THE INSULIN EQUIVALENCE OF SALICYLATE

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Interest in the action of salicylate in diabetes mellitus has been revived by the observation that aspirin is capable of controlling the hyperglycaemia and glycosuria and of abolishing moderately severe ketosis in diabetes mellitus (Reid, Macdougall, and Andrews, 1957). Disadvantages of the therapy are early development of nausea and vomiting in a few patients, and the more frequent but none the less annoying side-effects of tinnitus and deafness. Nausea and vomiting are due to unsuspected overdosage with salicylate and are associated with very high serum salicylate levels. They are serious because they give rise to a starvation ketosis which is difficult to distinguish from diabetic ketosis, and this confusion probably accounts for the abandonment of salicylate in diabetes long before the introduction of insulin. Fortunately, nausea and vomiting need not arise if salicylate dosage is controlled by serum salicylate estimations in the early days of treatment, so that none of the disadvantages really presents an insuperable problem to its use in diabetes. Indeed, the fact that long and continuous administration of aspirin is not accompanied by risk of serious toxic effects such as agranulocytosis is in its favour, for while this risk may be negligible in short-term treatment it is not in a treatment which lasts for life.

The practical value of aspirin in diabetes, however, cannot be decided until its effectiveness has been compared with that of insulin, the most powerful antidiabetic agent known. In this paper the insulin equivalence of aspirin has been investigated in a group of 14 patients whose insulin requirements as out-patients ranged from 14 to 112 units each day. The amount of insulin which could be replaced by a maximal tolerated course of aspirin was determined in each patient. The patients were referred to us from the hospital diabetic clinic. Some were well controlled with insulin, but a good proportion of difficult cases who were not well controlled were included in the series. The complete practical range of insulin requirements has been covered, and it may fairly be claimed that the group represents a cross-section of diabetics who require insulin.

Clinical Particulars and Methods

Clinical particulars are shown in Table I. Ages of the patients ranged from 33 to 74 years. Nine were females, five were males. The duration of the disease varied from 1 to 24 years, the carbohydrate intake from 104 to 295 g. daily, and total calories from 1,300 to 2,700. The diets which the patients were accustomed to take as out-patients were continued throughout their whole stay in hospital—that is, for the duration of the investigation—except in one patient in whom a slight alteration was made during the insulin period. The only notable change in insulin administration apart

TABLE I.—*Clinical Particulars*

Patient	Age and Sex	Duration of Diabetes Years	Out-patient Daily Insulin Requirement (Units)	Diet	
				g. Carb./Day	Total Cals./Day
K. L. ..	67 F	14	14 I.Z.S.	104	1,300
S. McR. ..	50 F	4	20 "	120	1,400
A. C. ..	68 M	4	20 "	197	2,100
S. M. ..	65 M	24	22 "	209	2,200
*E. J. ..	55 M	1	24 "	150	1,900
S. W. ..	65 F	13	28 "	165	1,700
J. C. ..	66 F	6	36 "	150	1,700
S. H. ..	74 F	7	38 P.Z.I.	104	1,400
C. McP. ..	67 F	6	40 "	198	2,000
H. McM. ..	58 F	7	56 I.Z.S.	130	1,500
D. L. ..	68 M	3	56 "	224	2,300
M. C. ..	74 F	12	60 P.Z.I.	104	1,300
R. C. ..	33 M	20	76 I.Z.S.	295	2,700
C. McR. ..	51 F	8	112 "	207	2,000

* Diet increased to 194 g. of carbohydrate a day during insulin therapy.

from small adjustments in dosage was to replace protamine zinc insulin (P.Z.I.) with insulin zine suspension (I.Z.S.) in three patients so that all received the same type of insulin. Therapy was controlled by fasting blood sugars estimated by Lehmann and Silk's (1952) modification of Folin and Wu's method and tests for glycosuria (Benedict, 1911).

After an initial control period of at least 10 days during which the patients received their appropriate doses of insulin, aspirin therapy was then started and insulin therapy continued. Aspirin was administered in doses to attain maximum therapeutic serum salicylate levels of 35 to 45 mg./100 ml. to give the drug every opportunity to exert a full therapeutic effect under well-controlled conditions. Estimations of the fasting blood sugar and urinary sugar were continued and insulin dosage was reduced progressively if warranted by the biochemical findings. This procedure was followed in 12 patients: the other two were new diabetics, and they were given a course of aspirin before insulin to find out if reversing the treatments had any effect. The amount of insulin which could be replaced by maximal therapeutic doses of aspirin was thus determined for each patient.

Insulin Equivalence of Aspirin

The main findings are presented in Table II, where it will be noticed that it was possible to reduce insulin requirement of every patient after two to three weeks' treatment with aspirin.

Eight patients with an initial requirement of 12 to 48 units of I.Z.S. were able to do without insulin

TABLE II.—*Insulin Equivalence of Aspirin*

Patient	Diet Carb. (g./Day)	Without Aspirin Control Period		During Aspirin 2-3 Weeks		Difference in Insulin Requirement (Units I.Z.S./Day)
		Insulin Requirement (Units I.Z.S./Day)	Fasting Blood Sugar (mg./100 ml.)	Fasting Blood Sugar (mg./100 ml.)	Insulin Requirement (Units I.Z.S./Day)	
S. Mc R. ..	120	12	100	100	0	12
K. L. ..	104	14	170	100	0	14
A. C. ..	197	20	272	160	0	20
*E. J. ..	150	24	134	132	0	24
S. W. ..	165	28	214	90	0	28
*J. C. ..	150	36	150	122	0	36
S. H. ..	104	36	165	150	0	36
M. C. ..	104	48	148	95	0	48
S. M. ..	209	22	48-272	135-300	12	10
C. McP. ..	198	32	96-284	75-326	16	16
H. McM. ..	130	42	55-360	51-336	28	14
D. L. ..	224	52	52-272	40-290	40	12
R. C. ..	295	76	72-262	71-255	56	20
C. McR. ..	207	112	255	135	40	72

* Aspirin preceded insulin therapy.

altogether while aspirin was being given. Their fasting blood sugars at the end of the insulin and the aspirin periods were quite steady, indicating stable control with both insulin and aspirin, though the sugar levels with aspirin tended to be lower and nearer normal than with insulin.

Another five patients had a modest reduction in insulin requirement of 10 to 20 units of I.Z.S., but the lability of the fasting blood sugars during the courses of insulin and combined insulin and aspirin indicated that they were not well controlled with either treatment.

The last patient, a severe diabetic, required 112 units of I.Z.S. daily, and this was reduced by 72 units while she was receiving aspirin. Stable fasting blood sugars were observed both with insulin and with combined insulin-aspirin, but the values from the combined course were about half those from the initial insulin course, indicating an insulin equivalence of more than 72 units.

FIG. 1.—Poor response to insulin and aspirin therapy as indicated by the fluctuations in fasting blood sugar and persistence of glycosuria. The only noteworthy change was the reduction in ketonuria with aspirin.

So much for the basic results. Individual and more detailed findings from representative patients in the classes of response to aspirin just described are given below.

Patient S. M.—A male diabetic aged 65 did not respond well to aspirin. The unpredictable variations in fasting blood-sugar level and in glycosuria and ketonuria before aspirin was given indicated that he was not well controlled with insulin alone (Fig. 1). Aspirin therapy had little effect on the blood-sugar level, though just before it started and during its administration the patient had a sharp bout of diarrhoea with a slight rise of temperature. Reduction in ketonuria during the combined aspirin-insulin therapy is noteworthy, and it may be that we are being a little hard on aspirin in allowing an equivalence of only 10 units, since the patient required about 32 units of I.Z.S. after the course of aspirin to achieve comparable results, though the intercurrent infection made more precise interpretation of the results impossible.

Patient M. C.—An overweight woman aged 74 was well stabilized with insulin before the start of aspirin. Glycosuria was slight. She had no ketonuria, and her insulin requirement before aspirin was 48 units a day. It was possible during the period of aspirin therapy to reduce

FIG. 2.—Results in patient who was well controlled with insulin and who had an excellent response to aspirin. It was possible to replace the total requirement of 48 units of I.Z.S. with aspirin.

progressively and finally discontinue insulin altogether (Fig. 2). In this patient the insulin equivalence of aspirin was some 48 units of I.Z.S.

Patient C. McR.—A fairly stable diabetic woman aged 51 required the largest dose of I.Z.S. (112 units a day). Insulin requirement in this case was reduced to 40 units a day, and this probably is an understatement, because fasting blood sugar and glycosuria were lower during aspirin therapy than they were in the control period with insulin alone (Fig. 3). The insulin equivalence was therefore more than 72 units a day.

Patient J. C.—This case shows what happens when the aspirin course precedes insulin administration. The high fasting blood sugar (240 mg./100 ml.) before aspirin administration is quickly brought under control (122 mg./100 ml.) (Fig. 4). After stopping aspirin the blood sugar takes just about as long to reach the pre-aspirin level as it took to come down to normal. Insulin therapy was then

FIG. 3.—Findings in patient who was stabilized rather than controlled with 112 units of I.Z.S. The main effects of aspirin were a fall in fasting blood sugar to normal and diminution in glycosuria, accompanied by a reduction in insulin requirement to 40 units daily.

started, and 36 units of I.Z.S. a day were required to maintain the fasting blood sugar at a slightly higher control level. The findings in this patient and similar observations in the other patient in whom aspirin came before insulin suggest that the order of treatment does not affect the results.

FIG. 4.—Course of events when aspirin therapy precedes insulin. Fasting blood sugar returns to normal during aspirin administration only to revert to diabetic levels after stopping the drug. Thirty-six units of insulin were required to bring the fasting blood-sugar level back to a slightly higher control level than with aspirin.

Dose of Aspirin and Serum Salicylate Levels

The serum salicylate levels, estimated by Trinder's (1954) method, which produced these antidiabetic effects are shown in Table III together with the doses of aspirin required and the body weights of the patients. The mean levels ranged from 37 to 47 mg./100 ml. and there was no obvious correlation between body weight, dose, and the serum concentration of the drug. The dose of aspirin required by each patient to attain a particular serum salicylate level was fairly constant for the individual, though some patients required twice the dose of others to achieve the same level of the drug. This is why it is so necessary to estimate serum salicylate levels to find out the precise dose required by each individual to control diabetes mellitus.

TABLE III.—Dose of Aspirin and Serum Salicylate Level

Patient	Weight (kg.)	Maintenance Dose Given 5 Times Daily		Serum Salicylate Level (mg./100 ml.)	
		gr.	g.	Range	Mean
S. McR. . .	67.6	20	1.3	34-53	42
K. L. . .	64.4	17½	1.2	38-44	41
A. C. . .	65.5	22½	1.5	35-51	41
E. J. . .	64.8	22½	1.5	40-52	45
S. W. . .	67.5	10	0.7	37-56	47
J. C. . .	63.8	17½	1.2	39-44	41
S. H. . .	79.9	17½	1.2	40-45	43
M. C. . .	76.6	12½	0.8	35-48	40
S. M. . .	47.6	17½	1.2	35-58	47
C. McP. . .	54.4	17½	1.2	35-45	39
H. McM. . .	73.0	22½	1.5	31-43	37
D. L. . .	78.5	17½	1.2	36-52	41
R. C. . .	59.1	22½	1.5	37-46	44
C. McR. . .	50.3	17½	1.2	35-46	42

Toxic Effects from Aspirin

The full course of aspirin gave rise, as expected, to undesirable effects. These were of two kinds: firstly, serious but transient effects due to overdosage with

aspirin in the early days of treatment; and, secondly less serious but nevertheless annoying symptoms of tinnitus and deafness. The transient but serious symptoms of anorexia and nausea developed in seven patients and went on to vomiting in one patient. These symptoms were controlled by reducing aspirin dosage and lowering serum salicylate level. The "special salicylate syndrome" of mental confusion, dehydration, and hyperventilation associated with a respiratory alkalosis (Reid, Watson, and Sproull, 1950) was encountered in mild form in one patient. This syndrome is associated with intensive metabolic stimulation from overdosage with salicylate, and all its signs and symptoms disappear when salicylate has been discontinued.

During salicylate therapy 12 of the 14 patients noticed varying degrees of impaired hearing, which reverted to normal after the drug was discontinued. Seven patients developed tinnitus, which, however, tended to disappear spontaneously as time went on.

These toxic effects from aspirin, particularly the early transient symptoms due to overdosage with the drug, present a real problem, and they will have to be avoided if aspirin is to find a place in treatment of diabetes. Control of therapy by dosage alone without reference to the serum level of the drug is not, in our view, feasible, because of the wide individual difference in dosage required to produce the same blood level (Table III). It is therefore necessary in the early stages to control therapy by serum salicylate estimations. After the dose has been found for each patient, which gives the desired serum level of the drug for effective control of diabetes, the estimations may be discontinued.

Discussion

Aspirin in full therapeutic doses is not so effective as insulin. The greatest amount of I.Z.S. which could be replaced by aspirin was more than 72 units a day, and this in the patient with the greatest insulin requirement. The maximum requirement which could be completely replaced by aspirin was 48 units a day, but responses like these were obtained only in patients who were well controlled with I.Z.S. alone. Patients who were difficult to control with I.Z.S. were equally difficult to control with aspirin. Another point worth mentioning is that the increasing response to aspirin as insulin requirement becomes greater suggests that the frequency of hypoglycaemic attacks in patients requiring large daily quantities of insulin may be reduced by combined aspirin-insulin therapy, and the fact that hypoglycaemia is not a feature of aspirin therapy may have a bearing on this.

These results place salicylate in the class of promising compounds for oral treatment of diabetes and justify carrying on investigations, firstly, to try to overcome the disadvantages of salicylate therapy already referred to; and, secondly, to find out how it acts. We are investigating the possibility of freeing salicylate from its undesirable side-effects, and Manchester, Randle, and Smith (1958) have observed that salicylate, like insulin, increases glucose uptake by isolated rat diaphragm. Unlike insulin, however, salicylate increases the potassium loss and diminishes the amino-acid incorporation in protein, and it is not without interest that these biochemical observations on isolated muscle agree in general with the changes from salicylate we have observed in rheumatic patients (Reid *et al.*, 1950).

Summary

The insulin equivalence of aspirin has been determined in 14 diabetics with insulin requirements of 12 to 112 units of insulin zinc suspension daily.

Nine patients, who were well controlled with insulin, also had good responses to aspirin. The largest quantity of I.Z.S. replaced completely with aspirin was 48 units; the largest reduction in insulin requirement was 72 units in the patient receiving 112 units daily.

Five patients who were poorly controlled with insulin were not materially improved by aspirin therapy. It was concluded that aspirin was most effective in patients who responded well to insulin, and vice versa. The findings in patients well stabilized with insulin also suggested that the higher the insulin requirement the greater was the amount of hormone that may be replaced by aspirin.

These results place salicylate in the class of promising oral antidiabetic substances, and should stimulate investigations to remove its undesirable effects and to find out how it acts.

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RESPIRATORY VIRUS INFECTIONS IN THE GLASGOW AREA

BY

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This paper summarizes further investigations of acute respiratory illnesses during two years after the period dealt with in a previous report (Grist *et al.*, 1957). In addition to observations during the epidemic of Asian influenza, further evidence was found of infections with adenoviruses and with agents related to the Sendai virus (Kuroya *et al.*, 1953).

Materials and Methods

Over 1,000 cases were investigated during the period July, 1956, to April, 1958. Most of these were patients admitted to adult and baby pneumonia wards; over 200 were adult cases seen in general practice (Blair *et al.*, 1959). Serological tests of paired sera were made in most cases, but virus isolation was attempted with necropsy material from 32 cases and with throat swabs, garglings, or stools from a number of other cases in hospital, general practice, or seen by public health officers.

Technical methods have been described previously (Grist *et al.*, 1957). So far as was possible, haemagglutination inhibition (H.I.) tests with Asian (A/Singapore/4/57), A-prime (A/Scotland/1/53), and A/PR8 influenza virus were performed in addition to routine complement-fixation (C.F.) tests on sera collected after February, 1957.

Adenovirus Investigations

Rising C.F. antibody titres were shown by 10 patients whose main features are summarized in Table I. Most of these patients had respiratory illnesses, but Case 2

TABLE I.—Cases With Evidence of Adenovirus Infection

No.	Age (Years)	Clinical Features	Adenovirus C.F. Titres	
			"Acute" Serum	"Convalescent" Serum
1	<1	Bronchitis ..	<2	8
2*	2	"Glandular fever" ..	<8	32
3*	3	Pneumonia ..	32	128
4	3	" ..	<4	8
5†	3	Tonsillitis ..	8	64
6	5	Bronchitis ..	<2	8
7	28	Rhinitis ..	<2	16
8	45	Pharyngitis ..	<2	16
9	54	"Influenza" ..	<2	16
10	61	Pharyngoconjunctivitis	8	32

* Monotypic type 2 neutralizing antibody response.

† Type 3 adenovirus isolated from stool.

presented gingivo-stomatitis with ulceration of tongue and exudative tonsillitis, enlarged tender cervical and axillary lymph nodes, and palpable spleen. The blood showed leucocytosis of 15,000 per c.mm., with 65% lymphocytes. The Paul-Bunnell test was negative on three occasions. The throat swab contained normal mixed bacterial flora. The illness did not respond to penicillin, but resolved slowly over a fortnight. Neutralization tests showed no antibodies to adenovirus types other than type 2, which gave titres of 8 and 16 in consecutive sera. A monotypic type 2 adenovirus response was also given by Case 3 (N.T. titres <8 and 32). Neutralizing antibodies to several adenovirus types were developed by three adults tested, the major responses being to type 7 (Case 7), type 2 (Case 9), types 2 and 3 (Case 10). Type 3 adenovirus was isolated from Case 3.

Sendai Virus Investigations

Serological tests showed rising C.F. titres in 10 cases whose main features are summarized in Table II. In view of the reported antigenic overlap between Sendai and mumps viruses, sera from these cases were also tested with mumps antigens where possible. The results, summarized in Table III, show various combinations of reactions. Two Cases (Nos. 12 and 19) showed increasing titres of mumps antibody, which in Case 19 were confined to the "V" antigen.

TABLE II.—Cases With Serological Response to Sendai Virus

No.	Age (Years)	Clinical Features	Sendai C.F. Titres		
			"Acute" Serum	Second Serum	Third† Serum
11	1	Bronchitis ..	<2	16	16
12*	2	Pneumonia ..	<4	8	16
13	4	" ..	<8	32	—
14	7	" ..	<4	8	—
15	20+	"Influenza" ..	<8	16	—
16*	20+	Febrile catarrh ..	16	64	—
17	31	Pneumonia ..	<8	16	8
18	49	" ..	<4	16	8
19*	55	" ..	4	64	—
20*	78	" ..	<8	64	—

* Also tested for mumps (Table III).

† Taken in 5th week after onset of illness.