Widely Varying Results Achieved in Ventilation Studies Prior to the Advent of Muscle Relaxants. (After Cordier, 1943.)

Experimental Conditions	Author	Lung Ventilation in c.c.m.	
		Schafer's Method	Silvester's Method
1. Subjects having voluntarily suspended their breathing	"Suspended Animation" Committee (1903) Schafer (1904) Burton-Opitz (1922) Ploman (1906) Hamburger (1909) Liljestrand <i>et al.</i> (1913) Eve (1932) Killick and Eve (1933)	366 520 504 (average) 500-600 616 500 1,000 350-550	458 178 — 1,200-2,000 454 540 — 200
2. Subjects in apnoea	Liljestrand <i>et al.</i> (1913) Héderer (1934)	170 100-150	190 250-280
3. Non-rigid cadaver	Héderer (1934) Bruns (1927) Bruns and Thiel (1930)	40-50 20 20	200 200 200
4. Apnoeic patients in moderately deep anaesthesia	Waters and Bennett (1936)	2 females, 180 (average) 2 males, 662 (average)	214 (average) 933 (average)

We furthermore believe that this method may have wider applications beyond those of the operating theatre—for instance, in coal-gas poisoning, drowning, electric shock, and so forth.

Summary

A new method of resuscitation after respiratory and circulatory arrest is described which has been successfully employed on eight children. There has not been one single fatality. The method consists basically in intermittently flexing and extending the whole body, to which may be added positive-pressure inflation of the lungs with oxygen.

It is believed that the method represents a sound and effective approach to dealing with cardiac arrest in children. Though it has been used by us only in the operating theatre, we think it may have wider applications.

It is more rapidly and more easily applied than other methods.

Five illustrative cases are reported.

We wish to acknowledge our debt to many house officers, anaesthetists, and nursing staff who have at various times helped us in the management of patients. We also thank Mr. John Holloway for the diagrams and Miss Barbara Houlton for preparing the manuscript.

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THE CLINICAL APPLICATIONS OF TRIIODOTHYRONINE

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Until recently thyroxine was considered to be the active thyroid hormone; however, its characterization by Harington (1926) and Harington and Barger (1927) was not followed by its extensive clinical use, desiccated thyroid being in general preferred. Gross and Pitt-Rivers (1952a) identified as triiodothyronine an unknown iodinated compound in the sera of patients treated with therapeutic doses of ^{131}I . Later this amino-acid was detected (Roche, Lissitzky and Michel, 1952a, 1952b; Gross and Pitt-Rivers, 1953a) in thyroid substance. The high biological potency of triiodothyronine, first observed by Gross and Pitt-Rivers (1952b) in rats, and by Gross, Pitt-Rivers, and Trotter (1952) in hypothyroid humans, has now been amply confirmed (MacLagan, Sprott, and Wilkinson, 1952; Colville and Bonnycastle, 1953; Deltour and Karamourtzounis, 1953; Heming and Holtkamp, 1953a, 1953b; Tomich and Woollett, 1953, 1954; Anderson, 1954). The results have shown that triiodothyronine is approximately five times as active as thyroxine on a molar basis. Some experiments, however, on intact animals have not shown any significant difference between triiodothyronine and thyroxine (Gemmell, 1953; Heming and Holtkamp, 1953a; Brown-Grant, 1955).

Various workers have compared the physiological effects of L-triiodothyronine and L-thyroxine in myxoedematous patients (Asper, Selenkow, and Plamondon, 1953; Lerman, 1953; Rawson, Rall, Pearson, Robbins, Poppell, and West, 1953; Blackburn, McConahey, Keating, and Albert, 1954; Blackburn and Keating, 1954; Starr, Snipes, and Liebhold-Schueck, 1955; Selenkow and Asper, 1955). It has been shown that L-triiodothyronine is three to five times as active as L-thyroxine on a molar basis: although there is a significant difference in the speed with which L-triiodothyronine produces metabolic changes, it appears to be qualitatively identical to L-thyroxine.

It has been suggested that triiodothyronine is formed as the result of the reductive deiodination of thyroxine (Gross and Pitt-Rivers, 1952b, 1953b) or by the coupling of one molecule of monoiodotyrosine with one molecule of diiodotyrosine (Roche, Lissitzky, and Michel, 1953). It is evident that coupling, as described above, can be expected to occur only in the thyroid gland. It has been shown by *in vivo* experiments on animals that thyroxine is converted to triiodothyronine in the peripheral tissues (Gross and Leblond, 1951; Flock and Bollman, 1955; Kalant, Lee, and Sellers, 1955; Hogness, Berg, Van Arsdell, and Williams, 1955). Pitt-Rivers, Stanbury, and Rapp (1955) demonstrated that triiodothyronine can be formed from thyroxine in human subjects in the absence of the thyroid gland. On the other hand, Roche and

Michel (1954) and Roche, Michel, and Tata (1954) have been unable to demonstrate the formation of triiodothyronine in the peripheral tissues, and have concluded that the thyroid gland is the only source of circulating triiodothyronine. Benua, Dobyns, and Nimmer (1955) studied the rate of appearance of triiodothyronine in the plasma of patients given therapeutic doses of ^{131}I for hyperthyroidism or cardiac disease, and concluded from its early appearance in the serum that it was released from the thyroid gland and was not simply a result of the deiodination of thyroxine in the peripheral tissues.

In vitro experiments have shown that conversion of thyroxine to triiodothyronine can occur in kidney slices (Albright, Larson, and Tust, 1954; Larson, Tomita, and Albright, 1955) and in homogenates of liver, kidney, and other tissues (MacLagan and Sprott, 1954). It is evident that the exact mechanism for the biological synthesis of triiodothyronine requires further study.

The iodinated organic compounds of the blood are closely associated with plasma protein and are precipitated with it. It has been shown by paper electrophoresis that thyroxine is associated with a globulin fraction between α_1 and α_2 (Deiss, Albright, and Larson, 1952; Robbins and Rall, 1952). Triiodothyronine is associated with this same protein fraction, but the α -globulin-triiodothyronine complex is less stable than that of thyroxine (Deiss, Albright, and Larson, 1953). This may account for the more rapid disappearance of triiodothyronine from the serum shown by Sterling, Lashof, and Man (1954), who compared the disappearance rates of ^{131}I -labelled thyroxine and triiodothyronine from the serum in euthyroid subjects.

Triiodothyronine differs from other thyroxine analogues in that it is a normal constituent of human plasma and is the only substance so far detected which has a greater activity than naturally occurring thyroxine. It differs from thyroxine in its speed of action, but there is no evidence of any qualitative difference between triiodothyronine and thyroxine. Any clinical applications must obviously depend on its rapid effect. It may be of interest to discuss certain conditions in which we have had experience of its use during the past two years.

Rapid Correction of Hypothyroidism

It is not usually necessary or even desirable to correct myxoedema rapidly. On rare occasions the correction of hypothyroidism may be a matter of urgency; this is illustrated in the following case history.

Case History

A man aged 52 was given a therapeutic dose of ^{131}I in December, 1953, to ablate the thyroid gland. He had suffered from severe angina of effort for several years, which was becoming progressively worse. He had been maintained on carbimazole prior to ablation of the thyroid, and had been greatly benefited by this treatment.

Following ablation of the thyroid he was kept on a maintenance dose of 0.1 mg. of L-thyroxine daily, on which dose he remained almost free of angina and was able to resume light work. He obtained his supply of thyroxine from hospital until September, 1954, at which time it was arranged that he should obtain further supplies from his local chemist. At his next attendance, in February, 1955, it was noted that his weight had increased by a stone (6.4 kg.), but he was otherwise well. Five weeks later, in April, 1955, he was seen at the request of his doctor, who reported that he had developed religious mania. His wife confirmed that

he had taken his dose of thyroxine regularly and that he had become mentally abnormal quite suddenly about a week before.

On examination it was apparent that he was suffering from a paranoid psychosis. He was not retarded, and maintained a degree of animation which might have been considered incompatible with a psychosis due to hypothyroidism. Knowing his usual appearance, a slight alteration in his facial expression and some puffiness of the lower lids was noticeable. The skin of his forearms was dry and scaly, but there were no other signs of hypothyroidism. It was thought that the paranoia had been precipitated by hypothyroidism, and a plasma cholesterol of 510 mg. per 100 ml. confirmed this opinion. It was difficult, however, to understand why this should have occurred after he had been maintained in a satisfactory state on a maintenance dose of 0.1 mg. of thyroxine daily for over a year.

Before he could be admitted to hospital he became violent and was admitted to an observation ward. He was transferred to Hammersmith Hospital the following morning. On admission he was given 10 $\mu\text{g.}$ of L-triiodothyronine intravenously followed by a maintenance dose of 0.1 mg. of L-

FIG. 1.—Effect of L-triiodothyronine and L-thyroxine on plasma cholesterol and body weight in a patient with hypothyroidism.

thyroxine orally. A perceptible increase in the peripheral circulation with cutaneous flushing was noted within two hours of giving triiodothyronine. Triiodothyronine was given by intravenous injection daily, the dose being increased by 10 $\mu\text{g.}$ a day. By the fourth day he was receiving 40 $\mu\text{g.}$, which together with the daily dose of 0.1 mg. of thyroxine constituted a full replacement dose of thyroid hormone. He now showed some evidence of hyperthyroidism with a marked increase in peripheral circulation and sweating of the palms of the hands, but there was no tachycardia or recurrence of angina. He was less co-operative and wished to be discharged from hospital. The dose of triiodothyronine was reduced. During the course of the next week noticeable improvement occurred from day to day, and within three

weeks of admission his mental state was normal. His progress is shown in the accompanying chart (Fig. 1). He has remained well since and has shown no further tendency to psychiatric disturbance.

It was later found that he was being supplied by his chemist with 0.1 mg. of DL-thyroxine,* thus explaining the development of hypothyroidism. Rapid correction of hypothyroidism was desirable because of the onset of mania, but a delicate balance had to be maintained to avoid any recurrence of angina. Triiodothyronine was eminently suitable in these rather unusual circumstances.

Thyroid Carcinoma

Patients with functioning thyroid carcinoma may require several doses of radioactive iodine: treatment is usually given at intervals of approximately three months. Thyroxine is given in the intervals between treatment, but has to be stopped at least one month before a further dose of radio-iodine is given. The schema of treatment has been clearly described by Hilton, Pochin, Cunningham, and Halnan (1956). If triiodothyronine is substituted for thyroxine the period of disability due to hypothyroidism is reduced to a minimum. A patient maintained in a euthyroid state on triiodothyronine becomes myxoedematous within 12–14 days of stopping the drug. A therapeutic dose of radio-iodine may then be given and triiodothyronine started again within 24 hours with a rapid return to the euthyroid state. Triiodothyronine used in this way has proved most useful in the management of patients with thyroid carcinoma.

Diagnostic Suppression of Thyroid Function

It has been shown that thyroid function is suppressed in normal subjects given desiccated thyroid (Stanley and Astwood, 1949; Greer, 1951) or thyroxine (Morgans, Oldham, and Trotter, 1952). Triiodothyronine was shown to be effective in suppressing thyroidal uptake of radio-iodine in normal subjects in a dose as low as 8 µg. daily (Starr and Liebhold-Schueck, 1953), but doses as large as 2 mg. a day did not affect thyroidal uptake of radio-iodine in Graves's disease (Werner and Hamilton, 1953). It was shown that euthyroid patients could be differentiated from hyperthyroid patients by their response to the administration of desiccated thyroid (Greer and Smith, 1954), or triiodothyronine (Werner and Spooner, 1955; Perlmutter and Slater, 1955).

The suppressive effect of thyroid substances on thyroid function is useful in determining the thyroid status in some patients in whom conventional radio-iodine tests are inconclusive. Triiodothyronine, which has a more transient effect, is probably preferable to thyroxine for this purpose, although it has not been shown that it suppresses thyroid uptake more rapidly than thyroxine.

The following examples show how euthyroid and hyperthyroid patients may be differentiated by their response to the administration of triiodothyronine.

Case 1.—Radio-iodine tests of thyroid function were carried out on a patient with suspected thyrotoxicosis. The results (Table I) show values for thyroid clearance (Myant, Pochin, and Goldie, 1949) and protein-bound ^{131}I (P.B. ^{131}I) (Ansell, Macgregor, Miller, and Wayne, 1953) to be within normal limits, but the "T" index derived from the figures for urinary excretion (Fraser, Hobson, Arnott, and Emery, 1953) is within the range for hyperthyroidism. The administration of 40 µg. of L-triiodothyronine thrice daily for nine days resulted in suppression of

*Pitt-Rivers and Lerman (1948) assayed the D- and L- forms of thyroxine in myxoedema; they found that the L- form was 8–10 times as active as the D- form. Tomich and Woollett (1956, personal communication) found that the potency of D-thyroxine was 5–10% that of L-thyroxine in experiments on oxygen consumption in intact rats. Sodium DL-thyroxine was introduced into the *British Pharmacopoeia* in 1932 and deleted in 1948. It was included in the 1934 edition of the *British Pharmaceutical Codex* and deleted in 1949. Sodium L-thyroxine was introduced into the 1954 edition of the *B.P.C.*, but is not at present in the *B.P.* We understand that it will probably be included in the next edition of the *B.P.*

thyroidal uptake of radio-iodine as judged by *in vivo* and urinary excretion measurements. Serial measurements of thyroidal uptake with ^{131}I suggest that suppression occurred gradually (Fig. 2). (The ^{131}I curves of thyroidal uptake have not been corrected for extrathyroidal activity to allow comparison with those made with ^{132}I .) The results make a diagnosis of thyrotoxicosis extremely unlikely.

TABLE I.—Effect of Triiodothyronine on Thyroid Function in a Euthyroid Patient

Date	Isotope	Thyroid Uptake of Administered Dose (A.D.) at 1 Hour	Thyroid Clearance	Urinary Excretion	Plasma 48 Hours Protein-bound ^{131}I (P.B.I.)
3/9/56	^{131}I	16.8%	37.5 ml. plasma/min.	0–8 hrs., 38.1% A.D. 8–24 „ 5.1% „ 24–48 „ 0.7% „ T=17.0 43.9% „	P.B.I. 0.11% A.D./L.
8/9/56 to 17/9/56. L-Triiodothyronine, 40 µg. t.d.s.					
12/9/56	^{132}I	14.6%	—	—	—
13/9/56	^{132}I	14.0%	—	—	—
14/9/56	^{132}I	10.3%	—	—	—
15/9/56	^{131}I	9.5%	—	0.8 hrs., 46.6% A.D. 8–24 „ 24.4% „ 24–48 „ 7.7% „ T=2.5 78.7% „	—
17/9/56	^{132}I	6.2%	—	—	—

FIG. 2.—Effect of L-triiodothyronine on thyroidal uptake of radio-iodine in a euthyroid patient (Case 1).

Case 2.—A patient who had had a partial thyroidectomy in 1943 developed symptoms and signs of recurrent thyrotoxicosis. Radio-iodine tests showed thyroid clearance to be within normal limits, but the T index and P.B. ^{131}I were within the range for hyperthyroidism (Table II). The administration of 40 µg. of L-triiodothyronine thrice daily for nine days did not affect

TABLE II.—Effect of Triiodothyronine on Thyroid Function in a Patient with Recurrent Thyrotoxicosis

Date	Isotope	Thyroid Uptake of Administered Dose (A.D.) at 1 Hour	Thyroid Clearance	Urinary Excretion	Plasma 48 Hours Protein-bound ^{131}I (P.B.I.)
13/6/56	^{131}I	26.25%	58.6 ml. plasma/min.	0–8 hrs., 28.10% A.D. 8–24 „ 4.99% „ 24–48 „ 0.84% „ T=16.6 33.92% „	P.B.I. 0.63% A.D./L.
18/6/56 to 27/6/56. L-Triiodothyronine, 40 µg. t.d.s.					
22/6/56	^{132}I	26.5%	—	—	—
25/6/56	^{131}I	24.5%	58.8 ml. plasma/min.	0–8 hrs., 26.8% A.D. 8–24 „ 4.1% „ 24–48 „ 1.47% „ T=20.3 32.37% „	P.B.I. 0.37% A.D./L.

thyroidal uptake of radio-iodine (Fig. 3) or produce any significant change in the urinary excretion pattern. The results supported the clinical diagnosis, and further confirmation was obtained by the patient's response to treatment with potassium perchlorate.

FIG. 3.—Effect of L-triiodothyronine on thyroidal uptake of radio-iodine in a patient with recurrent thyrotoxicosis (Case 2).

Therapeutic Test in Hypothyroidism

Mild hypothyroidism, giving rise as it does to symptoms without clinical signs, is difficult to diagnose and often overlooked. Laboratory tests provide little help in such cases and will confirm the diagnosis only where this is clinically obvious. It is perhaps not sufficiently realized that many symptoms such as irritability, nervousness, depression, restlessness, palpitations, fatigue, paroxysmal flushing and sweating, and loss of weight are common to both early hypothyroidism and hyperthyroidism. Other symptoms, such as insomnia, paraesthesiae, cramps, muscular and joint pains, headache, and angina, while commonly seen in hypothyroidism, are by no means specific. A doubtful diagnosis of hypothyroidism is best established by a therapeutic test with thyroid hormone. The therapeutic response to triiodothyronine is evident within two or three days, and is more readily appreciated by the patient in contrast to the less dramatic effects of thyroxine therapy.

Hypometabolism

It has been claimed that a condition of non-myxoedematous hypometabolism exists (Kurland, Hamolsky, and Freedberg, 1955; Tittle, 1956). The clinical features of this syndrome are said to include lethargy, nervousness, irritability, emotional instability, sensitivity to cold, headache, ill-defined muscular and skeletal pains, and periorbital puffiness. The B.M.R. is below normal, but other indices of thyroid function are within normal limits. There appears to be no difference between this new "syndrome" and mild hypothyroidism. It is difficult to understand why a new name should be applied to a condition which, from its clinical description, seems unquestionably due to thyroid hypofunction. Moreover, it is well recognized that a lowered B.M.R. is the most sensitive index and may be the only confirmatory evidence of hypothyroidism.

It has been reported that these patients are refractory to thyroid therapy, but respond to treatment with triiodothyronine alone or in conjunction with thyroxine. Explanations put forward to account for this phenomenon include possible defects in absorption or peripheral utilization of thyroxine or thyroid extract. These hypotheses might well be confirmed by studies with labelled thyroxine, but in the meantime the evidence for the existence of this syndrome is not convincing.

Myxoedema Coma

During the past three years 16 cases of myxoedema coma have been reported in this country (Le Marquand, Haus-

mann, and Hemsted, 1953, 1955; Summers, 1953; Malden, 1955; Karhausen and Zylberszac, 1955; Reid, 1955; Marshall and McCaughey, 1956; Dyson and Wood, 1956; Anderson and Hausmann, 1956). All these patients died except one in the series reported by Malden. The case reported by Dyson and Wood and that of Anderson and Hausmann were treated with triiodothyronine and thyroxine. It is well recognized that thyroid hormone must be given in small dosage and with extreme caution to patients with severe myxoedema. An even more conservative policy is indicated in the treatment of myxoedema coma. From examination of the case histories of patients with myxoedema coma it would almost appear that the administration of thyroid hormone caused further deterioration, the majority dying within two to four days of starting treatment.

We have not had an opportunity of using triiodothyronine in the treatment of myxoedema coma. In addition to measures to combat hypothermia and adrenocortical failure, triiodothyronine would seem to be the drug of choice in this condition. The therapeutic value of triiodothyronine, however, cannot be properly assessed when given in conjunction with thyroxine or thyroid extract. We would suggest that initially 10 μg. should be given every 12 hours by intravenous injection and the dose modified according to the response. There is evidence that a higher dosage may be dangerous in patients with extreme deficiency of thyroid hormone, and it must be emphasized that in any chronic hypothyroid state caution in therapy is strongly indicated because of the risk of acute heart failure.

Discussion

Most of the conditions discussed here in which triiodothyronine has proved useful are not commonly encountered in general medical practice. Triiodothyronine will be of value mainly in thyroid clinics and to individuals with a special interest in the treatment or investigation of patients with thyroid disease. It will, however, have a wider application as a therapeutic test in the diagnosis of equivocal hypothyroidism. Its use in this respect should be restricted to cases where there are reasonable grounds for a clinical diagnosis of hypothyroidism.

As already mentioned the metabolic effects of triiodothyronine have been studied after the administration of a single dose. Relatively enormous doses (up to 1 mg.) have been given to obtain measurable effects: this may have led to some confusion regarding the dose required to correct myxoedema. Although hypothyroidism of recent origin may be corrected rapidly with safety, a similar attempt to correct long-standing myxoedema rapidly may be fatal.

L-triiodothyronine has been estimated to be three to five times as active as L-thyroxine on a molar basis (Lerman, 1953; Blackburn *et al.*, 1954; Blackburn and Keating, 1954; Selenkow and Asper, 1955; Frawley, McClintock, Beebe, and Marthy, 1956). We estimate L-triiodothyronine to be about five times as active as L-thyroxine on a molar basis. This observation is based on studies in athyroidal patients who have been maintained in a euthyroid state with each compound. The replacement dose of triiodothyronine is 60–80 μg. daily, and 20 μg. of triiodothyronine is therefore approximately equivalent to 0.1 mg. of L-thyroxine or 1 gr. (65 mg.) of thyroid (B.P.).

Summary

Certain aspects of the biosynthesis and biological activity of triiodothyronine in animals and humans are discussed and the literature is reviewed. The use of triiodothyronine is preferable to that of thyroxine when its rapid action and transient effect are advantageous: hence its clinical applications are limited.

Triiodothyronine has proved very suitable in the treatment of a patient with coronary insufficiency who developed paranoia of hypothyroid origin.

The use of triiodothyronine in the management of patients with thyroid carcinoma and in the diagnosis of borderline hypothyroidism and thyrotoxicosis is described.

Some suggestions regarding its use in the treatment of myxoedema coma are made and the dangers in the treatment of this condition emphasized.

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MEASUREMENT OF GASTRO-INTESTINAL BLEEDING USING RADIOACTIVE CHROMIUM

BY

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There are a number of satisfactory chemical tests for the detection of occult blood in stools, but a precise quantitative method of measuring gastro-intestinal blood loss has not been available until recently. Owen *et al.* (1954a) used radioactive chromium for this purpose experimentally in dogs, and also applied the method to man (Owen *et al.*, 1954b; Cooper *et al.*, 1955). Radioactive iron has also been used in attempting to measure blood loss in hookworm infestation (Gerritsen *et al.*, 1954).

The purpose of this communication is to describe a simple method for the quantitative estimation of faecal blood loss, using radioactive chromium in tracer doses. The method is illustrated by detailed results in three patients selected from a small series. A comparison has also been made between the quantity of blood in the stool estimated by this method and the result of a commonly used benzidine occult blood test.

Radioactive Chromium Method

The principle consists in labelling circulating red cells with radioactive chromium and subsequently measuring and comparing the radioactivity of samples of venous blood and faeces.

Red-cell Labelling.—The patient's own red cells are tagged with ^{51}Cr , using a modification of the established method (Gray and Sterling, 1950; Mollison and Veall, 1955; Cooper and Owen, 1956). 20 ml. of venous blood is withdrawn into a sterile bottle containing 1,000 international units of heparin. The bottle is centrifuged and the supernatant plasma removed. A few millilitres (100–200 microcuries) of a sterile isotonic solution containing ^{51}Cr as sodium chromate, Na_2CrO_4 , in saline, is then mixed with the red cells and allowed to stand for half an hour at room temperature. The ^{51}Cr solution, which is obtained already diluted and sterilized from the Radiochemical Centre, Amersham, has an initial activity of 100 μC . per ml. and a specific activity of approximately 30 μC . per μg . After standing, the red cells are twice washed with saline to remove free unattached ^{51}Cr , and are resuspended in saline to a volume of 22 ml. Then 20 ml. of this suspension is re-injected intravenously into the patient. All these manipulations are carried out with the usual aseptic precautions. 1 ml. of the remaining suspension is diluted to 100 ml. with water in a volumetric flask, and the radioactivity of a 5-ml. aliquot is measured in order to calculate the total dose administered to the patient.

Sample Counting.—Venous blood and stool sample counts are made on 5-ml. aliquots placed in small flat-bottomed glass tubes, in a well-type scintillation counter. The scintillation counter is that described for use in routine radioactive iron studies (Wetherley-Mein *et al.*, 1956). All measurements are corrected for background activity and for radioactive decay.

Blood Radioactivity.—Blood samples are taken at intervals of one to three days, the activity is measured, corrected for background and decay, and plotted on a simple linear graph. From this graph the blood radioactivity at any time is calculated in counts per second per ml. (c./sec./ml.) (see Chart).