Intra-arterial transfusion has been shown experimentally to be no more effective than intravenous transfusion in correcting insufficient coronary flow after severe haemorrhage (Case *et al.*, 1953).

Intravenous L-noradrenaline has been used to combat hypotension both in severe haemorrhage (Goldenberg *et al.*, 1949) and in spontaneous cardiac infarction (Miller and Moser, 1959). As it increases coronary blood flow (Burn and Hutcheon, 1949) its use in the treatment of haemorrhage not responding quickly to blood transfusion would help to protect the myocardium (Vowles *et al.*, 1957). The latest pressor drug metaraminol bitartrate ("aramine"; laevo-1-(hydroxyphenyl)-2-amino-1-propanol hydrogen d-tartrate) has similar clinical effects (Stechel *et al.*, 1956; Besterman, 1959), and its intravenous administration has been shown to reverse the effects of induced coronary insufficiency in dogs (Sarnoff *et al.*, 1954a).

Summary

The clinical features and necropsy findings of three cases of myocardial infarction occurring after acute gastro-intestinal haemorrhage are presented. The pathogenesis of the condition is discussed, and the importance of early restoration of the blood volume after haemorrhage, especially in the elderly, is emphasized as a means of preventing this dangerous complication.

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CLINICAL ASSESSMENT OF INTESTINAL FAT-ABSORPTION USING RADIOACTIVE FAT

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When intestinal malabsorption is suspected in clinical practice a chemical fat balance is a standard method of investigation. Such a balance study requires admission to hospital, is time-consuming, and involves the unpopular and often inadequate collection and mixing of faeces. There is a need for a simple and rapid alternative to collection of faecal fat in the study of fat-absorption.

Thannhauser and Stanley (1949) pioneered the combined study of blood levels and excretion of radioactivity after an oral dose of natural unsaturated fat labelled with radio-iodine. In most of the subsequent reports on the use of this method to measure fat-absorption, attention has been paid almost entirely to the blood concentration and the faecal excretion of the isotope (Stanley and Thannhauser, 1949; Baylin *et al.*, 1955; McKenna *et al.*, 1957; Shingleton *et al.*, 1957a, 1957b; Grossman and Jordan, 1958; Lubran and Pearson, 1958; Ruffin *et al.*, 1958; Spector *et al.*, 1958; Berkowitz *et al.*, 1959). Other workers have described an analogous method in which the iodine present in the urine after an oral dose of lipiodol is estimated chemically (Groen, 1948; Silverman and Shirkey, 1955). In this communication we record our experience of the assessment of fat-absorption by giving radioactive

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neutral fat and measuring the subsequent blood concentration and the urinary excretion of the radioisotope. We find the urinary excretion of radioactive iodine to be a useful screening test for steatorrhoea.

Methods

Subjects.—Our normal group contained 32 adult volunteers, in hospital with disorders not known to affect absorption from the intestinal tract. The abnormal group consisted of six patients, four with idiopathic steatorrhoea, one with steatorrhoea after gastro-intestinal surgery, and one with obstructive jaundice: in two of these patients the test was repeated. The diagnosis of steatorrhoea was established by a six-day chemical fat balance and microscopical examination of the stools (Table I). No evidence of renal dysfunction was obtained from analysis of the urine or from the blood urea or creatinine concentrations.

TABLE I.—*Results of Tests on Patients with Steatorrhoea*

Case No.	Sex and Age	Diagnosis	Chemical Fat Balance	Plasma Specific Activity at 6 hrs.% Admin. Dose/l.	Urinary Excretion in 24 hrs.% Admin. Dose
1	F 60	Idiopathic steatorrhoea	87% absorption	0.43	8.8
2	M 79	Obstructive jaundice—ampullary carcinoma	Stools pale and offensive	0.66 pre-op. 2.3 post-op.	8.4 pre-op. 46.0 post-op.
3	M 57	Idiopathic steatorrhoea	24.3% absorption. 98.3% split	0.36	11.0
4	F 50	" "	84.4% absorption. 95.3% split	0.76	16.5
5	F 81	Total gastrectomy	68% absorption	1.6	15.5
6	F 53	Idiopathic steatorrhoea	Mean fat excretion over 7 days—21 g./day	0.16	6.6
7	M 58	" "	63.7% absorption. 77.7% split	0.54	5.5

Cases 3 and 7 are the same patient.

Preparation of Active Fat

The neutral fat was olive oil labelled with ^{131}I , supplied by the Radiochemical Centre, Amersham, England. It consisted of triglycerides of mainly unsaturated fatty acids, chiefly oleic acid with a single unsaturated bond. We specified that this oil should be only partly saturated with iodine—about 20% iodinated—in order to avoid free radio-iodine, and in the hope that the presence of many persisting unsaturated bonds would mean less upset of the normal handling of the fat in the body. Extraction tests on the oil, using a petroleum-ether and water mixture, failed to show any migration of activity into the aqueous phase. Nor did dialysis against water for 24 hours through a "cellophane" membrane result in any detectable radio-iodine in the water. We concluded that the oil contained no free inorganic radio-iodine.

Initially, several tests were vitiated by failure to achieve uniform dispersal of the labelled oil in the

diluent olive oil used to facilitate accurate dispensing. We found large variations in the specific activities of a number of successive aliquots, even after prolonged stirring, if the oils were mixed at their normal viscosity.

The following procedure proved reliable. The oil received contained 10 mc in approximately 1.5 ml.; it was weighed after transfer to a larger container. Natural olive oil was added to make a known weight of approximately 50 g. The viscosity was lowered by adding about 5 ml. of ethyl ether, and the mixture was stirred continuously for 24 hours. Repeated sampling of the mixture thus produced, both immediately after preparation and throughout its useful life, confirmed it to be homogeneous. Re-weighing after stirring showed that the spontaneous evaporation of ether was complete for practical purposes. The iodine number of one batch altered during stirring from 83 to 80.5, a very minor change. Individual doses were weighed in small glass bottles, so that each contained about 25 μc at the time of administration. The volume in the bottle must be sufficient to prevent a large fraction being left behind after administration; therefore, if the specific activity was high the active oil was added to a known weight of natural oil and mixed thoroughly. For counting, a weighed aliquot of the dose, containing about 2% of the activity, was added to the counter specimen tube and made up to the standard volume by adding an equal mixture of olive oil and carbon tetrachloride.

Administration

To avoid uptake of active iodine by the thyroid, each patient received 0.69 g. (10 gr.) of potassium iodide three times daily, for three days prior to the test and throughout the period of urine collections. After an overnight fast, the patient drank 60 ml. (2 oz.) of ordinary olive oil with added orange juice, followed by a few ml. of active oil, which was sucked from the bottle through a plastic "straw." The bottle and straw were weighed before and after use and the weight of active oil administered was calculated. On average, 8% was left in the bottle, the patient receiving about 23 μc . The patient was then given a standard breakfast of poached egg, toast, butter, and tea. Thereafter, the previous ward diet was resumed.

Measurements

Venous blood samples were removed into heparinized bottles at two, four, six, and nine hours after the dose. Urine was collected for three 24-hour periods, and, in 13 cases, for a fourth day. All bottles were previously treated with concentrated sodium iodide to minimize adsorption of radio-iodine on the glass. A well-type scintillation counter was used for radio-assay, and the results were expressed as a percentage of the given dose per litre of plasma, or as a percentage of the dose excreted in each period.

Results

Plasma

The curve of the mean values of the specific activity of the plasma for the 32 normal patients showed a flat

TABLE II.—*Mean Values and Standard Deviations for Normal and Abnormal Groups*

Subjects	Total	Plasma Activity % Admin. Dose/l.				Cumulative Urine Activity % Admin. Dose			
		2 Hrs.	4 Hrs.	6 Hrs.	9 Hrs.	24 Hrs.	48 Hrs.	72 Hrs.	96 Hrs.
Normal controls ..	32	1.97 $\pm$ 1.0	3.75 $\pm$ 1.0	3.89 $\pm$ 2.0	2.73 $\pm$ 1.3	52.0 $\pm$ 12.0	70.0 $\pm$ 12.0	74.5 $\pm$ 12.1	76.1 $\pm$ 15.0*
Steatorrhoea patients ..	6	0.26 $\pm$ 0.4	0.49 $\pm$ 0.44	0.64 $\pm$ 0.47	0.58 $\pm$ 0.37	10.4 $\pm$ 4.9	15.8 $\pm$ 8.7	19.0 $\pm$ 13.6	—

* This represents the mean of 13 control subjects.

maximum between four and six hours; at all times there was a wide range about the mean (Table II and Fig. 1). At six hours two-thirds of the values fell within

FIG. 1.—Plasma concentration: means of 32 normals and 6 abnormals. One standard deviation is indicated.

the range $3.9 \pm 2.0\%$ (mean and standard deviation) of the administered dose per litre of plasma. In contrast, the curve of mean values for the six abnormal patients was much flatter, and the maximum, reached at about six hours, was $0.64 \pm 0.47\%$ of dose per litre of plasma.

Since the scatter was wide in this group also, there was an overlap of results for normals and abnormals. No appreciable peak concentration occurred in any of the subjects.

Urine

The daily urinary excretion of radio-iodine was greatest in the first day and diminished progressively; on the fourth day, in those 13 normal individuals from whom this collection was made the mean excretion was 1.3% of the

FIG. 2.—Cumulative urinary excretion: means of 32 normals and six abnormals. One standard deviation is indicated.

dose administered. There was a clear separation between the normal and abnormal groups throughout the cumulative urinary excretion, and no overlap occurred (Table II and Fig. 2). The excretion during the first 24-hour period alone was sufficient to show this separation.

The concentration in plasma at six hours and the urinary excretion in the first 24 hours appeared to be the most useful differentiating factors provided by the two types of measurement. The values of these for each patient can be seen in Fig. 3, which shows the extent of the overlap between the normal and abnormal values in respect of plasma concentration, and the degree of separation in the urinary measurements.

The low values of radioactivity found in the abnormal group were in good agreement with the results of our other investigations, such as full chemical fat balances and direct examination of the stools, and with the clinical assessment of the patients (Table II).

FIG. 3.—Plasma concentration at six hours and urinary excretion in first 24 hours for each patient.

Discussion

The changes in radioactivity of plasma and urine after an oral dose of a labelled natural fat are here taken as indicating the degree of fat-absorption from the gut. It will be clear that this form of test gives no information on the cause of steatorrhoea. The subsequent use of labelled free fatty acid can indicate whether the pancreatic enzyme system is involved (Kaplan *et al.*, 1958).

Emulsifying agents were not administered with the radioactive fat, contrary to the practice of some other authors (Ruffin *et al.*, 1956; Lubran and Pearson, 1958; Veall and Vetter, 1958). Thus emulsification was dependent upon the patient's own bile-salt system. Failure of this system is illustrated in another patient with obstructive jaundice, in whom the results became normal four weeks after the restoration of bile-flow to the intestine (see Figs. 4 and 5).

The plasma concentrations of radio-iodine in our series of tests were similar to those reported by others; the shape of the plasma-activity/time curve was not of value, and of greater significance was the maximum concentration which occurred at about six hours (Shingleton *et al.*, 1955, 1957b; Duffy and Turner, 1958; Kaplan *et al.*, 1958). At this time the mean specific activity of the normal group was about six times that of the abnormals, but in both groups results were so widely scattered about the mean that there was an appreciable overlap (Fig. 3). The plasma activity is only partly due to lipid-bound iodine (Beres *et al.*, 1957; Van Handel and Zilversmit, 1957); it depends upon the rate of gastric emptying, on the rates of absorption, utilization, and excretion, and on the thyroid uptake (if this is not prevented by iodide premedication). We consider, therefore, that the concentration of radio-

iodine in the plasma used alone as a quantitative index of intestinal absorption is not reliable enough.

The excretion of radio-iodine in the urine in the first 24 hours after the test is probably much less affected by changes in the rate of gastric emptying or the rate of immediate utilization of absorbed fat than is the plasma radioactivity, and would seem to offer a more reliable

FIG. 4.—Plasma concentration in a man aged 71 before and after relief of obstructive jaundice.

FIG. 5.—Urinary excretion of patient as in Fig. 4 before and after relief of obstructive jaundice.

ability of the urine measurements may have been due to the care taken over some steps in the procedure. The separation can be made using the percentage of the dose excreted in the first 24 hours; in our normal group this never fell below 30%, and in the abnormal group it was never greater than 20%. This is a small series, but the results suggest that the criterion for detection of severe steatorrhoea should be an excretion in the urine of less than about 25% of the administered activity during the first 24 hours.

In this work we have contrasted patients believed to be normal with a number having clinical steatorrhoea. On the basis of 24-hour urine excretion, the normal group were clearly separated from the abnormal, but the two groups overlapped in respect of the plasma radioactivity levels at six hours (Fig. 3). Many authors have suggested that the plasma activity at six hours is sufficient for the detection of steatorrhoea. Our own results indicate that the urinary excretion at 24 hours is a better index of fat absorption and should therefore be considered, if not alone, then at least together with the plasma concentration of radioactivity. The occurrence of intermediate values is inevitable in any biological test, and from Fig. 3 we can foresee instances of borderline urine results where the addition of plasma values could often remove doubt.

A strong argument for using urine measurements alone is that the radiation dose can be greatly reduced. For plasma measurements it is not normally practicable to give an activity of much less than 25 μ c; many

authors have used much higher amounts (Stanley and Thannhauser, 1949; Malm *et al.*, 1956; Beres *et al.*, 1957; Shingleton *et al.*, 1957a, 1957b; McKenna *et al.*, 1957; Duffy and Turner, 1958). The consequent radiation doses are not as low as we would wish, particularly in malabsorption, when most of the activity is retained for perhaps two days in the intestinal tract. On the other hand, it is possible to obtain a quick and accurate measurement of the 24-hour urine activity corresponding to our borderline condition with an administered dose as low as 1 μ c. We feel that the radiation hazard involved in giving 1 μ c to an adult is not significant, and we are investigating, in a larger number of patients, the reliability of a screening test in which the only measurement is that of the radio-iodine excreted in the urine in the first 24 hours.

Summary

Olive oil labelled with radio-iodine was given to 32 normal subjects and six patients with steatorrhoea. The plasma concentration of radio-iodine was measured at two, four, six, and nine hours, and the fraction excreted in the urine was measured daily for several days. It is concluded that a measurement of the radio-iodine excreted in the urine in the first 24 hours is a relatively safe and reliable method of diagnosing malabsorption steatorrhoea.

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