Animal Experiments

Sir Victor was much interested in comparative anatomy and would go to any lengths in order to obtain the brain of some unusual animal. When a walrus died at the Zoological Gardens, the first time in years, he gave up all his consultations that morning in order to take out the brain. When I remarked about this, he said: "If people want me to learn they must be willing to wait." Whenever any of his former students went to the Tropics or Far East he urged them to send him brains of wild animals. One day while I was with him a huge barrel arrived from India. In it, packed in salt, was an elephant's head. One of his former assistants had taken with him on an elephant hunt formaldehyde and injection bottles to inject the carotids after decapitating the animal. The specimen was accompanied by a letter and photographs showing the natives standing around gaping while this performance was going on. Sir Victor got a great thrill from these pictures and immediately took out the brain. In this way he collected a large amount of material and had innumerable photographs of various brains. These he photographed himself in his laboratory in his home in Cavendish Square, but, so far as I have heard, none of this material has ever been worked up or published.

Sir Victor was one of the most prominent vivisectionists at that period; consequently when Parliament was reviewing the laws about vivisection he was one of the important witnesses. A disgruntled former laboratory boy testified before the commission that he had seen Sir Victor pull the heads off living cats. The next day, when Sir Victor appeared in the laboratory, he told the laboratory assistant to bring up a cat, killed it with chloroform, and then told the boy and me to pull at one end of the cat while he pulled at the other. Of course we all knew nothing would happen, but Sir Victor

had to have positive proof before he would testify before the commission. The episode illustrates one of his fundamental characteristics—every statement he made had to be backed up by incontrovertible evidence.

Wide Interests

In the autumn he always rented a place for the shooting rights and went at the shooting as strenuously and enthusiastically as he did everything else. But the first thing he did when he rented a new place was to familiarize himself with the surrounding country. By the time I went down for my Christmas holiday he took me around in his high-powered Daimler, which he loved to drive, and showed me an interesting church in one place, a beautiful rose window in another, and a Roman ruin in another place. His interest in art he came by quite naturally, for his father had been a Royal Academician and his uncle was the famous etcher Sir Francis Seymour Haden.

Of Sir Victor's many admirable qualities, not the least was his generosity towards his younger colleagues. Of this I had striking proof. When I had completed the research I had been carrying on in his laboratory, I presented him with the manuscript and, naturally, had put his name and mine on the title-page. He crossed out his name, with the remark: "As long as it is customary, when two men publish a paper, to give credit to the one who is better known, I shall not allow my name to appear." No amount of persuasion could make him change this decision.

As I look back upon the years I spent with Victor Horsley, I feel he gave me the best possible insight into the life of a broadminded, generous scientist of his generation.

He will always be remembered as one of the great figures in medicine.

GLUCOSE TOLERANCE IN PERIODIC PARALYSIS

BY

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Hypokalaemia and muscular paralysis were first associated clinically in patients with familial periodic paralysis (Biernacki and Daniels, 1934; Aitken *et al.*, 1937). Although the association has since been observed in several other conditions (Jackson and Oakley, 1955), the identity of the original disease remains distinct. Clinically it is characterized by a familial incidence in at least 80% of cases, by a tendency for the paralytic attacks to begin during sleep, and by the fact that the individuals affected are otherwise healthy (Talbot, 1941). Biochemically it is unique because the hypokalaemia is intermittent and evidence of potassium depletion is lacking (Gass *et al.*, 1948). The pattern of the disease is definite enough for "sporadic" cases without family history to be recognized, and exceptional cases without hypokalaemia are also described (Watson, 1946; Tyler *et al.*, 1951; Ecker, 1953).

The metabolic defect in this disease is not understood, but the response to stimuli which lower the plasma potassium level tends to be exaggerated (Aitken *et al.*, 1937). After the administration of glucose or insulin, for instance, hypokalaemia is often excessive, and paralytic attacks may sometimes be induced in this way to confirm the diagnosis. No undue external loss accompanies the fall in level of the plasma potassium, which is accounted for quantitatively by a transfer of extracellular potassium into the intracellular phase (Danowski *et al.*, 1948). In other words, hypokalaemia is

excessive either because too much potassium leaves the extracellular fluid or because too little returns to it. Which mechanism is operative and why it should occur is uncertain, but fortunately oral potassium controls the symptoms.

A sporadic case of periodic paralysis in which glucose tolerance appeared to be abnormal is described.

Case Report

A 33-year-old engineer complained of attacks of paralysis for 13 years. In the intervals between attacks his health was excellent and he often took part in weight-lifting contests. None of his relatives was similarly affected, nor was there a family history of migraine. The paralysis first occurred in 1943, when he was serving in the Royal Marines. At the end of an evening film show he was unable to rise from his seat because both arms and both legs were weak. All subsequent attacks began between 3 and 7 a.m. In a moderate attack he awoke unable to turn over in bed because his arms were weak and his legs were paralysed. In more severe attacks all four limbs were paralysed but he was able to move his head. Coughing and swallowing became difficult only in the most severe attacks, and speech, breathing, and eye movements were never affected. Micturition was impossible early in an attack, and he was constipated afterwards. Sensation was not disturbed, but his muscles were often painfully stiff next day. Consciousness was never impaired, although he became irritable and apprehensive when paralysed. Nothing was known to precipitate the attacks, but they were sometimes predictable from "a feeling

of stiffness" a few hours beforehand. They could not be "worked off," rarely followed undue exertion, and were unaffected by cold weather or a hot bath.

Most of the attacks were of mild-to-moderate severity, and the patient gradually recovered from them in from four to ten hours. With assistance he was able to eat meals and smoke a cigarette while paralysed, and after a few hours he was able to sit propped up in a chair even though his legs were useless. At first he suffered only three or four attacks a year, but their frequency increased, and in 1955 he had more than a dozen. Shortly before admission he gave up drinking beer (which contains potassium) and instead often ate sweets in the evenings. Attacks then occurred two to three times a week. He had no other complaints apart from infrequent unilateral headaches.

A provisional diagnosis of familial periodic paralysis was made when he was in the Services, but the only treatment he received was psychotherapy. In 1953 his complaint was again thought to be hysterical after brief investigation in hospital. He was later advised to take "Kruschen salts" (potassium 0.12 g. per drachm, or 3%) by a local chemist, but derived no benefit from this.

On examination after admission on March 5, 1956, the patient looked well, his physique was excellent, and no abnormal physical signs were found. The blood pressure was 120/80 mm. Hg, there was no proteinuria or glycosuria, and the specific gravity of the urine was 1016.

Investigations.—Haemoglobin, 15.7 g. per 100 ml.; blood urea, 24 mg. per 100 ml.; blood cholesterol, 200 mg. per 100 ml.; plasma bilirubin, 0.6 mg. per 100 ml.; alkaline phosphatase, 9 units; thymol turbidity, 6 units; zinc sulphate, 1 unit. Plasma electrolytes: potassium, 4.5 mEq/l.; sodium, 146 mEq/l.; bicarbonate, 29.7 mEq/l.; chloride, 90 mEq/l. Urinary steroids: 17-ketosteroids, 19 mg./24 hours; 17-ketogenic steroids, 20 mg./24 hours; aldosterone: normal by chromatographic technique (Dr. Ivor Mills). Radioiodine excretion test: normal thyroid function. X-ray examination of chest and pituitary fossa: normal. Electrocardiogram: sinus rhythm, normal complexes. Urinary potassium: on a daily intake of 100 mEq of potassium, the urinary excretion was 47 mEq and 53 mEq/24 hours, with a normal diurnal variation. During the first induction of paralysis the excretion fell to 19 mEq/24 hours.

Description of Attacks

1. When first seen as an out-patient on February 23, 1956, eight hours after the onset of a moderate attack, the patient said that his arms and legs were paralysed. Muscle tone, however, appeared normal, all tendon reflexes were obtained, and with persuasion slight movement of the shoulders occurred. When asked to sit up the patient was unable to do so, although his abdominal muscles were seen to contract and his face flushed with the effort. These findings and the patient's indifference to them suggested a diagnosis of hysteria. This false impression was quickly corrected when the plasma potassium was found to be 2.1 mEq/l., and the E.C.G. showed absent T waves and slight depression of the ST segments.

2. On being told that a balance diet was to start next day, he ate a quantity of fruit and sweets on his second evening in hospital. He awoke next morning (March 7) in a minor attack, during which he was unable to stand up straight or climb stairs. Proximal weakness of all four limbs, most obvious in the hip extensors, was found, although all tendon reflexes were present. The weakness lasted five hours, and three hours after its onset the plasma potassium was 3.7 mEq/l., and the E.C.G. showed slightly decreased amplitude of the T waves.

3. On March 13 the first attempt to induce an attack was made. After a 12-hour fast the patient was given 150 g. of glucose orally at 9 a.m. No weakness developed and he was given 150 g. of lactose with lunch three hours later. At 3.10 p.m. he "felt weak," but the only evidence of this was inability to adduct the extended fingers of the right hand. The plasma potassium fell to 2.9 mEq/l. (see Chart, A), and

the T waves of the E.C.G. became progressively flatter. Weakness of both arms persisted for eight hours, but the tendon reflexes remained brisk.

4. An attack was induced more successfully on March 14. The patient was given 250 g. of lactose with supper at 7.15 p.m. Before going to sleep three hours later he noticed weakness of his left hand and shoulder. At 1.30 a.m. on the 15th he awoke with a partial quadriplegia, affecting his arms more than his legs. Slight movement of his right shoulder was possible and he was still able to move both feet. He

Blood-sugar and plasma potassium levels during three induced attacks of paralysis. — blood sugar; - - - plasma potassium.

was unable to sit up but could move his head and face normally. His limbs were flail-like and only the ankle-jerks were obtained, although the muscles appeared to retain their tone. The plantar responses were flexor, but the abdominal reflex was present only in the right upper quadrant. The blood pressure was 135/90 mm. Hg. Half an hour later his condition was unchanged and he was given 1 g. of ammonium chloride orally. This was given as a control for his later treatment, because its taste resembles that of potassium chloride. Within the next hour the paralysis of his limbs became complete and the ankle and abdominal reflexes were no longer obtainable. He was therefore given, at 3 a.m., 5 g. of potassium chloride orally. His condition was unaltered 20 minutes later, but after 30 minutes his knee and triceps jerks returned. At 3.35 a.m. he was suddenly able to raise his right elbow from the bed, at 3.50 a.m. he could lift his left leg, at 4.20 a.m. he could move his right foot, and at 4.30 a.m. his left arm suddenly became responsive and stronger than the right one. Although hip extension was weak, he was able to stand unsupported at 5.30 a.m., and two hours later recovery was complete. In this attack the plasma potassium fell to 2.7 mEq/l., and it rapidly rose to normal after the potassium chloride was given (see Chart, B).

5. On March 22 an attempt was made to induce one further attack. The patient was given 300 g. of lactose with supper. On waking next morning his arms were weak and he was unable to move his hands, but his trunk and legs were unaffected. The weakness disappeared in two and a half hours and an E.C.G. showed T waves of normal amplitude. He was then given 150 g. of glucose with breakfast, and, because no weakness followed, a subcutaneous injection of 40 units of soluble insulin was given with lunch three hours later. Again no paralysis occurred, and two hours after the injection the plasma potassium was found to be 3.1 mEq/l. During the night, however, the patient noticed slight weakness of the shoulders and hips, and at 8.30 a.m. next day he was unable to extend the fingers of his right hand. There was demonstrable weakness of hip and elbow extension, but all tendon reflexes were present and the plasma potassium was 3.6 mEq/l. The patient was depressed and irritable and he was noticed to be sweating freely. He was given 5 g. of potassium chloride orally and 45 minutes later he was able

to extend all the fingers of his right hand except the third. His strength recovered fully and he was no longer moody half an hour later. The plasma potassium and blood-sugar changes during recovery are shown (Chart, C).

The Electrocardiogram

Serial E.C.G.s were obtained during the attacks, and the plasma potassium was estimated simultaneously with 22 of them. Flattening, and occasionally disappearance of the T waves with slight ST depression (best seen in Leads II and V5), always accompanied a decrease in the plasma potassium. Although in general the amplitude of the T waves followed the plasma potassium level, there was no exact correspondence between them. The reason for this was apparent in the serial records, which showed that the T-wave changes lagged behind alterations in the plasma potassium level. The time-lag was much shorter than that which often occurs in potassium-depleted subjects (Schwartz *et al.*, 1954), since it lasted only about an hour. A similar delay was observed in the recovery of muscular power after the plasma potassium was restored to normal.

There was no evidence that the E.C.G. was abnormally sensitive to changes in the plasma potassium, whether these were induced by carbohydrate, adrenaline, or insulin. An intravenous injection of 2 units of insulin, for example, produced the same degree of T-wave flattening and ST depression as it did in a control subject, and when the patient was fasting no alteration occurred.

Because hypokalaemia was recognizable from the E.C.G., a half-hourly record of Lead II was made throughout one night in order to discover whether the patient's plasma potassium level decreased significantly during sleep. No change in the T waves was observed, although the patient remained asleep for six hours.

Glucose Tolerance

Various tolerance tests were performed while the patient was on a diet containing 300 g. of carbohydrate, supplemented by the extra amounts used to induce paralysis. The true blood glucose was estimated by the method of King (1951), and the results are shown in the Table in the order in which they were obtained.

In the first test, a delayed rise from a low fasting blood sugar was observed after 150 g. of glucose was given orally. A week later 50 g. of glucose orally produced a "lag" curve; and when this amount was later given intravenously the response was normal. "Hypoglycaemia unresponsiveness" was revealed by a standard intravenous insulin-tolerance test; and when only 2 units of insulin was given intravenously the blood sugar again remained depressed longer than in a control subject. Since neither the intravenous glucose-tolerance test nor a 36-hour fast provoked hypoglycaemia, hyperinsulinism appeared to be excluded.

Two abnormalities are apparent in these results. There was initially a suggestion of increased glucose tolerance, and

there was also prolongation of the response to intravenous insulin. While the difficulty of interpreting tolerance tests is recognized, these findings are thought to be significant because they both independently imply that the storage of glucose was increased. The subsequent tests failed to show an increase in glucose tolerance, but the patient had by then received large amounts of extra carbohydrate and his attacks had become more difficult to induce. Few glucose-tolerance tests are reported in the published cases of periodic paralysis, and it is therefore particularly interesting that an apparent increase in glucose tolerance was also incidentally observed in cases described both by Aitken *et al.* (1937) and by Tyler *et al.* (1951). Their results are included in the Table for comparison. Painter (1955) reported a case with decreased tolerance, but as the patient required large amounts of potassium for several days to restore his plasma level we consider that he was suffering from potassium deficiency and not periodic paralysis. Decreased glucose tolerance is a feature of potassium depletion (Mahler and Stanbury, 1956) as shown by the example in the Table.

The plasma potassium levels observed during the carbohydrate tolerance tests are also shown in the Table. Acute fluctuations in level between estimations were excluded by serial E.C.G.s recorded throughout each test. The results show that in this patient the plasma potassium responded normally both to 50 g. and to 150 g. of glucose. Orally and intravenously, 50 g. failed to induce hypokalaemia, while the depression which followed 150 g. was not significantly greater than was found in the healthy control. It is of interest that the fall in plasma potassium after 150 g. of glucose was more profound in the case of potassium-losing nephritis than in either the patient or the control subject.

Progress

On discharge from hospital the patient was advised to restrict his carbohydrate intake and to take 1 g. of potassium chloride orally every night. Within a fortnight two attacks occurred, both of which were promptly relieved by 5 g. of potassium chloride. He has since remained free from attacks for three months on an unrestricted diet, while taking 2 g. of potassium chloride daily. If the potassium supplement is omitted for only one day attacks are apt to occur after sweets are eaten.

Discussion

The history and the biochemical findings in this case are typical of sporadic periodic paralysis. Hypokalaemic paralyses followed ingestion of carbohydrate, and the attacks were both relieved and prevented by small doses of potassium chloride. Muscle function, the E.C.G., and the plasma potassium were normal between attacks, and there was no evidence of hyperthyroidism, which occasionally precipitates the onset of the disease (Linder, 1955). During induction of an attack the excretion of potassium and creatinine in the urine decreased in the characteristic manner.

Results of Glucose- and Insulin-tolerance Tests

	Blood Sugar in mg. per 100 ml. at:												Comments	
	Fasting	20 mins.	Hours											
			$\frac{1}{2}$	1	1½	2	2½	3	3½	4	5	6		7
Case of Aitken <i>et al.</i> (1937) 50 g. glucose orally	66		50	84	101	80	73							Increased glucose tolerance
Case T. K. B., Tyler <i>et al.</i> (1951) 100 g. glucose orally	72 (4.7)		79	88 (3.6)	72	85 (3.7)		68	82 (4.0)					" "
Present case: 150 g. glucose orally	36 (4.0)		58	55	104 (3.4)	112	41 (3.1)							" "
10 units soluble insulin i.v. ..	90	37	50	48 (3.6)	56	65		148						" Hypoglycaemia unresponsiveness"
50 g. glucose orally	98		146	260 (4.0)	77	67 (4.3)	86	77 (4.2)						" Lag response "
50 " " i.v.	85 (4.1)		246			86		80		75	72	80	73 (3.7)	Normal
Control subject: 150 g. glucose orally	61 (4.3)		175	154	74	77	34 (3.6)							" "
Potassium-losing nephritis: 150 g. glucose orally	75 (4.7)		128	164	125	144	45 (3.0)	54 (3.7)						Decreased glucose tolerance

Figures in parentheses are plasma potassium in mEq/l.

Chronic potassium depletion was indirectly excluded by finding a normal plasma bicarbonate, no increase in urinary aldosterone, and a diurnal variation in the urinary excretion of potassium, which was itself within the normal range (Evans *et al.*, 1954). The depression of the plasma potassium by moderate doses of glucose was within normal limits, and it was less than that which occurred in a patient with potassium depletion. Large amounts of carbohydrate were required to induce paralysis, and with repeated attempts both the severity of the paralysis and the depression of the plasma potassium diminished. Talbott (1941) and Gass *et al.* (1948) also noted that attacks became more difficult to induce after repeated attempts.

The physical signs which appeared when the patient was paralysed were somewhat misleading. The paralysis was extremely variable in extent and severity, ranging from weakness of one finger to complete quadriplegia. The tendon reflexes were absent when paralysis was severe, but they returned during recovery before voluntary movement was possible. Furthermore, in slighter attacks the reflexes were retained despite widespread weakness. Sporadic periodic paralysis is often confused with hysteria, and in making the correct diagnosis the typical history is more helpful than the physical signs.

Gass *et al.* (1948) failed to establish an exact relationship between the severity of the paralysis and the plasma potassium level. Although the two severe attacks in our patient were associated with considerable hypokalaemia, in one of them the paralysis and the E.C.G. changes persisted for some time after the plasma potassium was restored to normal. Minor paralytic attacks occurred at low normal potassium levels, while levels lower than these were sometimes found when the patient was not paralysed. These findings make the occurrence of exceptional cases without hypokalaemia less remarkable, and, since the actual level of the plasma potassium is thus relatively unimportant, another factor must be responsible for the muscular dysfunction.

The abnormal mobility of potassium in this disease may be due to altered cellular permeability, to an unrecognized deficiency of tissue potassium, or to an increased demand for potassium in carbohydrate metabolism (Gass *et al.*, 1948). Of these alternatives the last-mentioned is perhaps the most likely, since paralysis follows carbohydrate ingestion, and potassium is known to participate in carbohydrate metabolism. Although carbohydrate metabolism is apparently qualitatively normal in this disorder, a quantitative disturbance may exist. The finding of increased glucose tolerance in our case and in those of Aitken *et al.* (1937) and Tyler *et al.* (1951) is thus relevant, since more potassium will be utilized if the normal process of glucose storage is exaggerated. The fact that a steadily falling blood-sugar level was twice found during attacks in our patient is in keeping with this suggestion, particularly since very low values were recorded on the second occasion.

Possibly, then, hypokalaemic paralysis follows ingestion of large quantities of carbohydrate simply because the mechanism for dealing with glucose is over-efficient, at the expense of the available potassium. When a small daily supplement is added to the pool of available potassium undue hypokalaemia is avoided and attacks no longer occur. Gass *et al.* (1948) thought that paralysis occurred because the contractile systems in muscle were deprived of adequate potassium, and this view is supported by the findings of Beccuau *et al.* (1955). These workers showed that attacks of periodic paralysis were relieved by adenosine triphosphate. This substance is the immediate source of energy in muscular contraction, and potassium is essential for its formation (Boyer *et al.*, 1943). The hypokalaemic paralysis may thus be analogous to that which is occasionally seen a few hours after glucose and insulin are given to patients with diabetic ketosis (Nabarro *et al.*, 1952). Admittedly the available potassium is already depleted in the diabetic cases before glucose storage is accelerated, but in attacks of periodic paralysis relative depletion may eventually develop. The fact

that hypokalaemia and paralysis become less easy to induce when large amounts of carbohydrate are repeatedly given suggests that the storage mechanism can become saturated. Conversely, patients are often more susceptible to attacks after exertion, when muscle glycogen is depleted.

Although the evidence on which it rests is scanty, several features of the disease support this theory. Periodic paralysis is relieved by limiting carbohydrate intake, and the potassium needed to prevent attacks is quantitatively related to the carbohydrate in the diet (Ziegler and McQuarrie, 1952). The condition is said to improve after middle age (Talbott, 1941), when a decrease in carbohydrate tolerance commonly occurs (Himsworth and Kerr, 1939). Attacks usually begin in the early morning, and since symptoms also tend to occur at this time in spontaneous hypoglycaemia it would appear that glucose storage is particularly active during the night. Irrespective of the time of day, the attacks are apt to start during sleep (Couston, 1955), when anabolism exceeds catabolism in the inactive muscles. Genetic disorders of carbohydrate metabolism are not unknown, and a similar familial incidence is found in idiopathic infantile hypoglycaemia (McQuarrie, 1954). Hypokalaemic paralyses have not been observed in this condition or in hyperinsulinism, but in the latter disorder (Conn, 1947) and in glycogen-storage disease (Creveld, 1939) muscular weakness occurs.

Zierler and Andres (1956) showed that there is a diurnal variation in potassium exchange between skeletal muscle and the extracellular fluid in normal subjects. Potassium tends to move into muscle during the night, and to leave muscle during the day. During the spontaneous development of a nocturnal attack of periodic paralysis, they observed a similar but much more extensive transfer of potassium into the forearm muscles. They therefore suggested that exaggeration of the normal diurnal variation in potassium exchange, due to unusual permeability of muscle membrane, is a fundamental defect in this disease. In the present case, however, there was no electrocardiographic evidence that hypokalaemia occurred spontaneously during the night, nor was the diurnal variation in urinary potassium excretion exaggerated. Hypokalaemic attacks were always related to carbohydrate ingestion, and only then was the excretion of potassium in the urine considerably reduced.

Since potassium normally moves into cells during glucose assimilation, the increased migration in periodic paralysis is again most simply explained by assuming that glucose assimilation is excessive. Zierler and Andres (1956) detected a disturbance of glucose metabolism in their cases, but no details of it were given in the brief report of their work. Grob *et al.* (1956) showed that after glucose administration the uptake of potassium by the muscles was greater than normal in periodic paralysis. They also found that in this condition insulin produced a migration of potassium into the muscles, which did not occur in normal subjects. In our patient insulin produced an abnormally prolonged depression of the blood sugar.

Many facts thus support the earlier suspicions of Allott and McArdle (1938) that "the activity of a normal mechanism involving hexosephosphate may be excessive in periodic paralysis." Our investigations suggest that the potassium migration, the hypokalaemia, and the paralysis are all secondary effects of overactive glucose storage. The qualitative response of these patients to influences affecting glucose assimilation seems to be normal, but the rate of assimilation, particularly in muscle, is apparently increased.

Summary

A sporadic case of periodic paralysis is described and the features of this condition are outlined.

A glucose-tolerance test in this patient revealed an apparent increase in tolerance, and an intravenous insulin-tolerance test showed "hypoglycaemia unresponsiveness."

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.

We thank Dr. C. L. Cope for his interest and advice, and for allowing us to investigate this patient; Dr. M. D. Milne for helpful comment; and Dr. M. E. MacGregor for anticipating the diagnosis by 13 years. We are indebted to Miss Margaret Mathew for performing the biochemical estimations, and to our patient for his willing co-operation.

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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