However, the reason for this may be that almost all the lesions were distal and the distance to be covered by the outgrowing axons was therefore not great. Secondary suture should be undertaken as soon as the primary wound has healed and the tissues are free from induration. Primary suture proved an unreliable operation, although some good results were seen. There are important technical reasons why secondary suture is more satisfactory. If, as is often the case, there has been intraneural damage it is much easier to recognize it some weeks after the injury than at the time, because it reveals itself as a palpable and, on section, visible zone of intraneural fibrosis. The resection can be planned accordingly. Furthermore, the epineurium becomes thickened after the injury, and after a few weeks is an ideal structure for holding fine sutures. Most of the repairs reported were secondary.

Where there is associated damage to tendons it is best to repair them at the time of injury and simply to approximate the severed nerves. When mobilization of the digits is well advanced secondary suture of the nerves is performed without disturbance of the tendons, which, at the wrist, lie on a deeper plane, and continued movement of the fingers has no adverse effect on the nerve suture.

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ASPIRIN AND DIABETES MELLITUS

BY

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Rheumatic fever and diabetes mellitus rarely coexist (Joslin *et al.*, 1952). An opportunity to investigate this unusual combination of disease was provided by a young male diabetic (Case 1), known to take insulin, who was receiving full salicylate treatment for acute rheumatism when admitted to hospital. At the outset we were confronted with a problem, for his urine was sugar-free and the fasting blood-sugar level was normal, though he was receiving only aspirin. The possibilities first entertained were that the previous diagnosis of diabetes was inaccurate or that spontaneous remission of the disease had occurred: neither seemed likely, and the diagnostic dilemma was resolved by the reappearance of sugar in the urine one week after discharge from hospital, when aspirin had been discontinued. On re-examination at this time he was found to have glycosuria, a high fasting blood sugar, and a diabetic glucose-tolerance curve (Fig. 1).

These findings imply that rheumatic fever and diabetes mellitus are in some way incompatible, or that aspirin, the drug used in treatment of acute rheumatism, is antidiabetic. Earlier reports indicate that salicylate was in fact used in the treatment of diabetes and that it prevented glycosuria (Gross and Greenberg, 1948). This information, together with the striking findings in our patient, led us to reinvestigate the effect of aspirin in diabetes mellitus, beginning with mild forms of the disease and, if necessary, progressing to severer types.

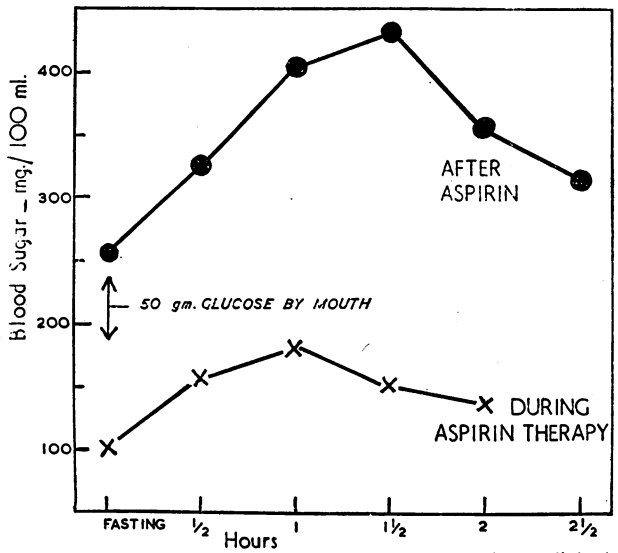

FIG. 1.—Results of oral glucose-tolerance tests in a diabetic patient (Case 1) while he was receiving aspirin treatment for acute rheumatism, and after the drug had been discontinued. During aspirin therapy the curve was almost normal; after stopping the drug it was diabetic.

Clinical Particulars and Methods

The effect of aspirin in another seven diabetics has been investigated. Four belonged to the overweight mild type; the other three were lean, more severe diabetics. Each patient was given a constant low-carbohydrate diet throughout the whole investigation, and this was given for about two weeks before aspirin administration to establish the effect of diet alone. Further particulars of the patients and the diets are given in Table I.

TABLE I.—*Clinical Particulars of Patients*

Case	Sex	Age in Years	Weight (Kg.)	Duration of Disease (Months)	Standard Diet	
					Carbohydrate (g.)	Calories
1*	M	26	56·3	24	124	1,600
2	M	58	76·0	8	150	1,950
3	F	55	82·6	48	150	1,950
4	F	52	76·8	60	130	1,700
5	F	65	69·5	48	104	1,350
6	F	58	54·9	5	104	1,350
7	F	53	56·2	4	170	2,200
8	F	15	44·5	1	130	1,700

* Patient with diabetes mellitus and acute rheumatism.

Aspirin Dosage.—An intensive course of aspirin controlled by serum salicylate estimations (Trinder, 1954) was given to each patient for 10 to 14 days. Doses of 1 to 1.6 g. were taken four-hourly, omitting one dose in the middle of the night, to maintain as high a serum salicylate level as possible without inducing serious undesirable symptoms. The effect of this intensive course of aspirin on the clinical manifestations of diabetes as well as on the principal biochemical features of the disease has been investigated. Blood sugar was estimated by Lehmann and Silk's (1952) modification of Folin and Wu's method, glycosuria by Benedict's (1911) method, and ketonuria by the method of Greenberg and Lester (1944). Oral glucose-tolerance tests were also carried out; in addition, basal metabolic rates (B.M.R.) of four patients, calculated by the method of Robertson and Reid (1952), were determined before, during, and after aspirin therapy in view of the recent establishment of the drug as a peripheral-acting metabolic stimulant (Sproull, 1954).

Fasting Blood Sugar

Table II shows the fasting blood sugars of all the seven patients at intervals throughout the investigation. The results during the week preceding aspirin administration indicate a comparatively stable pre-treatment state in all patients and

TABLE II.—*Aspirin and Fasting Blood Sugar*

Case	Fasting Blood Sugar (mg./100 ml.)						
	Before Aspirin		During Aspirin			After Aspirin	
	Day 4–5	Day 0	Day 3	Day 7–8	Day 13–14	Day 3–4	Day 6
2	140	121	76	80	73	76	98
3	163	178	108	97	80	118	—
4	196	186	140	118	95	125	129
5	194	196	212	111	—*	125	148
6	196	212	186	101	106	102	105
7	213	220	188	92	78	116	198
8	280	225	214	189	122	140	—
Mean	197	191	161	113	92	115	136

* Treatment with aspirin was given for only 10 days in this patient and the blood sugar on the 10th day was 104 mg./100 ml.

provide a satisfactory baseline to judge the effect of the drug. Without exception, aspirin reduced the fasting blood sugars and brought them to normal or near normal by the end of the course of treatment, and after it was discontinued the sugar concentrations started to rise again. These findings are well illustrated by the mean values of the group. Pre-salicylate blood sugars of 197 mg./100 ml. four to five days before and 191 mg./100 ml. on the actual day of starting aspirin fell to 161 mg./100 ml. after three days' treatment. The fall continued to 113 mg./100 ml. at the end of one week and to 92 mg./100 ml. after two weeks of aspirin administration. When the drug was discontinued the mean value rose to 115 mg./100 ml. on the third to fourth day, and to 136 mg./100 ml. on the sixth day.

These striking results indicate that a short but intensive course of aspirin lowers the fasting blood-sugar level in diabetes mellitus.

Glycosuria

The amount of sugar in the urine was estimated daily in six of the seven patients during the month that the investigation lasted. Difficulty in condensing all the results for presentation in a reasonable space made it necessary to confine our attention to the urinary glucose excretion on the days corresponding to fasting blood-sugar estimations, though such arbitrary selection in no way altered the general trend of the results presented in Table III. In two patients sugar either disappeared from the urine or only a small quantity persisted towards the end of the preliminary dietetic control period. The other four patients had considerable glycosuria at the end of the control period which progressively diminished during the period of aspirin administration, indicating that the drug had the same striking effect on glycosuria as it had on blood sugar.

TABLE III.—*Aspirin and Glycosuria*

Case	Total Urinary Sugar (g./24 hours)						
	Before Aspirin		During Aspirin Therapy			After Aspirin	
	Day 4–5	Day 0	Day 3	Day 7–8	Day 13–14	Day 3–4	Day 6
2	7	4	7	7	5	0	0
3	21	34	6	5	5	0	10
5	0	0	4	7	—*	0	0
6	22	20	3	3	3	7	0
7	88	117	61	43	4	0	15
8	55	55	38	17	7	39	—
Mean	32	38	20	14	5	8	5

* Total urinary sugar on the 10th day was 2 g.

One minor feature of the results requires amplification. It will be observed that the two patients with slight or no glycosuria at the end of the initial control period both had glycosuria amounting to 4 to 7 g. per 24 hours during the period of aspirin therapy: only after discontinuing the drug was the urine free from reducing substance. This paradox was cleared up when it was found that intensive treatment of rheumatic fever with salicylate may lead to the appearance of reducing substance in the urine, probably a salicylate conjugate, in amounts equivalent to about 5 g. of glucose per 24 hours. A blank value of up to 5 g. per 24 hours may thus be subtracted from the reducing substance found during the period of salicylate administration to the diabetics (Table III), and this will make the glycosuria negligible.

Oral Glucose-tolerance Tests

The next investigation was the response of the diabetics taking aspirin to a test dose of 50 g. of glucose by mouth. Glucose-tolerance tests were carried out before, during, and after aspirin, or during and after aspirin in five patients, including the original patient with acute rheumatism. The

TABLE IV.—*Oral Glucose-tolerance Tests*

Time	Blood Sugars (mg./100 ml.)											
	Case 5			Case 4		Case 6			Case 8			
	B	D	A	D	A	B	D	A	B	D	A	
Fasting	196	104	148	118	134	216	110	105	280	183	140	
½ hour	304	145	192	158	157	304	200	200	390	234	196	
1 ,,	322	200	248	208	207	384	230	266	450	—	—	
1½ hours	294	142	276	156	230	334	185	229	500	350	204	
2 ,,	304	—	276	132	230	288	154	171	450	383	—	

B, D, and A = before, during, and after aspirin treatment.

results (Table IV and Fig. 1) show that the blood-sugar curves during aspirin administration were uniformly lower than the values either before the drug was given or after it was discontinued, even though in three of the patients the fasting blood sugar had not reached its lowest value from aspirin therapy when the test was carried out.

Ketonuria

The effect of aspirin on another important abnormality of the disease—ketosis—has been studied by estimating the total ketone excretion of the only two patients in the group who had a positive Rothera test when admitted to hospital. Quantitative estimations of urinary ketones were carried out by the method of Greenberg and Lester (1944). The upper limit of normal ketone excretion has been taken as the recommended 50 mg. in 24 hours. By this standard only the two patients with a positive Rothera test had an abnormally high excretion of ketones before salicylate administration. The complete results in both patients, shown in Fig. 2, indicate that the ketone levels fell to normal at the end of the second week of aspirin treatment. This fall was preceded in one patient by fluctuation in ketone excretion

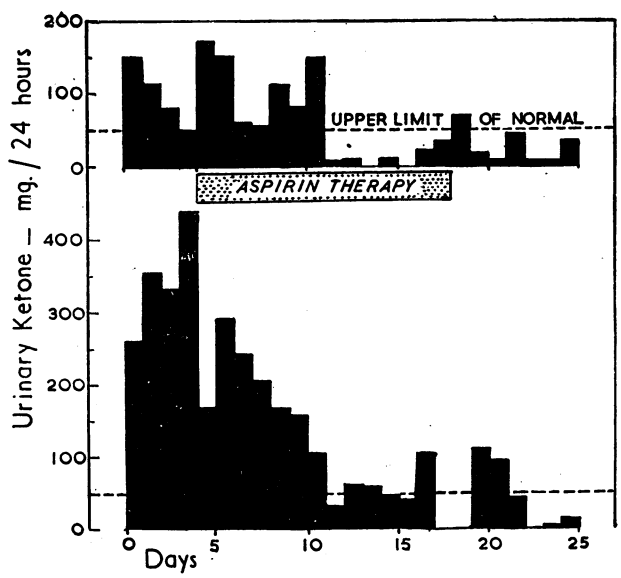

FIG. 2.—Daily urinary ketone output of two diabetic patients (Case 8, above: Case 7, below) before, during, and after a two-weeks course of aspirin. In both patients ketone excretion was normal at end of second week of treatment. In one the fall was precipitous and started immediately after aspirin therapy began. In the other ketonuria fluctuated during the first week and then fell to normal.

during the first week the drug was given. In the other the fall was precipitous and started when aspirin therapy began.

Body Weight

Seven patients were weighed a few days before aspirin was given, on the last day of aspirin therapy, and during the week after discontinuing the drug. One overweight patient lost 2.3 kg. during the period aspirin was given, but the other patients, including the lean and more severe diabetics, showed no significant weight change. All except two patients, however, lost 1 to 2.7 kg. in the week after aspirin was discontinued, and this was associated with a diuresis. A similar loss of weight, accompanied by diuresis, follows salicylate treatment of rheumatic fever (Reid, Watson, and Sproull, 1950).

Clinical Manifestations

So far it has been shown that aspirin has a definite beneficial effect on the blood sugar, glycosuria, and ketone excretion in diabetes of mild to moderate severity. It is therefore not surprising that the clinical symptoms of the disease, such as thirst, polyuria, and pruritus, which are intimately related to the high blood sugar and glycosuria, were completely relieved by the drug. The course of treatment was purposely intensive, particularly in the rapid build up to a high serum salicylate level shown in Table V, as we were anxious in this preliminary study to investigate the effect of maximum tolerated doses. This naturally led to the appearance of more serious side-effects like persistent nausea in two patients which went on to intermittent vomiting in one during the initial two or three days of treatment. At this time both patients had very high serum salicylate levels (52 mg./100 ml. on the third day of therapy), but these symptoms soon disappeared on reducing the dose and thereby lowering the salicylate level.

TABLE V.—*Serum Salicylate During Aspirin Therapy*

Case	Serum Salicylate (mg./100 ml.)			
	Day 3	Day 7–8	Day 13–14	Day 2–4 After Aspirin
2	42	45	37	0
3	39	38	35	0
4	40	52	39	0
5	39	38	—*	0
6	52	32	35	0
7	52	41	39	0
8	42	46	38	0
Mean	44	42	37	0

* Level on 10th day, when aspirin was discontinued, was 46 mg./100 ml.

While serious side-effects from salicylate were relatively uncommon and easily controlled, the less disturbing but nevertheless annoying symptoms of tinnitus and deafness were more frequent during the period aspirin was given. Two patients complained of tinnitus, but seven of the eight had dulling of hearing, which was mild in three and more severe in the other four. These symptoms also disappeared soon after aspirin was discontinued.

The only other noteworthy clinical observation during aspirin therapy was a change in vision in one patient (Case 7) reminiscent of the effect produced by sudden changes in blood sugar.

The final inquiry was to find out if the drug acts as a metabolic stimulant in diabetics as it does in normal individuals and in rheumatic (Cochran, 1952, 1954) and myxoedematous patients (Alexander and Johnson, 1956).

TABLE VI.—*Aspirin and Basal Metabolic Rate*

Case	B.M.R. (% Normal)		
	Before Aspirin. Day 0–1	During Aspirin. Day 8–13	After Aspirin. Day 2–6
2	112	161	108
3	139	166	—
6	98	120	95
7	108	160	104

Aspirin and the B.M.R. in Diabetes Mellitus.—The B.M.R. of four patients was determined before, during, and after aspirin; and from the results in Table VI it will be seen that diabetics behave in the same manner as other subjects, both in health and in disease, by showing a definite increase in metabolic rate in response to the drug.

Discussion

A short intensive course of aspirin lowers fasting blood sugar and leads to disappearance of glycosuria and reduction of ketonuria in mild to moderately severe diabetes mellitus. Clinical remission coincides with biochemical improvement, but diabetic symptoms are replaced by annoying side-effects from salicylate, principally tinnitus and deafness, which develop with serum salicylate levels required to control blood sugar. More serious symptoms, such as persistent nausea and vomiting, arise with higher drug concentrations, and their presence indicates immediate reduction in dosage unless "starvation ketosis" is to be added to existing abnormalities of the disease.

The findings presented in this paper are in keeping with earlier observations with salicylate in diabetes reviewed by Gross and Greenberg (1948) and fit in with recent results in experimental forms of the disease in rats. Ingle (1950) has shown that aspirin reduces glycosuria after removal of part of the pancreas, and Smith, Meade, and Bornstein (1952) demonstrated a similar effect in alloxan-diabetic rats. Thus, while the effect of aspirin on blood sugar and glycosuria of diabetes is indisputable, its mode and site of action are not so clear-cut. Theoretically, blood sugar may be lowered by increased renal excretion of glucose, by faulty assimilation of carbohydrate, and by increased utilization or storage in the tissues. The reduction in fasting blood sugar in our patients who were receiving a constant carbohydrate diet coincided with disappearance of glycosuria, indicating that the fall was not due to alteration in the renal threshold for glucose. Absorption of glucose was not impaired as judged by oral glucose-tolerance tests, and, while we have no direct information of the effect of aspirin on carbohydrate digestion, the observation of Dibenedetto dell'Aquila and Angarano (1954), that a single intravenous injection of sodium salicylate immediately lowers the fasting blood sugar in diabetes, points to the tissues as the site of action of aspirin. This deduction is of interest in the light of the recent establishment of salicylate as a peripheral-acting metabolic stimulant (Sproull, 1954).

While it would be premature to suggest that aspirin might regain a place in the treatment of diabetes mellitus, indications in favour and against such a possibility may briefly be considered. As already indicated, aspirin was used in treatment of diabetes mellitus and rejected because of serious toxic effects, probably the development of ketosis resulting from nausea and vomiting due to salicylate overdosage. These symptoms arise with blood concentrations of the drug that are higher than required to control hyperglycaemia, so that with proper control of therapy they need not appear. Minor symptoms such as tinnitus and dulling of hearing may be expected, but experience in other diseases requiring prolonged salicylate therapy indicates that they become less troublesome as time goes on. If there is a genuine need for an oral compound to control diabetes mellitus, aspirin has an obvious advantage over the sulphonylureas, in that it may be given for prolonged periods without risk of agranulocytosis. Another point in its favour is that maximal tolerated doses such as were given to our patients lower the fasting blood sugar to normal without inducing hypoglycaemia. There would therefore seem to be little risk of serious hypoglycaemic attacks from aspirin. Its place in the treatment of diabetes mellitus, however, will require further investigation, and in the last resort will depend on how well therapy can be controlled.

Summary

Disappearance of glycosuria and the return of fasting blood sugar to normal in a young diabetic during aspirin

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

BY

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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).