The significance of these findings is discussed, and it is suggested that in this disease the rate of glucose storage is excessive following the ingestion of large amounts of carbohydrate.

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MODIFICATION OF HYPOGLYCAEMIA WITH HEXAMETHONIUM BROMIDE*

BY

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It has been shown by Schachter (1951) that the combination of hexamethonium with insulin results in an augmented hypoglycaemic response, this being attributed to the drug's blocking effect preventing compensatory sympathetic activity in response to the fall of the blood-sugar level. Laurence and Stacey (1951) also observed that the degree of hypoglycaemia produced by a given dose of insulin was greater in the presence of hexamethonium, but that, paradoxically, the ensuing hypoglycaemic symptoms were either reduced or abolished.

In this investigation the effect of the administration of hexamethonium bromide on the response to both large and small doses of insulin is reconsidered, but with particular emphasis as to how far the findings are influenced by alterations in posture.

The reaction to small doses of insulin was assessed by insulin-tolerance tests. Blood-sugar levels were also estimated after injections of large doses of the hormone, but as their values bear no precise relation to the clinical levels of hypoglycaemia (Himwich, 1951a) the response to large doses was therefore determined by attempting to overwhelm the extreme insulin resistance occurring in some schizophrenics during insulin therapy.

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Methods

The insulin-tolerance tests were performed in the manner advocated by Fraser *et al.* (1941), and as the previous diet influences the response to the hormone (Himsworth, 1935) the patients were given at least 300 g. of carbohydrate daily for three days before each of the tests. The blood sugar was estimated by the method of Herbert and Bourne (1930). The reaction of the blood sugar in these tests can be differentiated into two phases: first, the initial decrease of the blood sugar, then the secondary rise which is indicative of the responsiveness to hypoglycaemia. The difference between the fasting and the 30-minute blood-sugar value was adopted as an index of the first function, the mean value of these being determined for the group. As suggested by Fraser and Smith (1941), a measure of the hypoglycaemia responsiveness was obtained from the product of the percentage blood-sugar values at 45, 60, 90, and 120 minutes after the beginning of the test and the time interval of each of these from the previous sample, a quarter of an hour being taken as unity. These products were added together and termed the "hypoglycaemia responsive index" (H.R.I.), the mean value for the H.R.I. being determined for the group.

Patients were therefore subjected first to conventional insulin-tolerance tests; then after the lapse of at least a week they were retested, but in this instance the dose of insulin was supplemented by an intramuscular injection of hexamethonium bromide (25–50 mg.). A variation of this modification was to stand the patient erect after the concomitant injection of insulin and hexamethonium until a vasovagal response with syncope occurred. However, as insulin-tolerance tests were being performed on patients standing erect for approximately 15 minutes after the injection of hexamethonium, it was essential to perform control tests on the same patients who stood erect for a similar period. It is known that the injection of hexamethonium by itself has no significant consistent effect on the fasting blood sugar (Schachter, 1951).

The patients comprising this series were all male schizophrenics, but Hemphill and Reiss (1948) have pointed out that if biochemical investigations are repeated frequently on such patients much day-to-day variation in findings becomes evident. Therefore, as it was intended to compare the results of insulin-tolerance tests repeated at short intervals, it was essential to ensure that sequential tests under standard conditions showed no significant statistical dissimilarity. This was done, and it was seen that although the results of such tests repeated at short intervals on schizophrenics revealed considerable variability, if the mean values of these were assessed for the group the results showed no significant statistical disparity (Marley, 1953a).

No patient was accepted for testing if he was much underweight, if he had been treated within the preceding two months with either electroplexy or deep or modified insulin therapy, or if he had been receiving other drugs regularly within the previous two weeks, as it is known that in such circumstances there are alterations in the fasting blood-sugar levels, in the response to small doses of insulin, or in resting eosinophil counts (Tod, 1937; Gellhorn and Safford, 1948; Henneman *et al.*, 1951; Hunter and Merivale, 1954; Marley, 1955).

A total of 24 patients were given both standard and modified insulin-tolerance tests, each patient serving as his own control for the comparison of sequential tests.

The final part of the investigation comprised the attempted modification of extreme insulin resistance in six male schizophrenics. In three of these cases the patient remained recumbent after the injection of insulin and hexamethonium, whereas the other three patients were stood erect until syncope occurred after the administration of the two substances. In all instances the modified hypoglycaemias were preceded by and separated from the control reaction by a period of at least three rest days. In order that the transitions from one hypoglycaemic level to another could be formulated with precision, a slightly modified form of the classification of

hypoglycaemia proposed by Frostig (1940) was adopted. This includes five phases, the most important being stage 3 hypoglycaemia presenting with loss of consciousness, motor restlessness, clonic twitchings, and torsion spasms; and stage 5 hypoglycaemia, which corresponds to deep coma and is associated with much-reduced or absent corneal reflexes and pin-point pupils without a light reaction. The definition of insulin resistance was arbitrary, and was presumed to be present when no advance beyond a stage 3 hypoglycaemia ensued after the injection of approximately 500 units of insulin.

Eosinophil counts were performed both immediately before the insulin-tolerance tests and during the deep insulin treatments. The initial counts were made at 9 a.m., as the eosinophils tend to become stabilized about this time following the eosinopenia during the early hours of the morning (Rud, 1947). The eosinophils were also counted at 1 p.m., as hypoglycaemia is accompanied by an eosinopenia, which is most marked four hours after stress (Perlmutter and Mufson, 1951). The differences between the 9 a.m. and 1 p.m. counts were calculated, and were termed the mean eosinopenia. Capillary blood was used in eosinophil counting, and both the technique and the phloxine-urea diluent proposed by Manners (1951) were employed, the results being determined from the mean of two pipette counts.

In the attempt to produce syncope the patient would be stood erect immediately after the injection of the insulin and the hexamethonium, and would be supported by two attendants. It was usual for the patient to collapse within 15 minutes, and, following this, frequent estimations of the blood pressure and the pulse rate would be made. In order to record the cardiovascular changes accurately, Grant and Reeve's (1951) classification of circulatory patterns associated with injury was employed. The only patterns seen in the present investigation were the vasovagal and, in one instance, that of warm hypotension. Methylamphetamine hydrochloride was always immediately available for injection as it accelerates recovery after vasovagal collapse (McMichael, 1945).

Modification of Response to Small Doses of Insulin

The mean percentage blood-sugar values for the results of the standard insulin-tolerance tests and those modified with hexamethonium bromide in recumbent patients are depicted in Fig. 1, the other related findings being included in Table I, A and B. It can be seen from these that the combination of small doses of insulin with hexamethonium results in an augmented hypoglycaemic effect but a diminished response to hypoglycaemia with a decline in the mean eosinopenia. On further analysis of these figures it becomes clear that the increased fall in blood sugar after insulin and hexamethonium is statistically significant ($t=5.06$; $P<0.05$), as is the decrease in the mean H.R.I. ($t=3.22$; $P<0.05$) but not the decrease in the mean eosinopenia ($t=1.25$; $P>0.05$).

The results of the comparison of insulin-tolerance tests with those modified by the induction of syncope are considered next, the relevant data being presented in Fig. 2 and Table I, C, and D. It is apparent from these that the induction of syncope with hexamethonium leads to a significantly diminished fall of blood sugar ($t=3.85$; $P<0.05$), a significant increase of the mean H.R.I. ($t=2.28$; $P<0.05$), but an insignificant decrease of the mean eosinopenia ($t=1.17$; $P>0.05$). The assumption of the erect posture in the absence of syncope seems also to modify the test results, insomuch that the standard deviations were consistently lower in this series (Table I, C) than those obtaining in the other tests.

Marked dilatation of the pupils occurred in the tests modified with hexamethonium, and was presumably due to the effect of the drug rather than to hypoglycaemia. Perspiration also seemed to be reduced by hexamethonium. All patients received their normal breakfasts after the completion of

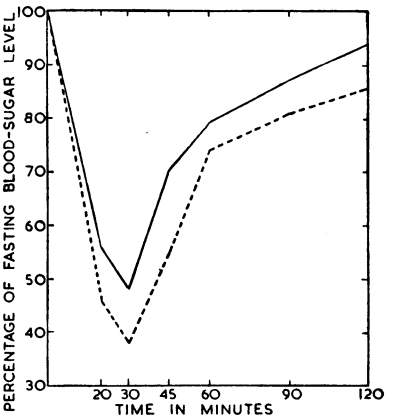

FIG. 1.—Mean percentage blood-sugar levels for standard and modified insulin-tolerance tests in recumbent patients. Continuous line = standard insulin-tolerance tests (12 patients). Interrupted line = Insulin-tolerance tests modified with hexamethonium bromide (12 patients).

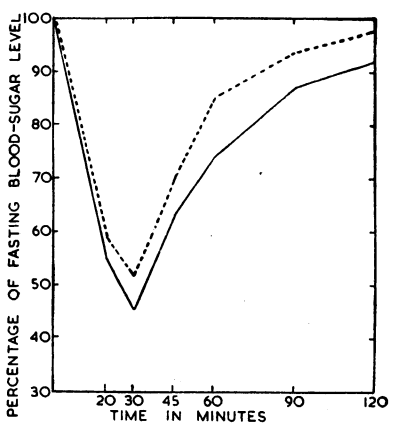

FIG 2.—Mean percentage blood-sugar levels for standard and modified insulin-tolerance tests in patients temporarily erect. Continuous line = Standard insulin-tolerance tests (12 patients). Interrupted line = Insulin-tolerance tests modified with hexamethonium bromide (12 patients).

TABLE I

	Blood-sugars (percentages of fasting level)							Hypoglycaemic Effect (%)	H.R.I. (Units)	Eosinopenia (%)
	Fasting	20 min.	30 min.	45 min.	60 min.	90 min.	120 min.			
A. Results of Insulin-tolerance Tests on 12 Recumbent Patients										
Mean	100	56·1	47·7	69·9	79·4	87·3	93·9	52·3	511·8	79·8
Range	—	40–65	36–59	49–98	62–104	67–116	74–121	41–64	410–674	49–98
Standard deviation	—	4·53	7·66	13·53	14·25	15·36	10·69	7·62	72·82	15·27
B. Results of Insulin-tolerance Tests Modified with Hexamethonium (12 Recumbent Patients)										
Mean	100	46·1	38·1	54·9	74·2	80·9	85·6	61·9	461·9	68·2
Range	—	38–55	25–54	41–78	56–104	59–99	67–103	46–75	358–569	35–98
Standard deviation	—	5·47	8·97	10·70	12·34	12·62	11·39	9·15	64·23	20·75
C. Results of Insulin-tolerance Tests on 12 Patients Stood Temporarily Erect										
Mean	100	55·2	45·7	62·7	74·2	86·5	92·1	54·3	494·3	83·2
Range	—	46–74	36–55	51–76	58–95	77–97	80–108	45–64	460–546	65–95
Standard deviation	—	6·70	4·69	8·20	9·00	8·06	7·44	4·57	30·81	7·81
D. Results of Insulin-tolerance Tests Modified with Syncope (12 Patients)										
Mean	100	58·6	51·4	70·4	84·8	94·0	98·3	48·6	539·9	79·8
Range	—	35–80	40–64	49–100	63–112	67–115	79–110	36–60	417–632	48–97
Standard deviation	—	11·10	6·54	14·08	13·75	13·60	11·51	6·52	69·77	15·07

the tests, and even in the case of those who had received hexamethonium with insulin there was no instance of later hypoglycaemic or hypotensive episodes.

Modification of the Response to Large Doses of Insulin

Only a précis of the findings will be presented, as the clinical results of the modification of the reaction to large doses of insulin are presented elsewhere (Marley, 1956).

The administration of hexamethonium bromide to recumbent insulin-resistant schizophrenics receiving deep insulin therapy led to more profound levels of hypoglycaemia than obtained with insulin alone. Thus in three patients doses of respectively 480, 480, and 560 units of insulin given intramuscularly led barely after 210 minutes to the appearance of a stage 3 hypoglycaemia. When the identical doses of insulin were combined in the same patients with 100 mg. of hexamethonium, injected subcutaneously or intramuscularly, a stage 5 hypoglycaemia developed within the same period.

The technique of inducing syncope with hexamethonium early in hypoglycaemia was more successful still. For instance, in another three patients doses of 520, 560, and 640 units of insulin injected intramuscularly failed after 210 minutes to produce even a stage 3 hypoglycaemia, whereas doses of 480, 480, and 520 units in the same patients, but combined with 100–150 mg. of hexamethonium and a syncope induced early in hypoglycaemia, resulted within 150–180 minutes in the emergence of a stage 5 hypoglycaemia.

In both types of modification with hexamethonium the hypoglycaemias differed from the conventional response to insulin in that the customary profuse salivation and perspiration were much reduced and even completely abolished in one patient. Comas tended to develop much more rapidly, and it was noted that the deepest level of hypoglycaemia was accompanied by widely dilated pupils in place of the pinpoint pupils that are normally to be anticipated. It was found imperative to terminate the modified hypoglycaemias by the intravenous route, as the stomach appeared not to absorb substances following the combination of insulin with hexamethonium, and even after intravenous interruption the period for complete recovery was longer than that after insulin alone. It was also necessary to keep the patient in bed until the effect of the hexamethonium had worn off, for there was a marked susceptibility to further hypoglycaemic reactions, apparently determined by the assumption of the erect posture.

The blood-sugar levels for both the conventional and the modified hypoglycaemias are shown in Table II, and, although both pursue a very similar pattern, there is a tendency for the blood sugar to fall to lower levels at an earlier stage with the modified than with the orthodox insulin techniques.

In addition, the eosinopenias associated with both types of hypoglycaemia are included in Table III. It can be seen that the decline of the eosinophils in the modified techniques was sometimes greater and sometimes less than in the eosinopenias accompanying the control reactions.

TABLE III.—*Reaction to Large Doses of Insulin: Eosinopenias Accompanying Conventional and Modified Insulin Techniques*

Case No.	Conventional Insulin Techniques			Modified Insulin Techniques		
	Eosinophils per c.mm.		Eosinopenia %	Eosinophils per c.mm.		Eosinopenia %
	9 a.m.	1 p.m.		9 a.m.	1 p.m.	
1	—	—	—	—	—	—
2	137	17	87	136	6	95
3	498	160	68	320	50	84
4	160	11	94	115	21	82
5	79	3	96	84	12	85
6	101	10	90	108	3	97

Cardiovascular Responses Following Combination of Insulin with Hexamethonium

In the erect subject the radial pulse would increase in rate and decrease in volume until syncope occurred. The latter was vasovagal in character and usually brief in duration. In two patients this vasovagal pattern—that is, a systolic blood pressure below 100 mm. Hg, a pulse rate of 70 or fewer beats a minute, cold extremities with pallor of the facies—persisted for longer than 15 minutes. In another instance the brief vasovagal pattern was succeeded by that of warm hypotension, which by definition includes a systolic blood pressure below 100 mm. Hg, a pulse of 90 or more beats a minute, warm extremities, and a face that might be flushed or pale. No irregularity of the pulse was noted after syncope, and the peripheral circulation invariably improved without recourse to methylamphetamine hydrochloride.

Discussion

The finding of an increased hypoglycaemic effect of small doses of insulin following the administration of hexamethonium confirms, but is still merely a restatement of, the conclusions of Laurence and Stacey (1951) and Schachter (1951), although these authors make no mention of the subsequent delayed and reduced recovery from hypoglycaemia as was observed in the tests on recumbent patients. The increased resistance to the hypoglycaemic effect of small doses of insulin following syncope has, so far as is known, not been recorded, and seems reminiscent of the work of Selye and Dosne (1939), who demonstrated that insulin hypoglycaemia may be reduced although not completely abolished by the simultaneous administration of cortin. A similar diminished response to insulin has been recorded after the injection of toxin (Lawrence and Buckley, 1927), during artificial pyrexia (Ohtake, 1939), after short periods of anoxia (Gellhorn and Packer, 1939), and in association with electric-shock (Delay and Soulairac, 1944).

It was Engel (1949) who suggested that an increased need for carbohydrate was the first effect of stress, and it is therefore topical that the induction of syncope with hexamethonium results in a significant hyperglycaemia and eosinopenia (Marley, 1953b). Previously, Engel (1945) had stated that the initial rise of blood sugar after stress was due to the hepatic glycogenolysis by adrenaline, and that it was only later that endogenous adrenal cortical hormone secretion

TABLE II.—*Reaction to Large Doses of Insulin: Blood-sugar Values (mg. per 100 ml.) for Conventional and Modified Insulin Techniques*

Case No.	Conventional Insulin Techniques						Modified Insulin Techniques					
	1	2	3	4	5	6	1	2	3	4	5	6
Insulin (units)	480	480	560	520	560	640	480	480	560	480	480	520
Hexamethonium (mg.)	—	—	—	—	—	—	100	100	100	150	100	100
Posture	R	R	R	R	R	R	R	R	R	S	S	S
Blood sugar:												
7.30 a.m.	75	79	104	75	91	86	71	88	97	79	79	91
8.00 ,,	67	68	43	57	34	61	56	67	73	45	33	58
8.30 ,,	58	56	30	31	29	32	43	65	53	27	24	30
9.15 ,,	52	43	33	25	20	25	27	49	33	22	19	21
10.00 ,,	47	27	25	23	25	24	16	35	28	21	18	19
10.45 ,,	42	29	30	17	24	23	25	21	24	18	15	18
Stage of hypoglycaemia	1	2	1	3	2	3	5	5	5	5	5	5

R=Recumbent. S=Syncope induced.

reached levels sufficient to initiate the protein catabolic impulse. Presumably it is the initial and exaggerated adrenaline response that accounts for the diminished hypoglycaemic effect seen in the insulin-tolerance tests modified by syncope. That this is not so paradoxical as it might seem is confirmed by Paton (1954), who mentions that vigorous adrenal medullary discharge can take place in the presence of ganglion block by hexamethonium.

An apparently different result accrued from the combination of hexamethonium with massive doses of insulin, for not only was there an increased depth of clinical hypoglycaemia in recumbent insulin-resistant schizophrenics, but also the induction of syncope with hexamethonium early in hypoglycaemia proved even more effective in overwhelming insulin resistance. Himwich (1951b) described three mechanisms to prevent the complete cessation of brain metabolism during hypoglycaemia. The most valuable of these was the release of hepatic glucose to the blood stream, for it not only acted over a longer period than the other but was quantitatively the most important. It would seem that the induction of syncope with hexamethonium so expedites this second mechanism that even in association with an augmented protein catabolic impulse the stored reserve of carbohydrate is not later available for implementing cerebral metabolism.

Laurence and Stacey (1951) were also at pains to point out that one of the practical applications of their investigation was the recognition of the additional risk incurred by diabetics receiving both insulin and hexamethonium, for such patients were very liable to develop hypoglycaemia in the absence of the usual signs and even to lose consciousness without warning. From the above investigations, this would seem a negligible hazard if the dose of insulin is small; however, in view of the increased sensitivity to insulin following the combination of large doses of the latter with hexamethonium, it is obvious that if large doses of the hormone are required for the satisfactory control of the diabetes, and particularly if the patient has also the tendency to develop hypotensive attacks after the injection of the ganglion-blocking drug, then the risk of hypoglycaemia is considerably augmented. In such an instance, great emphasis should be placed upon restricting the dose of either insulin or hexamethonium and insisting that these patients should remain recumbent until the likelihood of postural hypotension has worn off.

It would be no exaggeration to comment that the assumption of the erect posture in such patients is tantamount to a vastly increased liability to hypoglycaemic episodes further complicated by the fact that they are atypical in presentation. Moreover, while the oral administration of glucose is satisfactory for aborting early and minimal hypoglycaemic symptoms in a patient receiving both hexamethonium and small doses of insulin, once deeper hypoglycaemic levels have appeared, particularly coma, then the administration of sugared water either orally or by stomach tube is both valueless and dangerous. Interruption in this case must be by the intravenous route, a stricture endorsed by the work of Kay and Smith (1950) and Douthwaite and Thorne (1951), who reported that hexamethonium interferes with the motility and secretion of the stomach.

The fall of eosinophils was thought originally to be a specific if indirect index of adrenocortical activation, but this view has now been discarded, as in certain circumstances it proved to be misleading (Bayliss, 1955). Consequently it would be presumptuous to offer any categorical interpretation of the alterations in the values for the eosinophil counts. Speirs and Meyer (1949) had demonstrated that by increasing the amount of stress a greater fall of eosinophils ensued, but the eosinopenia following syncope and insulin was sometimes in excess and sometimes less than that recorded with conventional insulin techniques. The same was found for the combination of small doses of insulin and hexamethonium, although in the latter if the eosinopenia was determined for the group it was found to be diminished in comparison with the eosinopenia associated with standard insulin-tolerance tests. It is therefore interesting that Gaarenstroom *et al.* (1953) noted that hexamethonium delayed the eosinopenia normally occurring in rats following blood sampling.

The decrease in salivation after hexamethonium is in accord with the experimental findings for animals, as Paton (1951) reported that the parasympathetic ganglion to the salivary glands was the most sensitive of all ganglia to the action of the drug. He also commented on the decrease of perspiration with hexamethonium.

Finally, it is worth alluding to the large values of the standard deviations for the test results, as they are a constant feature of investigations performed on schizophrenics (Hoskins, 1946) and not entirely attributable to the small size of the samples here under scrutiny.

Summary

The combination of small doses of insulin and hexamethonium in recumbent patients results in an augmented hypoglycaemic effect but a decreased response to hypoglycaemia with a decline in the eosinopenia.

The combination of large doses of insulin with hexamethonium in recumbent patients leads to more profound depths of clinical hypoglycaemia.

The combination of small doses of insulin with syncope induced by hexamethonium leads to the appearance of relative insulin resistance associated with an augmented hypoglycaemic response.

In contradistinction, the combination of large doses of insulin with hexamethonium and the induction of syncope early in hypoglycaemia is capable of significantly diminishing resistance to massive doses of this hormone.

The risks incurred by diabetics receiving both insulin and hexamethonium are re-emphasized.

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