron is available for excretion (Fahey *et al.*, 1961; von Schnack, 1961). For this reason there seems little advantage in giving continuous therapy, and intermittent courses would probably be the most effective and economical way of using the material.

Fahey *et al.* (1961) have attempted to correlate the amount of iron removed with the extent of iron overload. If such a correlation could in fact be made a desferrioxamine test might usefully be applied—for example, for detection of affected relatives of patients with haemochromatosis. In this connexion it is of interest to note that our patient with partially treated haemochromatosis excreted less iron per gramme of desferrioxamine than the untreated patients. This, however, could equally well be interpreted as indicating that the readily mobilizable iron had already been removed by venesection and that the iron remaining was less easily available for excretion.

In haemochromatosis the amount of iron removed is small when compared with the much greater quantity which may be removed by venesection, and the latter clearly remains the treatment of choice in this condition. However, where venesection is impracticable, as in patients with refractory anaemia requiring blood transfusion, desferrioxamine given in anticipation before the patient is already becoming loaded with iron may well be a useful adjunct in treatment. Thalassaemia major provides an outstanding example, and Sephton Smith (1962) is investigating the application of such treatment to the problem of iron overload in these children.

There are two acute situations in which desferrioxamine might be of great value in immediately rendering iron non-toxic and removing it through the urine. The first is in the treatment of acute iron-poisoning—for example, in children who have ingested ferrous sulphate tablets. The second, more speculative, is in the treatment of the acute shock-like episodes which have been reported in haemochromatosis and are supposedly due to the sudden release of ferritin.

Wöhler (1962) has presented results of some metabolic studies with desferrioxamine and ^{59}Fe-tagged ferrioxamine. After intravenous injection more than 90% of the radioactivity of ^{59}Fe-ferrioxamine was accounted for in the urine within two days. This is in contrast to our finding in a single normal subject, who excreted only 55% and utilized approximately half of the amount retained in red-cell formation. Our differing results may be due to variations in dosage and technique, and further investigation along these lines is clearly desirable.

The effect of oral administration of desferrioxamine raises some very interesting possibilities. Wöhler (1961) has reported that an oral dose of 600 mg. in two patients with haemochromatosis resulted in the excretion of between 7.5 and 8 mg. of iron per 24 hours. We observed only a doubtful increase after 600 mg. given in divided doses. It is difficult to reconcile the view that desferrioxamine is readily absorbed so as to be available for the removal of iron from the body with the suggestion that it may chelate iron in the gut and reduce absorption (*Lancet*, 1962). Preliminary results testing its effects on absorption of labelled inorganic iron in animals (J. Kebrle, 1961, personal communication; Bannerman, unpublished observations, 1962) indicate that absorption of iron in this form may be reduced. This cannot necessarily be extrapolated to mean that the absorption of food iron can be reduced by desferrioxamine, and in the observations that we have made with ^{59}Fe-tagged haemoglobin we have been unable to demonstrate any consistent effect (unpublished observations). Blocking the absorption of food iron would be an important aid in treatment of iron overload and the effect of desferrioxamine merits further investigation.

Summary

The excretion of iron in the urine has been studied before and during treatment with a new chelating agent for iron, desferrioxamine.

Three male subjects with presumably normal iron stores showed an increased iron excretion of 1 to 1.5 mg. of iron after 600 mg. of the chelate.

Patients with various types of iron overload all showed a marked increase in iron excretion when the material was given parenterally (8 to 33 mg./g. of chelate).

A similar effect was noted in one subject with siderosis given D.T.P.A.

The possible therapeutic uses of such chelating agents are discussed.

We are grateful to the Geigy Company for supplies of D.T.P.A. and to Ciba Ltd., of Horsham and Basle, for a generous supply of desferrioxamine B and for unpublished information about this material. We also thank Professor L. J. Witts and Dr. E. M. Buzzard for permission to study patients under their care.

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IRON EXCRETION IN THALASSAEMIA MAJOR AFTER ADMINISTRATION OF CHELATING AGENTS

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Blood transfusion is at present the only treatment for the refractory anaemia of thalassaemia major, and by this means, together with improved general medical care, the survival of children with this condition can be greatly prolonged. As a consequence iron accumulates from the repeated transfusions, together with that absorbed from food, and is deposited in the tissues. Eventually impaired organ function and pathological changes closely resembling those of idiopathic haemochromatosis may be found (Whipple and Bradford, 1936; Ellis *et al.*, 1954; Witzleben and Wyatt, 1961).

Removal of significant quantities of iron from these children would represent a major advance in treatment. Recently two new chelating agents have been introduced which have a high affinity for iron, and both have been shown to promote significant iron excretion when given parenterally to adults with iron overloading due to haemochromatosis or transfusion haemosiderosis. Fahey *et al.* (1961) reported the use of trisodium calcium diethylenetriamine-penta-acetate (D.T.P.A.) in three patients, including one 33-year-old woman with thalassaemia and transfusion haemosiderosis. More recently, iron excretion following the administration of desferrioxamine (" desferal ") to a number of adults with haemochromatosis or transfusion haemosiderosis has been reported (Ciba, 1961; Bannerman *et al.*, 1962b). In the present study urinary iron excretion was measured in a group of thalassaemic children following parenteral doses of desferrioxamine or D.T.P.A.

Materials and Methods

Of the 18 patients studied 17 were classical cases of thalassaemia major. All had a refractory anaemia with a greatly increased proportion of alkali-resistant haemoglobin, hepatosplenomegaly, and radiological bone changes. The majority had been transfused at regular intervals, and some showed clinical evidence of iron overloading. One patient with congenital pure red-cell aplasia (Case 18) who had been regularly transfused since the age of 3 months is also included. Relevant details are shown in Table I.

As supplies of desferrioxamine and D.T.P.A. were limited, it was decided initially to study the effect of single treatments in a fairly large group; later it became possible to study the effect of repeated doses in a few patients. The chelating agents were usually given intravenously at the time of blood transfusion. When a patient received several treatments, these were given with successive transfusions at intervals of 5 to 12 weeks, depending on the patient's transfusion requirements. Half the dose was usually given immediately before transfusion, and the remainder afterwards: in each case it was given by slow infusion in 100–400 ml. of saline, according to the size of the child. Infusions of 100 mg. in Case 4 and of 200 mg. in Case 18 were given undivided before transfusion.

In a few patients desferrioxamine was given intramuscularly; it was found that 200 mg. could be dissolved in 3 ml. of saline. In Cases 4 and 18 the intramuscular dose was given three days before an equal intravenous dose; the repeated intramuscular doses in Case 6 were given on successive days, and in Case 10 the two intramuscular doses were given 24 and 48 hours after the intravenous infusion. At first 100–400 mg. of desferrioxamine was given, as preliminary experience in adults suggested that no additional advantage was gained by increasing the dose above 800 mg. (Ciba, 1961). D.T.P.A. was given in doses of 500–2,000 mg. in view of the experience of Fahey *et al.* (1961), who used doses of 2,500–4,000 mg. in adults.