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 of venous blood is withdrawn into a sterile bottle containing 1,000 international units of heparin.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).

Gradual fall in blood radioactivity after red cells are labelled with radioactive chromium (Case 1). Values corrected for radioactive decay and background.

Stool Radioactivity.—All stools passed by the patient are collected in successive 24-hour periods during the investigation. The faeces are transferred from a bedpan into weighed jars, or directly into the metal container of an ordinary domestic electric mixer. Each 24-hour collection is weighed and a known amount of water added, so that after mixing a thick homogeneous suspension is obtained. The quantity of water added depends on the consistency of the stool, and it is usually necessary to dilute the stool to about twice its original volume. After mixing, approximately 5 g. of the diluted suspension is poured at once through a funnel into a weighed counting-tube, which is reweighed so that the exact amount of the diluted sample is known. The radioactivity of the sample is measured and the result corrected for background and decay. From the activity of the sample the total radioactivity of the 24-hour collection is determined.

Calculation.—The amount of blood in millilitres present in each 24-hour collection is then obtained from the expression:

$$\frac{\text{Total activity of stool collection in counts per second}}{\text{Activity of blood in counts per second per ml.}}$$

Since the exact time at which bleeding occurred, and thus the time the blood has spent in the bowel, is unknown, an assumption has to be made to decide which blood-activity value is to be used in the calculation. In this study the value two days before the stool was passed has been used. In practice the fall in blood radioactivity during the test period is usually so gradual that the possible inaccuracy of this assumption has little effect on the result.

Occult Blood Test

The occult blood test employed in this study, which is a modification of the Gregersen benzidine test described by Needham and Simpson (1952), is that used in routine practice in this hospital (J. S. Staffurth, 1952, personal communication). A smear of faeces from each 24-hour collection is made on a filter-paper before dilution. A suspension of the prepared powder (a mixture of benzidine hydrochloride, 25 mg., and barium peroxide, 200 mg., individually wrapped in waxed papers, and supplied by Messrs. Allen & Hanburys) in 5 ml. of glacial acetic acid, is poured on the smear. The appearance of a deep blue colour indicates a positive reaction, and the speed with which it appears is some measure of the amount of blood present. The gradations recognized are as follows: strongly positive (++), an intense colour appearing immediately; positive (+), a deep blue colour appearing within 15 seconds; weakly positive (±), a greenish-blue colour appearing within 30 seconds; negative (—), no colour within 30 seconds.

Results

To illustrate the results which may be obtained with this method, the findings in three patients are set out in detail in the Table. These have been selected from the small series of nine cases, each followed for at least 10 days.

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The first was an elderly man apparently bleeding from a hiatus hernia. Using this method, his daily blood loss, averaged over 10 days, was estimated to be 14 ml., with a range of 3 to 46 ml. It will be seen that there was no significant radioactivity in the stools passed during the first four days after cell labelling, although the benzidine test was positive throughout. Provided that the patient is passing stools regularly, such a delay in the appearance of radioactivity in the stool samples may be interpreted as indicating that the blood is coming from high up in the gastro-intestinal tract, a conclusion in accord with the clinical diagnosis in this patient.

The second patient, again an elderly man, had iron-deficiency anaemia due to chronic intestinal bleeding for which no cause could be found. His average daily loss over 14 days was 6 ml., with a range of 3 to 25 ml. The early appearance of radioactivity in the stools suggested, in contrast to the previous patient, that the site of bleeding was low in the gastro-intestinal tract. This has not yet been confirmed, and the patient is still under investigation.

The third patient, a middle-aged woman, had a profound iron-deficiency anaemia—initially 4.14 g./100 ml. (28% Haldane)—due to menorrhagia and to the bleeding from a

Results in Three Cases

Day of Investigation Following Red-cell Labelling	Weight of Stool (g.)	Total Stool Radioactivity (c./sec.)	Blood Radioactivity 2 Days Previously (c./sec./ml.)	Calculated Amount of Blood (ml. Stool)	Gregersen Benzidine Test
Case 1. Man aged 72. Hiatus Hernia					
1	166	0	0	0	±
3-4	88	0	15	0	++
4-5	64	0	14.5	0	++
5-6	106	600	14	42	++
7-8	88	632	13.5	46	++
9-10	90	37	12.7	3	±
12-13	291	151	12	12	±
13-14	232	181	11.5	15	±
15	469	226	11	20	±
18-19	69	70	10	7	±
Case 2. Man aged 61. Chronic Intestinal Bleeding, Cause Unknown					
1	60	0	0	0	—
3	216	117	17.5	6	—
4	90	59	17	3	—
5-6	89	78	16.5	4	+
7-8	56	109	15.5	7	++
9	123	123	14.7	8	++
12	129	117	13.5	8	++
14	695	165	12.5	13	++
15-16	324	173	11.7	14	++
17	764	282	11	25	+
Case 3. Woman aged 38. Duodenal Ulcer					
2	94	24	7.0	3	±
4	140	55	6.5	8	±
7	72	84	6.0	14	±
10-11	389	42	5.5	7	±
11-12	99	Activity too low for counting	5.5	Less than 3	±

duodenal ulcer. Her average daily loss over 10 days was estimated to be 3 ml., with a range of 3 to 14 ml. (the daily average is low because she did not pass a stool every day; the average per stool collection was approximately 7 ml.). During the period of investigation there was no uterine bleeding, and, in spite of continued bleeding from the ulcers, the haemoglobin rose very rapidly with iron therapy. This is explained by the very small daily loss demonstrated.

The quantitative estimate of blood loss by this method usually corresponded well with the results of the benzidine test. As would be expected, the bulk of the stool, and hence the dilution of the blood in the faeces, is important in determining the intensity of the reaction. For example, a relatively large amount of blood in a bulky stool—for example, 20 ml. measured by the chomium method, in 470 g. of faeces—has given only a weakly positive (±) benzidine reaction, whereas in stools of average bulk (50-200 g.) only 7 ml. upwards has been required to give a ++ reaction, 3-14 ml. has given a + reaction, and 0-10 ml. a ± reaction.

At times a lack of correspondence has been observed between the two methods. On the one hand, significant radioactivity has been found with negative benzidine tests (as in days 3 and 4 of Case 2); and on the other, weakly positive benzidine reactions have been observed with no significant radioactivity in the faecal samples. These discrepancies have always been when the amount of blood was small as indicated by one test or the other.

Discussion

Quantitative chemical methods for determining the amount of blood present in faeces are laborious and inexact (Andrews and Oliver-González, 1942). For this reason very little information is as yet available about the daily blood loss in many common diseases.

The radio-isotope method is simpler, and its general validity was carefully worked out in experiments with dogs by Owen *et al.* (1954a). They labelled dogs' own red cells with ^{51}Cr , placed known quantities of this labelled blood in the dogs' stomachs, then measured the faecal radioactivity and obtained very good correspondence. They also found that in dogs with ^{51}Cr -labelled red cells the amount of ^{51}Cr passing into the bowel in the absence of bleeding was less than 0.1% of the original dose daily, equivalent to less than 1 ml. of blood daily. A larger amount (1% a day) was excreted in the urine. They concluded that the method can reasonably be applied to man (Owen *et al.*, 1954b; Cooper *et al.*, 1955).

The studies reported here confirm their view that the ^{51}Cr method provides a simple reliable way of quantitatively estimating faecal blood loss. Our experience with patients in whom chronic or subacute gastro-intestinal bleeding was known or suspected indicates that the method may be of considerable value not only in research but also in diagnosis. It may give evidence not only of the quantity of blood lost daily, but also sometimes an indication of whether the site of bleeding is high or low in the gastro-intestinal tract.

The accuracy of the ^{51}Cr method described is clearly least when the blood is in high dilution, because the radioactivity of the stool sample becomes nearer background activity. The present findings show that the method is not capable of measuring accurately very small amounts of blood—that is, of the order of 3 ml. or less—in an average stool. It is thus probably less sensitive in detecting bleeding than is the Gregersen benzidine test. This is a limitation of the method which must be accepted, for, although it could be overcome by using a larger dose of ^{51}Cr , a dose greater than 300 μc . is probably not justified (Mollison and Veall, 1955).

The present study also confirms the conclusion of Needham and Simpson (1952) on the value of the modified Gregersen benzidine test. They found that a minimum of 3 to 5 ml. of blood administered by stomach-tube was necessary to produce a positive (+) result. In the present study + results were obtained with stools of average bulk (50–200 g.) when they contained 3–14 ml. of blood as estimated by the ^{51}Cr method. The Gregersen benzidine test is, of course, not intended to be quantitative, and, as pointed out above, the gradations in intensity noted have relatively little significance unless the bulk of the stool is taken into account. For example, on different occasions in this study a blood loss of 10 ml. has been associated with benzidine test results of $\pm$, +, and ++. Further, as Needham and Simpson pointed out, occasional false positives are obtained, and the test is most useful when it is repeated on a series of samples.

Summary

A method using tracer doses of ^{51}Cr for the quantitative estimation of gastro-intestinal blood loss is described. Detailed results from three patients are given to illustrate the value of the method in expressing clinical observations in quantitative terms, and sometimes in indicating the possible site of bleeding. A comparison is made between the findings with this method and results of a commonly used qualitative benzidine occult blood test.

On the whole there is good correlation between the tests. The chromium method has least value when blood loss is 3 ml. or less in the stool samples analysed.

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ADDENDUM.—Since submitting this paper for publication the technique has been much simplified by the introduction of a modified turret counter of the type described by Veall (Veall and Vetter, 1952). This was constructed by the hospital Physics Department. Each stool is collected into a large wax carton which can be placed directly in the counter. The activity of the whole sample can thus be determined without the elaborate manipulations described in the text.

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LEUKAEMIA, AMYLOIDOSIS, AND RENAL VEIN THROMBOSIS IN IRRADIATED ANKYLOSING SPONDYLITIS

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Interest has recently been stimulated in two syndromes—namely, leukaemia following irradiation for ankylosing spondylitis (Court Brown and Abbott, 1955; Abbott and Lea, 1956) and renal vein thrombosis following amyloidosis (Harrison *et al.*, 1956). A case, in our experience unique, is reported showing both syndromes.

Clinical History

A store manager aged 32 was discharged from the Army in 1945 with a diagnosis of ankylosing spondylitis. From 1945 to 1948 he was treated by deep x rays to his spine. The total dose received was about 1,200 r. He was subsequently encased in a spinal jacket, which he had worn for the nine months previous to his first presentation at our hospital in June, 1948.

He then complained of pain in the back of both thighs and in the back on sitting down. His spine was completely rigid and movement of the hips was limited. The Wassermann and Kahn reactions were negative, the E.S.R. was 40 mm., and the x-ray examination was typical of spondylitis. He removed to another area and from 1948 to 1950 he was treated at another hospital with further deep x rays to the spine to a total dosage of between 1,000 and 1,500 r.

In 1953 he had renal symptoms for the first time. At one hospital he complained of left and then right renal colic,