stosstherapy so far reported. With the newer more soluble sulphonamides such as sulphadimidine, this danger is a remote one.

The general management of patients treated by stosstherapy is no different from that of patients treated by standard methods; but with stosstherapy the patient and his disease are treated rather than the disease alone. Friderichsen and Walther (1950) have pointed out that clinicians do not feel tempted to give up a certain form of treatment while good results have been so obtained. I hope, however, by having illustrated the advantages of this successful method of chemotherapy, that more will use it. I am sure that those who do so will find the change justified.

Summary

Fifty-two children with acute lower respiratory infection were treated with stosstherapy, a single massive combined dose of sodium penicillin by injection and sulphadimidine by mouth or with penicillin alone, and their response was compared with that of 54 similarly affected children treated by repeated chemotherapy given for five days or more.

The analysis of the cases was based on the overall results (successes, failure, relapses, and complications); and on the response of pyrexia, pulse, and respiratory rates; rate of disappearance of physical and radiological signs; and length of stay in hospital. The analysis showed that those children treated by stosstherapy responded at least as well as those treated by repeated chemotherapy.

The appearance of fever, most commonly occurring between the third and sixth days after both stosstherapy and standard chemotherapy, is described.

It is suggested that, as equally good results are obtained with stosstherapy, its many advantages imply that it should be the method of choice for acute infections of the lower respiratory tract in children.

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MEASUREMENT OF RED-CELL LOSS FROM GASTRO-INTESTINAL TRACT, USING RADIOACTIVE CHROMIUM

BY

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When ^{51}Cr -labelled red cells are introduced into the stomach or duodenum, more than 90% of the chromium can be recovered in the faeces (Owen *et al.*, 1954; Roche *et al.*, 1957). This is not altogether surprising, since chromic oxide is virtually unabsorbed by the gastro-intestinal tract, and has been used as an index material in digestion studies in animals and in man (Hamilton *et al.*, 1928; Kreula, 1947). Roche *et al.* (1957) used the technique of injecting ^{51}Cr -labelled red cells intravenously and then estimating ^{51}Cr loss in the stools to determine the extent of red-cell loss into the gastro-intestinal tract in hookworm disease.

In the present investigation six anaemic patients who were known to be losing red cells in their stools were studied. After the intravenous injection of ^{51}Cr -labelled red cells, the loss of ^{51}Cr in the stools was estimated, and these estimates were used to correct the ^{51}Cr -survival curves. It was thus possible to discover whether or not the blood loss in the stools accounted for the diminished survival of red cells in the circulation.

Methods

Labelling of Red Cells with ^{51}Cr .—Red cells were labelled with approximately 100 μC of ^{51}Cr by the method of Mollison and Veall (1955), using ^{51}Cr with a specific activity of 10–30 μC per μg . of chromium.

Estimation of ^{51}Cr Content of Stools.—Two methods were used. *Method 1:* Daily collections of stools were made in tins (diameter, 12.5 cm.; length, 16.5 cm.), except in patient G.B., from whom collections every three to four days were made. The radioactivity in each tin was measured in a ring counter containing 32 Geiger-Müller tubes, as described by Booth and Mollin (1956). A known aliquot of the injected dose of ^{51}Cr was mixed with 100 g. of sugar and estimated at the same time, as a standard. *Method 2:* Water was added to the faeces, which were then weighed and homogenized. The radioactive content of a 10-ml. aliquot was estimated in a pillar-type scintillation counter. As a standard a similar volume of a 1 in 100 dilution of the injection suspension of red cells was used. The ^{51}Cr content of the stools on any day was expressed as a percentage of the injected ^{51}Cr .

Accuracy of Method 1.—The Geiger-Müller ring counter had a background count of 220 c.p.m., and 1 μC present in the tin gave approximately 130 c.p.m. Thus, with 20 minutes' counting of the background alone and 20 minutes with the source, 1 μC of ^{51}Cr could be estimated with a co-efficient of variation of 4%. If 100 μC of ^{51}Cr was injected, and the subject's red-cell volume was 2 litres, then this quantity of ^{51}Cr would represent 20 ml. of red cells. The presence of 0.1 μC of ^{51}Cr , representing 2 ml. of cells, could just be detected if the background counts alone and the background counts together with the ^{51}Cr source were each counted for one hour.

Accuracy of Method 2.—A concentration of 1 μC in 100 ml. gave 1,200 c.p.m. in the scintillation counter and the background counts were of the order of 40 c.p.m. 2,500 counts were usually made, and the coefficient of variation was 2%. A concentration of 0.004 μC per 100 ml. could

just be detected, representing 0.04 ml. of red cells per 100 ml. of homogenized stool, at the beginning of the experiment.

Red-cell Survival Estimates

Blood was collected 10 minutes after injection, and this value was taken to represent 100% survival. Blood samples were withdrawn at suitable intervals thereafter. Corrections for changes in the packed cell volume were made during the first three days only; thereafter it was assumed that the blood volume remained constant. The figures published by Mollison and Veall (1955) were taken to represent the normal survival curve.

Correction of the Observed ^{51}Cr -survival Curve for the Loss of ^{51}Cr in the Stool

The percentage of the blood volume lost in the stool on any day, t , was obtained, using the following formula:

$$L = S \times \frac{100}{B}$$

where L = percentage of the blood volume lost in the stool on day t

S = percentage of the injected ^{51}Cr in the stool on day t

B = ^{51}Cr survival in the blood on day t (expressed as a percentage).

This calculation was made for each day on which stools were obtained. The ^{51}Cr survival in the blood was obtained by interpolation from the graph of the ^{51}Cr -survival curve, and the value used was that for the middle of the stool collection period.

When ^{51}Cr -labelled red cells are lost in the stools, then the subsequent ^{51}Cr concentration in the blood of the remaining cells will be diminished in proportion to the percentage of labelled cells left in the circulation—that is, by “the percentage of the blood volume not lost in the stools.” Thus the correction of the survival curve for the ^{51}Cr loss in the stools was carried out by multiplying the observed ^{51}Cr -survival estimate on any day, t , by the values

$$\frac{100}{\text{percentage blood volume not lost in the stools}}$$

for each of the preceding days—that is:

$$B \times \frac{100}{100 - L_1} \times \frac{100}{100 - L_2} \times \frac{100}{100 - L_{(t-1)}}$$

where B = the observed ^{51}Cr -survival value on day t
 $L_1, L_2, L_{(t-1)}$ = percentage of the blood volume lost in the stools on day 1, 2, etc.

Calculation of Red-cell Loss in Stools

The following formula was used for this calculation:

$$\text{Red-cell loss (ml.)} = \frac{P}{C} \times B.V. \times \frac{PCV \times 0.91}{100}$$

where P = ^{51}Cr in the stool, as a percentage of the dose injected as labelled cells

C = percentage ^{51}Cr survival in the blood on that day

PCV = packed cell volume, as a percentage of venous blood, after correction for trapped plasma. The factor 0.91 is introduced into the formula to take into account the “body haematocrit/venous haematocrit” ratio (Chaplin *et al.*, 1953).

BV = total blood volume (ml.). This was obtained from the ^{51}Cr data. For the purpose of the calculations it was assumed that the total blood volume remained constant through the observations.

Occult Blood Test on Stools.—The modified Gregerson test, described by Needham and Simpson (1952) was used.

Results

Absorption of ^{51}Cr by the Gastro-intestinal Tract

^{51}Cr -labelled cells were introduced into the stomachs of two patients who were undergoing milk-drip therapy for

peptic ulcers. One patient (A) was given 1.4 ml. of cells labelled with 21 μC of ^{51}Cr (1.5 μg . of chromium), and the other patient (B) was given 2.5 ml. of cells labelled with 8 μC of ^{51}Cr (0.6 μg . of chromium). The stools were then collected daily until their ^{51}Cr content had fallen to zero. The ^{51}Cr content was estimated by both methods (see above), and the results were found to agree closely (see Table I). Patient A excreted 66% and patient B 87% of the administered ^{51}Cr .

TABLE I.—Percentage Recovery of ^{51}Cr in Stools (Estimated by Two Methods) Following Introduction of ^{51}Cr -labelled Red Cells Into the Stomach

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Total
Patient A	Method 1	46.4	20.2	0				66.6
	“ 2	47.2	17.6	0				64.8
“ B	“ 1	17.6	33.4	31.6	2.2	1.9	0	86.7
	“ 2	17.0	36.6	31.0	—	—	—	

^{51}Cr Excretion in Patients not Losing Blood in the Stools

Investigation was made of two patients who were thought not to be losing red cells in the stools. One (A.S.) was a 34-year-old man undergoing radiotherapy for seminoma of the testis, the other (M.H.) was a 57-year-old woman with a normochromic anaemia of unknown aetiology. During the course of the investigations all occult blood tests on the stools were negative. Six collections of stool were made from each patient; the percentage of the injected dose of ^{51}Cr excreted each day, together with the red-cell equivalent, is given in Table II. In A.S. not more than a ten-thousandth

TABLE II.— ^{51}Cr Excreted Daily in the Stool in Two Patients Without Gastro-intestinal Bleeding, After Injection of ^{51}Cr -labelled Cells

Day	Patient M. H.		Patient A. S.	
	^{51}Cr Content of Stool as Percentage of Injected Dose	Red Cell Equivalent (ml.)	^{51}Cr Content of Stool as Percentage of Injected Dose	Red Cell Equivalent (ml.)
1	0.008	0.09	0.004	0.09
2	0.015	0.17	0	0
3	0.013	0.15	0.003	0.07
4	0.019	0.24	0.007	0.16
5	0.005	0.07	0.004	0.1
6	0.014	0.19	0.008	0.2

The chemical tests for occult blood in the stools were negative throughout.

part appeared in the stool each day, and in M.H. not more than a two-thousandth part. If this amount of ^{51}Cr in the stool were due to the presence of red cells it would represent approximately 0.1 and 0.2 ml. of red cells lost per day respectively.

^{51}Cr Excretion in Patients Losing Blood in the Stools

Patient G. B.—Woman aged 50. Diagnosis: cavernous haemangioma of the small gut. For eight years she was persistently anaemic and had required over 100 transfusions. She had never had a melaena stool, but examinations for occult blood were almost always positive. Apart from iron-deficiency anaemia, no haematological abnormalities were found. The stools were of a slate-grey colour probably due to oral iron therapy. **^{51}Cr investigations:**—Her own red cells were labelled with ^{51}Cr and injected. On the third day after the injection she gave clinical evidence of the rapid loss of blood, and the haemoglobin concentration was found to have fallen from 8.6 to 5.4 g./100 ml. The stools were collected for 17 days, and the amount of red cells in the faeces, together with the observed and corrected ^{51}Cr concentration curves in the blood, are given in Fig. 1. On the 17th day the corrected ^{51}Cr curve was only 6% below the normal value. During this period the patient lost red cells equivalent to 79% of her red-cell mass (as estimated at the onset of the investigations). Despite this, the stools did not alter from their slate-grey colour. Later 70 cm. of jejunum was removed at operation. One small cavernous haemangioma was found.

Patient E. B.—Man aged 45. Diagnosis: aplastic anaemia. He had anaemia, leucopenia, and thrombocyto-

penia, and was originally diagnosed as suffering from thrombocytopenic purpura. However, there was no improvement after splenectomy, and in the following 18 weeks he required 81 pints (46 litres) of blood. The occult blood test on the stools was persistently positive, but it was not certain whether the loss of blood by this route was sufficient to account for the anaemia or whether a

FIG. 1.—Patient G.B. Cavernous haemangioma of small gut. The observed and corrected ^{51}Cr concentrations in the blood are shown, together with the red cell loss in the stools, after the injection of ^{51}Cr -labelled red cells. ● = Observed ^{51}Cr concentration in the blood. × = ^{51}Cr concentration in the blood, corrected for red-cell loss in the stools (for method of calculation, see text). - - - = normal ^{51}Cr survival curve (from Mollison and Veall, 1955).

FIG. 2.—Patient E.B. Aplastic anaemia. (Symbols as in Fig. 1.)

haemolytic process was also present. ^{51}Cr investigations:—Compatible red cells from a donor were labelled with ^{51}Cr and injected. The stools were collected for the following 19 days; the amount of red cells in the faeces and the observed and corrected ^{51}Cr concentrations in the blood are given in Fig. 2. During this period the patient lost 400 ml. of red cells in the stools, which were dark brown in colour throughout. On the 19th day the corrected ^{51}Cr concentration in the blood was only 5% below the normal value.

Patient G.G.—Man aged 37. Diagnosis: ulcerative colitis. He was investigated during a relapse of his disease. Blood was not usually visible macroscopically in his stool, but the occult blood tests were positive. The haemoglobin concentration varied between 9.5 and 12.5 g./100 ml. and the reticulocyte count was between 1 and 4%. ^{51}Cr investigations:—His red cells were labelled with ^{51}Cr and injected. The stools were collected for the next 24 days. The faecal loss of red cells and the observed and corrected ^{51}Cr con-

centrations in the blood are shown in Fig. 3. The corrected ^{51}Cr value on day 24 was 50%—that is to say, 2% below the normal value.

FIG. 3.—Patient G.G. Ulcerative colitis. (Symbols as in Fig. 1.)

Patient V.P.—Woman aged 57. Diagnosis: hereditary haemorrhagic telangiectasia. She had been intermittently anaemic since the age of 18. When seen she had an iron-deficiency anaemia with a haemoglobin concentration of 7 g./100 ml. The occult blood test in the stool was persistently positive. ^{51}Cr investigations:—Her red cells were labelled with ^{51}Cr and injected. During the following seven days 10% of the injected ^{51}Cr was lost in the stools. The corrected ^{51}Cr concentration in the blood on the seventh day was 77% (normal value, 78%).

Patient J.H.—Girl aged 18. Diagnosis: Fanconi type of refractory anaemia. She had received several hundred pints of blood during her lifetime; she was losing blood through the nose, mouth, rectum, and vagina, but it was not certain whether this loss, together with the aplastic marrow, would account for the degree of anaemia, or whether a haemolytic process was also present. ^{51}Cr investigations:—Compatible cells were labelled with ^{51}Cr and injected. All stools and vomit were collected over the next 21 days, together with swabs containing blood from the nose and vagina. During this period 16% of the injected dose of ^{51}Cr was lost; the corrected ^{51}Cr concentration in the blood on the 21st day was 58%, compared with the normal value of 55%.

Patient R.G.—Woman aged 61. Diagnosis: iron-deficiency anaemia. Barium enema showed multiple diverticula of the sigmoid and descending colon, and the occult blood tests were positive throughout the observation period. ^{51}Cr investigations:—Her own cells were labelled with ^{51}Cr and injected. The stools were collected during the next 13 days; their ^{51}Cr content varied between 0.03 and 0.21% of the injected dose and the total excreted during this period was 1.1% (average daily excretion, 0.083%). This represented a total loss of 13.5 ml. of red cells, or, on the average, 1 ml. of red cells a day. The loss of ^{51}Cr in the stools of this patient was 7 and 20 times greater than that found in patients A.S. and M.H., who were thought not to have lost red cells in their stools. The loss of ^{51}Cr in the stools was too small to affect the ^{51}Cr survival curve.

Discussion

Neither Owen *et al.* (1954) nor Roche *et al.* (1957) were able to recover all the ^{51}Cr in the stools after introducing ^{51}Cr -labelled red cells into the stomach or duodenum of their subjects. The estimates of recovery made on eight patients by Roche *et al.* were between 90 and 103%. Recoveries of only 65 and 88% were obtained in the present investigation. A small quantity of the ^{51}Cr introduced into the gut as ^{51}Cr -labelled red cells must therefore be absorbed. Nevertheless the amount of ^{51}Cr absorbed must be extremely small, as the quantity given was only of the order

of 1 μ g. Other estimates of the absorption have been made in man, using the insoluble chromic oxide (Kreula, 1947; Irwin and Crampton, 1951). These investigators stated that it was virtually unabsorbed, but they were given 4–15 g. and hence the absorption of μ g. quantities could not be detected.

In four of the five patients presented here the corrected ^{51}Cr concentration in the blood at the end of the investigation was between 1 and 6% lower than the normal ^{51}Cr value. It is reasonably certain that this discrepancy was due to reabsorption of some of the ^{51}Cr by the gut. It would be difficult to correct precisely for this absorption, because the amount absorbed probably varies with the site of bleeding—that is, there would be greater absorption after bleeding into the stomach than after bleeding into the descending colon. It remains possible that the apparent slight diminution of ^{51}Cr survival in the blood was due to a haemolytic process. However, the process would have had to be very mild. Thus, in patient G.B., in whom ^{51}Cr curves showed the greatest departure from normality, the apparent loss of red cells was only 0.25% a day, whereas in haemolytic anaemia of clinical significance the loss is from 3 to 20% a day.

Roche *et al.* (1957) found that the excretion of ^{51}Cr in the stools in 10 subjects without evidence of gastro-intestinal bleeding was equivalent to 1.27 ml. of blood a day. As their subjects had approximately normal haemoglobin concentrations, this amount of blood probably represented about 0.5 ml. of red cells. The quantities found in the two subjects studied here were less than this—namely, 0.1 and 0.2 ml. of cells a day. Roche *et al.* did not wash the red cells after labelling with ^{51}Cr , and hence approximately 10% of the injected ^{51}Cr was present in the plasma. This unattached ^{51}Cr may account for their higher normal values. Owen *et al.* (1954) found a greater amount of ^{51}Cr in the stools after the injection of sodium chromate intravenously than after the injection of ^{51}Cr -labelled red cells. In the present investigation the red cells were washed free from unabsorbed ^{51}Cr before injection.

Owen *et al.* (1954) have also shown that ^{51}Cr is excreted in the stools after the intravenous injection of trivalent ^{51}Cr (red cells are not labelled by trivalent ^{51}Cr); thus the ^{51}Cr found in the stools in normal subjects could be derived either from the ^{51}Cr which elutes out of surviving red cells or from that which is freed from cells destroyed within the body. On the other hand, there may be a small loss of red cells into the gut each day.

Both the ^{51}Cr -labelling and the occult blood tests using benzidine are unsatisfactory when only small amounts of red cells are lost in the stools. The occult blood tests using the peroxidative activity of haemoglobin are limited, because if they are made too sensitive other peroxidases present in faeces will give false-positive results. The ^{51}Cr -labelling method is limited because ^{51}Cr is normally excreted in the stools after the injection of labelled cells. Needham and Simpson (1952) recommended the use of 0.5% benzidine solution for the occult blood tests, and they found that it was necessary to give approximately 2 ml. of cells by mouth before a positive occult blood test could be obtained. The use of ^{51}Cr will enable 2% of this amount of red cells to be detected—that is, 0.04 ml. of cells (see method 2)—but this advantage will be offset by the normal excretion of ^{51}Cr , equivalent to 0.1–0.5 ml. of cells a day. Hence the ^{51}Cr method is useful only when the chromium excreted exceeds the equivalent of 0.5–1 ml. of red cells a day.

Summary

Blood loss in the stools can be estimated quantitatively by labelling a sample of the subject's red cells with radioactive chromium (^{51}Cr), reinjecting the cells into the circulation, and subsequently estimating the ^{51}Cr content of the stools. This method of investigation was used in six patients known to be bleeding from the

gastro-intestinal tract. As expected, the rate of loss of ^{51}Cr from the blood stream was increased, and this was almost completely accounted for by the amount of ^{51}Cr lost in the stools. The fact that the amount of ^{51}Cr in the stools did not completely account for the rate of loss of ^{51}Cr from the blood stream indicates that some ^{51}Cr is reabsorbed from the gastro-intestinal tract (but is not reutilized). Thus the ^{51}Cr method slightly underestimates the amount of blood lost in the stools.

In two control subjects who were thought not to be bleeding into the gastro-intestinal tract, the amount of ^{51}Cr excreted in the stools following the intravenous injection of ^{51}Cr -labelled cells was very small (equivalent to 0.1 to 0.2 ml. of red cells a day). Because of this slight excretion of ^{51}Cr in the stools of normal subjects whose cells have been labelled with ^{51}Cr , the daily loss of blood in the stools must exceed 1 ml. a day before it can be detected by this method.

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EFFECT OF RESERPINE IN THERAPEUTIC DOSAGE ON EXCRETION OF 5-HYDROXYINDOLEACETIC ACID

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Recent investigations into the biochemistry of 5-hydroxytryptamine (H.T.) have provided evidence that the endogenous H.T. in the mammalian brain is mobilized and disappears from the organ following the injection of reserpine (Brodie *et al.*, 1955); the hypothesis has been advanced that the latter drug owes its pharmacological properties, hypotensive and ataractic, to its ability to set free H.T. or, as an alternative, to interfere with the H.T.-binding sites, the immediate liberation being incidental.

Reserpine will also set H.T. free from blood platelets *in vitro* (Shore *et al.*, 1956) and *in vivo* in animals and man (Haverback *et al.*, 1956a), but the stores of this compound in the intestinal cells are not so readily liberated, although this has been reported following high dosage in the rabbit (Pletscher *et al.*, 1955). A resultant increase in the excretion product, 5-hydroxyindoleacetic acid (H.I.A.A.), has been demonstrated in the dog following massive doses of reserpine; the dose used, 5 mg./