treatment for acute rheumatism led to reinvestigation of the effect of salicylate in diabetes mellitus.

An intensive two-weeks course of aspirin abolished glycosuria and lowered the fasting blood sugar to normal or near normal in seven mild to moderately severe diabetics.

No decisive effect on glucose tolerance was obtained, though the blood-sugar curves were always lower during aspirin administration than they were either before or after.

Moderate ketonuria in two patients was reduced to normal with aspirin.

Clinical improvement accompanied the biochemical changes induced by aspirin, and, while serious toxic manifestations were not conspicuous, tinnitus and deafness were annoying. The possible place of aspirin in the treatment of diabetes mellitus is discussed.

The action of aspirin in diabetes mellitus has been located in the tissues, and this is of interest in the light of the proper establishment of the drug as a peripheral-acting metabolic stimulant.

We thank Miss M. McCombie and staff of the dietetic department of the Western Infirmary for careful preparation and supervision of the diets.

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METABOLISM OF ^{59}FE-DEXTRAN COMPLEX IN HUMAN SUBJECTS

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The introduction of an iron-dextran complex ("imferon") isotonic with tissue fluids and having a *p*H of 6–7 enabled intramuscular therapy to be established in the treatment of certain iron-deficiency anaemias (Fletcher and London, 1954). The efficiency and advantages of this form of iron therapy have been shown in a number of papers (Baird and Podmore, 1954; Cappell, Hutchison, Hendry, and Conway, 1954; Cope, Gillhespy, and Richardson, 1956; Scott, 1956), and there is information concerning its rate of release and utilization as determined by serial serum iron and haematological measurements (Baird and Podmore, 1954). The metabolism of this compound has been further studied in animals, using histological and chemical techniques (Pinniger and Hutt, 1956; Beresford, Golberg, and Smith, 1957; Golberg, Smith, and Martin, 1957), and these results have indicated the pathways followed by the complex after intravenous and intramuscular injection.

Despite these studies certain problems require clarification in the metabolism of this compound in man. These include information concerning the clearance from intramuscular sites and the percentage of iron utilized for haemoglobin synthesis in different circumstances. It was felt that the production of an iron-dextran complex containing radioactive iron would enable some of these problems to be elucidated. Such a product was prepared by Bengers Ltd., and as a result of their co-operation these studies were made possible.

Materials and Methods

A radioactive iron-dextran complex was prepared by Bengers by incorporation of an isotope of iron (^{59}Fe) into a small process unit similar to that used in routine manufacture. The tracer dose of radioactive iron did not appear to affect the biological properties of the compound, and *in vitro* and animal experiments conducted by Bengers showed the radioactive complex to be similar to that in routine use. This radioactive preparation was administered so that a normal dose of iron (250 mg. in 5 ml.) contained approximately 10 microcuries of radioactivity.

The measurements of radioactivity were made by techniques described previously (Wetherley-Mein, Hutt, Langmead, and Hill, 1956). External body surface counts were made over the liver, spleen, sacrum, and heart, and after intramuscular injection external body surface measurements were recorded as the maximum radioactive counting rate over the site of the injection. Control measurements were made over the opposite buttock so as to correct for the radioactivity of blood flowing in the area measured by the scintillation counter.

Estimation of the percentage of the iron utilized in haemoglobin formation was calculated from the activity of the injected dose and the activity in whole blood after various time intervals. Blood volume was calculated either from the body weight and venous haematocrit (Mollison, 1951) or from plasma clearance data.

Results are expressed as plasma and buttock clearance rates and, with surface counting measurements, as a counting rate—that is, counts per second—at various times.

Patients Studied

The limited supply of radioactive iron-dextran and its decay rate necessitated the investigation of cases that happened to be available for studies lasting up to two weeks. They therefore fulfilled rather wider criteria than would have been decided by choice.

The studies were designed to follow the metabolic routes of the iron-dextran compound after intravenous and intramuscular injection in both normal and iron-deficient subjects. In some cases further doses of non-radioactive imferon were given as required for the clinical management of the patients. Data for the patients studied and the doses administered are shown in Table I.

Results After Intravenous Administration

The object of intravenous injection of iron-dextran was to follow the metabolic pathways of the material uncomplicated by its slow release from the temporary depot site produced by intramuscular injection.

1. *Plasma Clearance.*—In Fig. 1 is shown the plasma clearance of iron-dextran from the five patients studied (Cases 1–5). Despite the differing doses administered (Table I), the general configuration of the clearance is similar in all cases. When these figures are plotted with a logarithmic ordinate scale expressing the activity injected, the clearance initially approaches an exponential form. In those cases where it was followed in the later stages the clearance was asymptotic. No significant difference was observed between the clearances of normal and of iron-deficient subjects (Table II).

TABLE I.—*Summary of Cases*

Case	Sex and Age	Programme of Dosing Values in mg. Iron on Day				Radioactivity Injected in Counts/sec.	Absolute Values at Zero Time			Diagnosis
		0	1	2	3		Hb %	P.C.V. %	M.C.H.C. %	
1	F 34	275*	—	—	—	23,840	97	41	35	Normal
2	M 54	100*	—	—	—	18,840	104	43	35	Carcinoma of lung
3	F 16	250*	100	—	—	26,050	33	20	24	Menorrhagia
4	M 66	200*	—	—	—	30,000	59	32	26	Iron-deficiency anaemia
5	M 60	250*	250	250	—	23,840	58	30	28	Carcinoma of caecum
6	M 43	250*	—	—	—	24,860	105	43	36	Duodenal ulcer (no bleeding)
7	M 84	250* R	—	250 L	—	29,980	32	24	20	Peptic ulcer
8	M 80	215*	—	—	—	24,035	50	27	27	Carcinoma of stomach
9	F 58	250 L	250 R	250 L	200* L	24,590	54	28	28·5	P.U.O.
10	F 45	250*	—	—	—	28,850	75	36	31	Rheumatoid arthritis

* Denotes iron-dextran containing ^{59}Fe. R and L denote right and left buttock respectively.

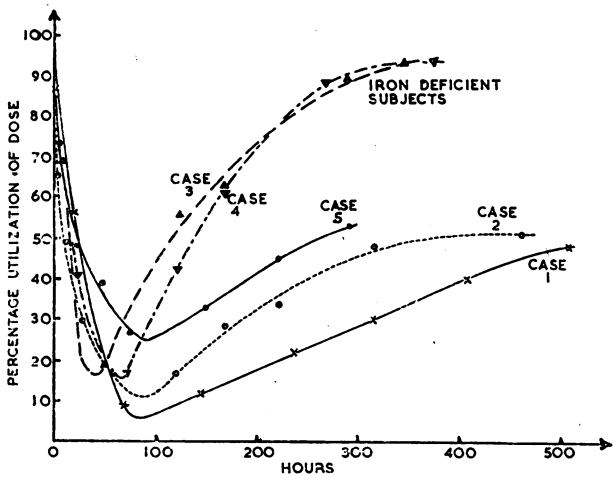

FIG. 1.—Cases 1-5. Clearance and re-entry in whole blood after intravenous injection of iron-dextran.

TABLE II.—*Clearance and Utilization of Radioactive Iron-dextran After Intravenous Administration*

Case	Plasma Half-clearance in Hours	Percentage Utilization of Dose	Time in Hours	Blood Volume in ml.	
				P.C.V./WT.	Iron-dextran
1	26	48	504	3,341	3,406
2	14	60	720	5,300	5,340
3	17	93	342	3,418	3,006
4	19	93	370	3,820	4,610
5	23	53	290	4,400	3,909

As is apparent from Fig. 1, the values for the percentage utilization are not the highest values attained even at the times given, since in none of the cases had an equilibrium been reached.

2. *Utilization of Injected Iron for Haemoglobin Synthesis.*—In Fig. 2 is shown the distribution of radioactivity between plasma and red cells in Case 2. It is apparent that radioactive haemoglobin appears in the circulation within a few hours of an intravenous injection of iron-dextran. The rate of this appearance reaches a maximum at about 150 hours and then declines to substantially steady values. In Case 5 the utilization of the radioactive material in an iron-deficiency state appears low because of the subsequent administration of non-radioactive imferon, but in Cases 3 and 4 utilization of the injected iron is almost complete after 350 hours, being more than 90% (Table II). Cases 1 and 2, in which there was normal erythropoietic function, are of particular interest. In these two patients there was no evidence of depleted iron stores, but 48 and 54% of the dose respectively was incorporated into haemoglobin after 21 days.

Surface Counting Patterns.—The patterns obtained by the external body-surface counting technique have certain features in common. There is a conspicuous increase in activity over the liver, marrow, and spleen; and the take-up of ^{59}Fe in these organs reached a maximum within 100 hours

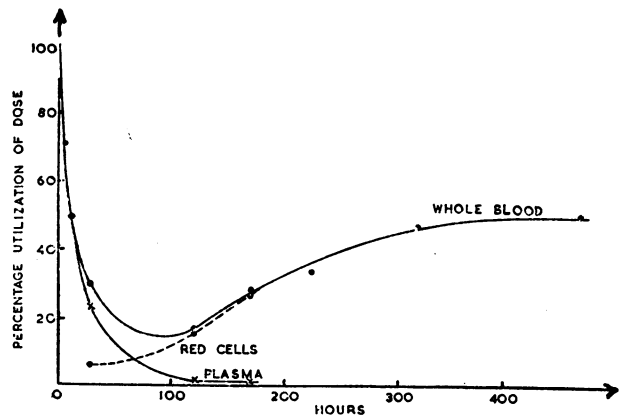

FIG. 2.—Clearance and re-entry of radioactive iron (injected as iron-dextran) in the plasma and red cells of a normal subject.

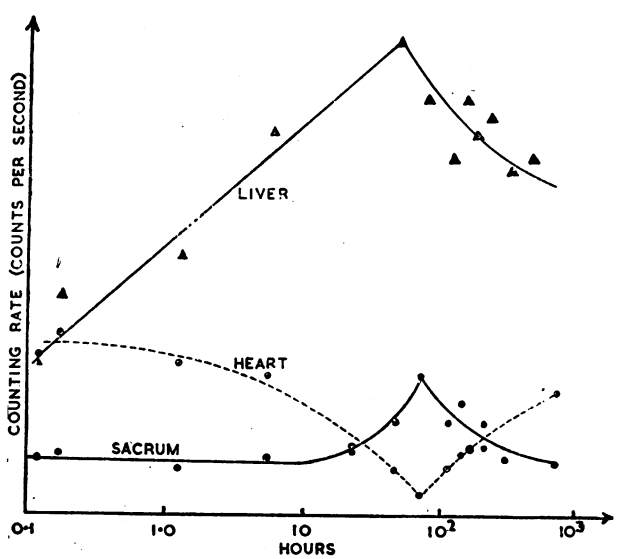

FIG. 3.—Body surface counts after intravenous injection of iron-dextran. The curves are for a normal subject.

(Fig. 3). This concentration of activity in the three organs was paralleled by a decreased radioactivity measured over the heart, reflecting plasma clearance. Subsequent to this maximum there was a decline in activity measured over the liver, spleen, and marrow, with a complementary increase in activity over the heart as radioactive erythrocytes appeared in the blood. The decline of the liver curve from the maximum was greatly retarded in Cases 1 and 2, and in fact appreciable activity was present at the conclusion of the experiment. This finding is supported by the lower utilization of ^{59}Fe in these two subjects. The curves obtained by measurement over the heart were similar in form to those

obtained from the whole blood activity. It is of interest to compare this pattern with that obtained after the intravenous injection of a tracer dose of inorganic ^{59}Fe (10 μC.) (Wetherley-Mein *et al.*, 1956).

Results After Intramuscular Injection

Following intramuscular injection there was a very variable clearance rate, which, in our studies, does not depend on the presence or absence of iron deficiency (Fig. 4). The disposal after clearance is similar to that which might be expected after a very slow intravenous infusion: there is a slow rise of blood activity, and the surface counts show

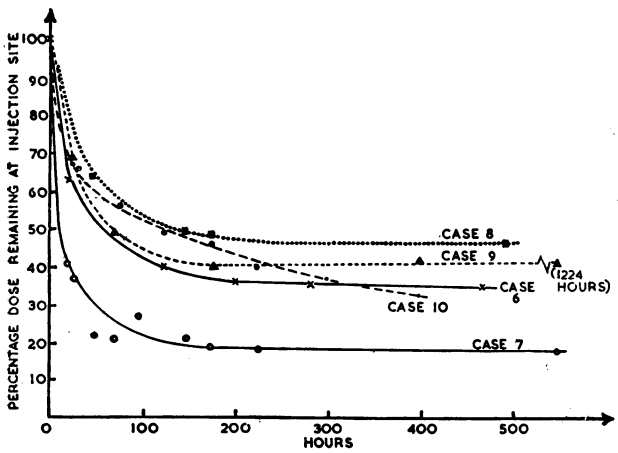

FIG. 4.—Cases 6–10. Clearance of iron-dextran from site of intramuscular injection.

delayed rises in the liver, sacrum, and spleen, followed by slow falls as these reticulo-endothelial sites are cleared and the iron is used for erythropoiesis.

The curves also show clearly that a certain proportion of the injected dose remains at the local site and that after about 140 hours little further absorption occurs for periods up to 400 hours. Table III shows an estimate of the percentage

TABLE III.—*Clearance and Utilization of Radioactive Iron-dextran After Intramuscular Administration*

Case	Buttock Half-clearance in Hours	Percentage Utilization of Dose	Percentage Utilization of Absorbed Dose	Time in Hours	Percentage Dose Remaining at Site
6	28	29	44	450	34 (450)
7	10	63	76	522	17 (528)
8	140	*			45 (474)
9	66	6†	10	385	40 (1,224)
10	110	44	63	456	30 (400)

Figures in parentheses in last column indicate times in hours corresponding to the percentage dose remaining at the site.
* Not estimated because of bleeding from primary lesions
† Low figure accounted for by previous high dosage of imferon.

utilization of the total dose of injected iron and also of the percentage utilization of iron assumed to be absorbed from the buttock. It is evident that the effective utilization in the normal subject (Case 6) is similar to that found after intravenous injection. In Case 7, an iron-deficiency anaemia, the effective utilization was high, 76%, and would probably have been greater if a further dose of non-radioactive imferon had not been given. The lowest utilization, in Case 9, resulted from giving the radioactive iron-dextran after three injections of non-radioactive imferon. This explains the storage of iron in the liver in this patient as shown by the concentration of activity throughout the period with no apparent clearance from this organ.

In one of the patients (Case 10) the radioactivity of the stools was measured during the experiment. The procedure adopted was that of R. O. Bannerman (1956, personal communication) where the radioactivity was determined on a weighted aliquot of macerated 24-hour stool. No evidence could be obtained that after intramuscular injection into the patient, who subsequently utilized 44% of the dose, there was any excretion of iron-dextran. In this same patient when surface count measurements were made over the testes there was no evidence of testicular deposition of iron-dextran.

Discussion

The results of these studies confirm the metabolic pathways taken by the iron-dextran compound previously studied by serum-iron estimations in man and by histological techniques in animals.

Following intravenous injection the compound is cleared by the reticulo-endothelial system, where the iron is rapidly liberated from the dextran complex and enters the labile iron pool, from which it passes to erythropoietic tissue, where it is utilized for haemoglobin synthesis. The initial exponential clearance is unaffected by iron deficiency and reflects reticulo-endothelial activity. The failure of the plasma clearance to maintain an exponential clearance may be due to alterations, of the iron-dextran complex after its injection or to alterations of reticulo-endothelial activity. The utilization of the iron injected intravenously appears to be virtually complete in iron-deficient subjects, and the high utilization of the iron in the normal subject bears out the concept of a metabolically labile iron pool which is used preferentially.

Following intramuscular administration a variable proportion of the dose is very rapidly absorbed, the remainder appearing to be fixed locally, or only slowly absorbed, for periods up to four weeks. The curves obtained from the buttock clearances are similar in form to those found in experimental animals by Beresford *et al.* (1957), though the percentage absorption in animals is much greater. Our absorption figures are also less than those observed by A. R. Stevens (1957, personal communication), who found 90% clearance of ^{59}Fe iron-dextran from the vastus muscle of an iron-deficient patient and confirmed this clearance by demonstrating 87% utilization of the injected dose after 30 days.

The discrepancy between our results and those of Stevens may be related to anatomical differences at the sites of injection and/or to differences in the surface counting measurements. There is histological evidence (Cappell *et al.*, 1954) and further evidence from ^{59}Fe iron-dextran studies that a proportion of the residual dose is retained for some time in local lymphoid tissue following administration into the buttock (Lynn Evans and N. W. Ramsey, 1957, personal communication). It follows that absorption data based on surface counting measurements must be interpreted with the proviso that such measurements do not distinguish between unavailable iron remaining at the site of injection and available iron in regional lymph nodes (Beresford *et al.*, 1957).

A further possibility accounting for the lower absorption figures is that a small proportion of the dose became trapped in the subcutaneous fat. In view of the occasional gross skin-staining seen after injections of imferon the usual precautions were taken to ensure deep intramuscular injection. None of these patients showed skin-staining, though one cannot exclude that some of the dose might enter fatty tissue, particularly in obese subjects (Scott, 1956). A further factor influencing absorption is the mobility of the limb following intramuscular injection. Four of our patients were confined to bed at the time of injection, and the most immobile showed the least eventual clearance. The results emphasize that injections of this complex must be given with care, and suggest that if the limb is exercised afterwards absorption may be increased.

The clinical value of imferon has already been established, and our results indicate the ready utilization of the iron-dextran complex after absorption. The variable absorption patterns demonstrated may explain some of the delayed responses occasionally seen after intramuscular injection, and suggests that one should administer a dose slightly higher than the calculated requirement of iron, particularly in obese immobile patients.

Finally, we would emphasize that in our experience the iron-dextran complex can be administered intravenously

without reactions and that this results in a more rapid utilization of the injected iron when treatment is urgently required.

Summary

A radioactive iron-dextran complex was administered intravenously and intramuscularly to normal and iron-deficient patients. Measurements were made of the distribution and movement of the complex.

After intravenous injection the complex was cleared from the plasma by the reticulo-endothelial system, and the iron was then utilized for haemoglobin synthesis. In iron-deficient patients there was substantially 100% utilization of the injected dose.

After intramuscular administration approximately 60% of the injected dose was rapidly absorbed; thereafter clearance occurred only slowly.

Our thanks are due to the physicians of St. Thomas's Hospital for permission to study the patients under their care, and to Benger Laboratories Ltd. for their co-operation in the preparation of the radioactive iron-dextran. The expenses of this investigation were partly defrayed by a grant from the Endowment Fund of St. Thomas's Hospital.

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HAEMOPHILIA-LIKE DISEASE DUE TO AN AUTO-ANTIBODY

BY

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Haemophilia is a congenital disease which is determined by the well-known mode of inheritance. Occasionally it arises *de novo* as a fresh mutation. Recently there has been an increasing awareness of the existence of a haemophilia-like state which affects patients hitherto free of bleeding disorders. Such a condition may be brought about by the development of a factor (antithromboplastinogen) which interferes with plasma thromboplastin formation. The interference may take the form of destruction or neutralization of one or more of the components of thromboplastin or, as Hougie and Fearnley (1954) suggest, of inhibition of interaction between these components. The recorded examples comprise in the main those encountered in pregnancy and, relevant to this paper, a more heterogeneous group where a haemophilia-like state appeared after a variety of disorders (Loznor *et al.*, 1940; Conley *et al.*, 1948; Quick and Stefanini, 1948; Dieter *et al.*, 1949; Tzanck *et al.*, 1949; Singer *et al.*, 1950; Collins and Ferriman, 1952; de Vries and Shafrir, 1952; Nilsson and Wenckert, 1953; Hardisty, 1954; Bartorelli and Vanacore, 1955; Evans, 1955). In a number of cases no association with another disease was established (Joules and Macfarlane, 1938; Harrington *et al.*, 1950; Pons and Torregrosa, 1952; Hougie, 1953; Spaet and Kinsell, 1954; Evans, 1955).

Other inhibitors of coagulation have been recorded, and one of these is a heparin-like material (Biggs and Macfarlane, 1953). In the case described below there is reason to believe that both an antithromboplastinogen and an excess of a heparin-like material were present.

Case History

A married woman aged 46 was admitted to hospital on January 1, 1956, with a history of tonsillitis three weeks previously. This throat infection subsided after three injections of penicillin, an antibiotic she had never had before. A day or two after the injections a papulo-vesicular eruption appeared on the palms of her hands. This eruption became infected and caused much burning and itching. It gradually became more widespread, involving mainly the limbs. Soreness of the throat recurred after a further few days. On December 25, 1955, she developed a pleuritic pain in her right lower chest, and her right knee became red, swollen, and painful. A day or two later the left big and second toes became similarly affected. The patient was febrile but did not feel particularly ill, and an attempt to treat her with chlortetracycline was given up because she was unable to tolerate it.

On admission she showed discrete papules, some of which were infected, on her hands, arms, abdomen, back and to a less extent on her legs. There were effusions into the right knee and into the joints of the left big and second toes. The chest was clear. Blood cultures were sterile. A swab from a skin pustule grew coagulase-negative staphylococci only. She was treated with systemic penicillin and streptomycin, and locally by chlortetracycline cream. On this treatment the pustules began to clear, but the fever continued and the affected joints remained swollen. The arms were noticed to be oedematous too. Her temperature eventually began to settle, and, although the right knee was still stiff and swollen, her condition was sufficiently improved for her to be allowed up on January 17. Three days later she became pale and was found to have many spontaneous bruises in all limbs. The legs assumed an icteric tinge. Her haemoglobin, which on admission was 11.2 g. per 100 ml., was found to have fallen to 4.6 g.

She was placed on prednisolone, 20 mg. three times a day for two days, and thereafter the dose was reduced to 10 mg. three times a day. A transfusion of 5 pints (2.8 litres) of blood was given without any reaction, although cross-matching was difficult owing to rouleaux formation.

It was observed that a venepuncture performed for the transfusion went on oozing for two days, and a wound in the arm, made to expose another vein to complete the transfusion, continued to bleed for four days. Thereafter the patient began to improve, although on February 3 the cut used for the transfusion began to bleed again, and continued to do so for another four days. The total period during which she bruised and bled intermittently extended over 18 days.

The prednisolone was reduced gradually until by February 22 the dose was only 5 mg. daily, and this was maintained for another three weeks.

When the patient left hospital (February 24) her haemoglobin had risen to 12.6 g. per 100 ml., and her general condition was fairly good. Subsequently she was seen in the out-patient department on several occasions. She gradually regained her strength, and up to the time of writing had not experienced any further bleeding. Two months after leaving hospital she had a recrudescence of the papulo-vesicular eruption on the palms of her hands, and this responded to chlortetracycline cream. On March 5 she was seen with a fresh crop of papules, mainly on her wrists and forearms, and a few on her trunk.