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Part I.—Original Articles.

THE EFFECTS OF INTRAVENOUS INSULIN IN SAKEL'S HYPOGLYCAEMIC TREATMENT.

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THE use of intravenous insulin in Sakel's shock treatment as an alternative to intramuscular insulin was first reported by Ventriglia (1939), whose findings may be summarized as follows:

(1) Hypoglycaemic symptoms appear more quickly than with intramuscular insulin, so that the pre-shock period is shortened.

(2) The coma dose of insulin is reduced by 50 per cent. on an average, but may be reduced by considerably more.

(3) In some cases the hypoglycaemic symptoms are more abrupt and violent.

(4) There is a greater tendency to tonic-clonic spasms and convulsions generally.

Ventriglia's experience led him to prefer intravenous insulin to intramuscular, but apart from the saving of the insulin, he gives no reasons for this decision. No definition is given, either, of the standard of coma adopted. This is unfortunate, since the standard of coma adopted by different workers varies considerably and makes comparison of their results very difficult.

In the same year Bardenat and Leonardon (1939) administered insulin intravenously in an attempt to overcome the resistance to insulin not infrequently found in Sakel's usual treatment. They found that the pre-coma stage was shortened by about two-thirds, and that pre-coma excitement was almost entirely abolished, but their work did not enable them adequately to compare the results of the two methods of administration.

The next paper on the subject to appear was that of McGregor and Sandison (1940), who used intravenous insulin as a possible means of economizing its

use during wartime. They found that the intravenous " coma-dose " varied from 25 per cent. to 75 per cent. of the intramuscular coma-dose, the average for 8 patients being 53·4 per cent. This result is, therefore, in agreement with that of Ventriglia. Unfortunately, it is not possible to assess the validity of the authors' conclusions, as they do not mention (*a*) their standard of coma or (*b*) the exact circumstances under which the comas they refer to were induced. This latter point is an important one, for no patient has a constant " coma-dose." Once coma has been induced it is usually possible to induce it with progressively smaller doses on following days owing to the patient becoming sensitive to the insulin. Corwin (1939) pointed out this and it would be insufficient to determine a given patient's coma-dose with intramuscular insulin and then immediately switch over to intravenous insulin. On such a procedure the intravenous dose would almost certainly be less than the intramuscular one, but only because the decreased resistance to hypoglycaemia induced by the intramuscular insulin had been ignored.

It is very difficult to obtain standardized conditions for a comparison between the effects of intramuscular and intravenous insulin, as it is almost impossible to keep such factors as the body weight of the patients constant during the experiments. The method adopted in the experimental portion of this study would appear to be as valid as possible under the circumstances. By this method the *intramuscular* coma-dose of alternate patients was first ascertained and then the patients were " rested " for 14 days before their intravenous coma-dose was determined. The remaining patients were then taken and their *intravenous* coma-dose found, followed by 14 days' rest, after which their intramuscular coma-dose was ascertained.

A few weeks after the publication of the above paper Maxwell Jones (1940) published his findings in a series of seven cases. Unlike Ventriglia and McGregor and Sandison, this author found that the coma-dose was the *same* for intramuscular and intravenous insulin, but that the time before the onset of coma was shortened by an average of 45 minutes. Jones states that a patient was judged to be in a coma " when there was no voluntary response to external stimuli, extensor plantar response was present and the corneal reflex absent." This is the standard adopted in the present work and must be considerably " deeper " than McGregor and Sandison's standard, as they allowed their patients to remain in coma for 1½–2 hours, a procedure which would have resulted in a high proportion of prolonged comas had Jones's standard been followed.

In the same year Polatin, Spotnitz and Wiesel (1940*a* and 1940*b*), unaware of Ventriglia's work, used intravenous insulin in the treatment of mental disorder. They endeavoured to determine " whether hypoglycaemic shock itself, without prolonged coma, might be of benefit in the treatment of patients with mental disorder." The dose used varied between 27–90 units and no attempt was made to induce coma. It was found that no convulsions occurred and that spontaneous recovery was the rule. This, however, would probably have been the result had these comparatively small doses been used intramuscularly. The authors note one interesting point, that a biphasic or delayed reaction may occur with intravenous as with intramuscular insulin.

" These biphasic effects were also repeatedly seen after the injection of insulin intravenously. One patient, about one and a half hours after injection, was alert and drank dextrose, only to slip back within five minutes into a state of coma deeper than the primary reaction. About 30 minutes later she again recovered spontaneously." This suggests that as far as one of the complications of intramuscular insulin—the delayed reaction—is concerned, intravenous insulin has no advantage.

Horvath and Friedman (1941) gave up to 500 units of insulin intravenously, but their purpose was to observe the effect upon the blood sugar and blood lactate. Contrary to Damashek *et al.* (1935), who found that the intravenous injection of 8–80 units intravenously caused a definite increase in the blood lactic acid, these authors found that insulin did not affect the blood lactate except in resistant cases. They also noted that " the response to intravenous insulin was similar to that of intramuscular insulin, no ill effects were observed. The coma produced by intravenous insulin is, in general, much quieter than that induced by intramuscular insulin. Recovery was, in many cases, spontaneous after two hours and no recurrences of coma or convulsions were observed." A number of anomalous results were encountered. In one patient 20 units of insulin were as efficacious in lowering and keeping the blood sugar down, as were 100 or 160 units, and in another patient 160 units failed to lower the blood sugar to the same extent as 50 units had done previously.

Sherman, Mergener and Low (1941) observed the effects of intravenous and intramuscular insulin in 13 patients. Their method was to divide the cases into two sets. To the first set insulin was given subcutaneously in increasing doses until coma was reached and then " the dose was gradually diminished until coma was produced within a fairly constant time with what appeared to be a minimal dose." The patient was maintained on this dose for about 5–10 days, after which blood-sugar studies were made. Then the insulin was given intravenously and the dose increased or decreased, depending on whether coma was produced. The dose by this second method of administration was stabilized and blood-sugar studies made again. To the second set of patients the insulin was first given intravenously and, following the same procedure, was later replaced by subcutaneous insulin. This method of comparison is open to only one objection. It ignores the usual trend of a patient's coma-dose, which, following the initial reduction owing to " sensitization," usually increases as the treatment proceeds, and the second method of administration may have bee nadopted just when the patient would be requiring these larger coma-doses in any case. It would have been preferable to have found the sensitized coma-dose by either route and then, following an adequate rest period, to have started *de novo* with the alternative mode of administration and found the patient's sensitized coma-dose by that route.

The authors found that in every case the precoma time was shortened from a minimum of 24 minutes to a maximum of 90 minutes. As regards the coma-dose, 6 patients required the same by either route, 3 required more by the intravenous route and 2 required less by this route than subcutaneously. They conclude " that there is no appreciable difference in the coma-doses required between intravenous and subcutaneous insulin." They also found

that there was no significant difference in the incidence of complications and that spontaneous emergence from intravenously induced coma was rare.

Mention should be made of the authors' standard of coma, which was apparently a light one. "The patient was called loudly three times; if there were no verbal or facial response, he was pricked three times around the upper lips and nostrils. Failure to respond by some facial grimace or other protective movement suggested the presence of coma." This standard of coma is, of course, much lighter than that of Jones (1940).

In 1942 Sandison and McGregor amplified their results reviewed above on the basis of a year's experience with intravenous insulin. Their earlier work was confirmed, except that in the additional 24 patients treated the intravenous dose required to produce coma was 71·7 per cent. of the intramuscular dose compared with 53·4 per cent. in the earlier series. A number of the points raised in this paper will be discussed later, when the mode of action of intravenous insulin is discussed, but attention may be drawn to the method used of determining the coma dose for intravenous insulin. The patients apparently were first given intramuscular insulin until coma was induced. On the following days intravenous insulin was given, until the most satisfactory coma dose was found. As would have been expected, the intravenous coma dose was invariably the lower. Such a method of comparison is unsatisfactory as the patient would be developing sensitivity to insulin when on intramuscular insulin, the effect of which would be to lower the coma dose of intravenous insulin, since this followed immediately after the intramuscular doses. As mentioned earlier, the only adequate method of comparison is to find a patient's coma dose on intramuscular insulin, give seven to fourteen days' rest and then find the coma dose in intravenous insulin and compare the two. Even with this method, the results can only be approximate unless extreme care is taken to provide a diet with a constant carbohydrate content for the whole period of the experiment, since, as Himsworth (1939) has shown, sensitivity to insulin is directly proportionate to the absolute amount of carbohydrate in the diet.

In this paper Sandison and McGregor also refer to their definition of coma. It has already been pointed out that several workers on intravenous insulin have not specified the exact stage of unconsciousness which they designate as coma. Some authors regard a patient as being in coma as soon as he becomes unconscious. Sherman *et al.* (1941). Others, e.g. James, Freudenberg and Cannon (1938) state that coma is present when the patient is unconscious and the plantar responses are extensor. Still others, e.g. Maxwell Jones (1940), Mahoney and Herskovitz (1942) following Wilson (1937) adopt as criteria of coma, unconsciousness, a positive Babinski and absent corneal reflexes. The point is of considerable importance, as absence of the corneal reflex indicates a much "deeper" state of hypoglycaemia than does the presence of unconsciousness with a Babinski response and it is possible that the more quickly acting intravenous insulin might be able to produce the latter sooner than the more slowly acting intramuscular insulin, but that its action might not be sufficiently prolonged to induce the deeper state indicated by absent corneal reflexes. The conflicting reports which have already been noticed as to the

relative amounts of intravenous and intramuscular insulin required to induce coma may, therefore, possibly be accounted for by the different standards of coma adopted.

Sandison and McGregor (1942) state that " in all our work we have defined insulin coma according to Sakel's original description, that it to say, a condition in which the patient's normal responses to stimuli are lost. There is sweating, flushing of the skin and usually profuse salivation; the reflexes are all lost excepting the corneal reflex and the plantar response is extensor." In view of the importance of the definition of coma, Sakel's own description may be quoted. In the original German text (Sakel, 1935*a*) the following passage occurs (p. 9): " Diese konnen entweder mit einen profusen Schweissausbruch beginnen und dann in allmählich zunehmende Somnolenz, zeitweise auch unterbrochen durch psychotische Erregungen, und schliesslich in Koma übergehen. Dieses Koma kann nun eine verschiedene Tiefe erreichen. In der Somnolenz ist Patient noch weckbar, es ist aber kein Kontakt mehr möglich. Es bestehen noch sämtliche Reflexe, man kann noch durch sehr energisches Zurufen den Patienten zum reflektorischen Schlucken bringen. Allmählich nimmt das Koma an Tiefe zu. Es verschwinden alle Reflexe. In dieser Phase treten bereits pathologische Reflexe auf; Babinski, Oppenheim, Mendel-Bechterew u.a. Bei langerem Zuwarten kann das Koma eine solche Tiefe erreichen, dass sämtliche Reflexe, inklusiv Schluck, Corneal, und Kitzelreflexe, auch die in der früheren Stufe aufgetretenen pathologischen Reflexe, erlöschen. Also vollige Areflexis mit volliger Atonie der gesamten Muskulatur."

This is translated in the first and revised English translations (Sakel, 1935*b*, 1938) as: ". . . the shock starts with profuse perspiration and progressive somnolence and may be interrupted by psychotic excitement, but ends typically in coma. This coma may attain a varying depth. If the patient is merely somnolent he can be awakened, but contact is no longer possible. All the reflexes at this stage are still intact and energetic commands can rouse the patient's swallowing reflexes to the point where the patient will swallow food. But *as the coma deepens* the reflexes become pathological and finally disappear. The patient at first shows positive Babinski, Oppenheim and Mendel-Bechterev reflexes, but *later the coma may become so deep* that all the reflexes disappear, including the corneal and swallowing reflexes, as well as the pathological reflexes which had appeared in the preceding stage, so that we have a complete areflexia with complete atonia of the entire musculature."

It will be seen, therefore, that Sakel made no precise definition of the term " coma," but used it to cover all degrees of the effects of hypoglycaemia from somnolence to complete areflexia. Most British workers have adopted Wilson's (1937) standard of absent corneal reflexes, while the initial unconsciousness. from which the patient cannot be roused and in which the plantar response is frequently extensor is termed " sopor " (von Angyal, 1937). These criteria are adopted in the present paper.

Adopting Wilson's standard of coma, Mahoney and Herskovitz (1942) found that the treatment period was not shortened by intravenous insulin,

that about the same amount of insulin was required to induce coma when given intravenously or intramuscularly, but that the onset of coma occurred about half-an-hour earlier with the former type of administration. The same amount of glucose was required to bring the patient out of coma and one of their patients had 12 convulsions during the course of intravenous insulin. The authors conclude, " our findings indicate that this (intravenous) method of producing hypoglycaemia is not superior to the Sakel method and is not recommended."

Reznikoff and Scott (1942), using a solution of zinc insulin crystals, following Jones (1940) found that there was no economy in the amount of insulin required to produce coma intravenously compared with that needed intramuscularly. Four of their twenty patients developed convulsive seizures, but in general they found that the hypoglycaemia induced was quieter than that of intramuscular insulin. These authors gave up to 1,200 units intravenously to some insulin-resistant cases without producing signs of hypoglycaemia. No allergic reactions followed the use of the zinc insulin crystals. Hypoglycaemia was interrupted two hours after the injection of the insulin, so that complications such as protracted coma were not encountered.

Olsen (1942) followed up McGregor and Sandison's work (1940), but restricted himself to the use of intravenous insulin and glucose with potato starch as a means of preventing after-shock. Using larger quantities of glucose than the latter authors he found the method successful. Olsen does not compare the relative amounts of intravenous and intramuscular insulin required to produce coma.

Polatin and Spotnitz (1942*b*) followed up their earlier work and assessed their results in a series of 33 patients. These do not appear to have been any better than those obtainable with intramuscular insulin, but the authors found that when improvement occurred, it set in more rapidly. This they ascribed, probably correctly, to the more rapid onset of hypoglycaemic symptoms with consequently a greater degree of shock. Low doses with a normal maximum of 40 units were used and it was found that with higher doses "*a protracted coma . . . might ensue.*" It was confirmed that after-shock occurred repeatedly after the injection of insulin intravenously. Although no details are given, apparently a number of patients were allergic to intravenous unmodified insulin and these were switched over to zinc-insulin crystals. This is a point of some importance. Hinko, Fenton and Balberor (1941) record a case of anaphylactoid shock occurring in a patient receiving Sakel's treatment. Generalized pruritus, oedema of the face and cardiovascular collapse were marked and for some time the patient's condition was extremely grave. Later intradermal tests showed him to be definitely sensitive to insulin. Had this patient been given insulin intravenously a fatal outcome of the anaphylactoid shock would have been almost certain.

Goldfarb (1943) states, following his experiment with intravenous and intramuscular insulin, " the production of hypoglycaemic coma by the intravenous route requires essentially the same amount of insulin as the intramuscular route, but the onset of coma occurs earlier after intravenous glucose." This author gives no details of his standard of coma.

In the same year, Peterson and Lutz (1943) reported their findings in a series of cases treated in 1938. They do not compare the relative efficacy of intravenous and intramuscular insulin, but mention that several patients, treated intravenously, went into " after-shock " with low blood sugars when interrupted by nasal glucose. This was prevented by interruption with intravenous glucose. These authors' experience shows, however, that intravenous insulin can, under certain circumstances cause after-shock and that it is not an adequate safeguard by itself against this complication.

It will be seen from the above review of the literature that the effect and value of intravenous insulin in Sakel's treatment are both undecided, as the reports on its use conflict considerably. There is general agreement that the pre-coma time is shortened, but the following summary brings out the conflicting results observed by the various authors on other aspects of this mode of administration as compared with intramuscular injection.

TABLE I.

Authors.	Intravenous coma-dose compared with subcutaneous coma-dose.	Tendency to convulsions.	Coma quieter or not.	After shock.	Incidence of protracted coma.
Ventriglia (1939)	Reduced 50%	Increased	No quieter	—	—
Bardenot and Leonardon (1939)	—	—	Quieter	—	—
McGregor and Sandison (1940)	Reduced 52·4%	—	,,	—	—
M. Jones (1940)	Same	—	—	—	—
Polatin, Spotnitz and Wiesel (1940)	—	Reduced	—	Same	—
Horvath and Friedman (1941)	—	—	Quieter	Less	—
Sherman, Mergener and Low (1941)	Reduced (2), increased (3), same (6)	Same	Same	Same	—
Sandison and McGregor (1942)	Reduced 28.3%	—	Quieter	Less	—
Reznikoff and Scott (1942)	Same	Increased	,,	—	—
Olsen (1942)	—	—	—	Less	—
Mahoney and Herskovitz (1942)	Same	Increased	—	—	—
Goldfarb (1943)	,,	—	—	—	—

In particular, the effect of intravenous insulin on the encephalopathies which complicate intramuscular insulin, such as prolonged coma, have not been reported on, except very briefly by Polatin and Spotnitz (1942*a*) and the experimental work now to be described was undertaken in order to clarify the position as far as possible.

The first part of the experimental work may be outlined as follows:

Twelve patients, 8 male and 4 female, were given intramuscular and intravenous insulin and the coma dose for each method of administration determined. It was found that while the pre-coma time was shortened *all* the patients required larger doses intravenously than intramuscularly to produce coma. This is at variance with the results obtained by earlier authors, excluding Sherman, Mergener and Low (1941) and an explanation was sought. Three possible explanations suggested themselves:

(1) Some of the intravenous insulin might be excreted rapidly in the urine.

(2) Some of the intravenous insulin might be inactivated by an anti-body in the blood.

(3) While intravenous insulin produces a more rapid fall in the blood sugar than intramuscular insulin, this fact can only be achieved at the cost of considerably more insulin, which is, therefore, more rapidly used up. Despite the greater initial fall, therefore, the intravenous insulin might be unable to maintain the lowered blood-sugar level sufficiently long for coma to supervene unless it were given in greater amounts than when injected intramuscularly.

Experiments were designed to test these hypotheses and the last was found to be correct.

Details of Experimental Work.

I. *The Comparative Coma Doses of Intravenous and Intramuscular Insulin.*

(1) *Standard of Coma.*

A patient was adjudged to be in coma when he was unconscious, with Babinski plantar responses and absent corneal reflexes. This follows Wilson's (1937) standard and is mentioned in view of the varying standards of coma adopted by various authors. It is considerably deeper, for instance, than Sandison and McGregor's standard (1942) in which the corneal reflexes are present. The point is stressed because a given method of injection of insulin may be able to produce the earlier stages of unconsciousness sooner than another, but, through being exhausted by its more rapid action, it may be unable to produce the deeper stages, which are here designated as coma.

(2) *Method of Ascertaining Coma Dose.*

In general, all patients were given daily injections of insulin at 7 a.m. with one rest day a week. To commence, 4 male and 2 female patients were given 20 units intravenously and the dose increased by 20 units daily until "sopor" was obtained, after which the daily increment was reduced by varying amounts until coma was reached. Thereafter, with the onset of sensitivity the dose required to induce coma was found to be progressively less until a minimum was reached, below which the dose could not be reduced if coma were to result. The patients were then "rested" for 14 days and the process repeated with intramuscular insulin. It was found that the degree of sensitivity developed was approximately the same with both methods of administration (see Table III). This is contrary to Sandison and McGregor's (1942) findings, who found a greater sensitivity to intravenous than to intramuscular insulin. As there was no difference in the sensitivity induced by the two methods, it was concluded that it would be sufficiently accurate to determine only the dose required to induce the initial coma and this was done in a further 6 patients, making a total of 8 male and 4 female cases.

(3) *Blood-Sugar Estimations.*

In view of the findings of previous workers, e.g. Norgaard and Thaysen (1929) and Sherman, Mergener and Low (1941) that the lowest blood-sugar level following intravenous insulin is found from 25–40 minutes after injection,

the blood sugar was usually estimated at the following intervals after injection : 25, 30, 35, 40, 50, 60, 70, 90, 110, 130, 160, 180, 210, 240 and 270 minutes. The blood was drawn from the distal phalanx of the thumb, a small rubber tourniquet being wound around the thumb proximal to the site of puncture. This probably resulted in a certain amount of tissue exudation, but as with practice the withdrawal of the blood into the pipette could be done very quickly this factor does not appear of practical importance, especially as a more liberal quantity of blood was consistently available than could have been so with, say, non-pressure pricking of the lobe of the ear. The blood sugar was estimated by a modified method of Hagedorn and Jensen (1923) as follows :

One c.c. of 0·1 NaOH and 5 c.c. of 0·45 per cent. zinc sulphate solution were pipetted into a test-tube (15 × 150 mm.) ; 0·12 c.c. of blood was introduced from a capillary pipette and the mixture placed in a boiling-water bath for 3 minutes, following which it was cooled and diluted to 12 c.c. The blood protein which has been precipitated by the zinc hydroxide formed by the interaction of the sodium hydroxide and zinc sulphate was then filtered out on a funnel of 3–4 cm. diameter, prepared with a dry, acid-washed, No. 40 Whatman filter paper, following the assertion of Kramer and Steiner (1931), that the variable density of the cotton filter recommended by Hagedorn and Jensen gave rise to erroneous results. 10 c.c. of the filtrate, corresponding to 0·1 c.c. of blood were taken and neutralized with 0·30 of 0·1N sodium hydroxide in order to prevent changes in the alkalinity of Hagedorn-Jensen potassium ferricyanide reagent, 2 c.c. of which were then added to the 10 c.c. of filtrate. This mixture was then heated in a boiling-water bath for 15 minutes. After cooling, 3 c.c. of iodide-sulphate chloride solution ($KI + ZnSO_4 + NaCl$) and 2 c.c. of 3·per cent. acetic acid solution were added. The amount of the potassium ferricyanide reduced by the glucose was determined by finding the amount of iodine set free through titration with 0·005 N sodium thiosulphate using as an indicator 2 drops of 1 per cent. solution of soluble starch in saturated sodium chloride solution.

The principal reactions of the process are :

$$2H_3Fe(CN)_6 + 2HI = 2H_4Fe(CN)_6 + I$$
$$2K_4Fe(CN)_6 + 3ZnSO_4 = K_2Zn_3(Fe(CN)_4)_2 + 3K_2SO_4.$$

The reversal of the reduction process is prevented by the precipitation of the ferrocyanide formed as a zinc salt by the zinc sulphate.

Calculation.—(*a*) A blank was first obtained by carrying through the whole process, but without the addition of blood. This blank was never allowed to exceed 0·2.

(*b*) The thiosulphate burette reading was multiplied by the factor for the thiosulphate (2·00 c.c. thiosulphate required for 2 c.c. of 0·005 N potassium sulphate). This gives value (A). This value (A) was expressed for the unknown and for the blank by consulting tables provided. The glucose value of the blank was subtracted from the glucose value of the unknown to give the mgm. glucose in 0·1 c.c. of blood, from which the amount present in 100 c.c. of blood was calculated.

Interpretation of results.—The method of Hagedorn and Jensen for estimating the blood sugar was selected in preference to that of Folin and Wu, as it gives more accurate results in the very low blood-sugar levels encountered in Sakel's hypoglycaemic treatment. In addition to the glucose, the blood contains 20–30 mgm.—as glucose—per 100 c.c. of non-fermentable reducing substances, chiefly glutathione which is present in the red blood corpuscles. It is, however, incorrect to calculate the true glucose by deducting the amount of the non-fermentable reducing substances from the "enhanced-glucose" values because in different methods varying proportions of these non-fermentable reducing substances are included. In the Hagedorn and Jensen method 4 mgm. per 100 c.c. only are to be deducted, while in the Folin and Wu method 11 mgm. per 100 c.c. have to be deducted. If, therefore, the blood-sugar values obtained in this present study are reduced by 4 mgm. per cent., the resulting figures give an approximate true glucose value (Harrison, 1945).

(4) *Results Obtained.*

The blood-sugar values obtained in the 12 patients following the intramuscular and intravenous injection of insulin in increasing doses from 20 units to coma dose are set out in Table II.

From Table II the doses of insulin required initially to induce "sopor" and coma were abstracted and are set out in Table III, along with the doses needed to induce these states after the patients had become sensitized to the insulin.

The results summarized in the above table differ from those of previous workers except Sherman, Mergener and Low (1941), three of whose patients required more insulin intravenously than subcutaneously to induce coma. It will be seen that all of the 12 patients in the series required more intravenous than intramuscular insulin for the production of coma. The percentage difference has not been calculated, as such figures are unreliable under the non-standardized conditions of Sakel's treatment as usually practised, and especially in view of the variation in the response to insulin of individual patients. McGregor and Sandison (1940) found that the intravenous "coma dose" varied from 25 per cent. to 75 per cent. of the intramuscular coma dose. With such widely divergent figures, percentage averages are of little value unless very large numbers of patients are being considered. It will be noticed that while more intravenous than intramuscular insulin is needed to induce coma with areflexia, less is needed to induce "sopor" (unconsciousness). In Table II usually 20 units less is required, but the actual figure is probably lower than this, as the insulin at this stage of the experiment was being increased by 20 units daily, and had the increment been smaller, the patients would probably have gone into "sopor" on intramuscular insulin on a slightly lower dose. The figures for the differences between the sensitized "sopor" doses are probably more accurate, as these were arrived at over a period of some days. In view of the consistency of the above results, an explanation was then sought to account for the way in which they differ from those of earlier workers, who had found either a smaller or the same amount of intravenous insulin was

TABLE II.—*Blood-sugar Values Following Injection of Intramuscular and Intravenous Insulin in Increasing Doses from 20 Units to Coma Dose.*

The doses required to induce "sopor" are marked with †.
The doses required to induce coma are marked with an asterisk.
I.M. = intramuscular; I.V. = intravenous.

Units of insulin.	Fasting blood sugar.	Minutes after injection.												
		25.	30.	35.	40.	50.	60.	75.	90.	120.	150.	180.	210.	240.	270.
Patient 1—Male:															
20 I.M.	75		56				47		50	47	50	48	47	54	54
20 I.V.	83	38	29	31	25	30	38	45	53	66	72	81	81	83	83
40 I.M.	90		79				45		34	41	43	48	47	47	51
40 I.V.	81	34	30	32	29	32	33	35	39	48	59	70	78	79	79
60 I.M.	90		70				45		45	45	41	41	41	43	45
60 I.V.	78	42	37	35	32	37	38	42	47	54	64	66	76	78	78
80 I.M.	92		65				35		35	41	34	34	38	38	36
80 I.V.†	88	39	31	31	25	24	29	32	39	51	56	72	83	85	87
100 I.M.†	100		72				38		36	36	34	34	34	36	36
100 I.V.	92	35	27	23	23	22	29	31	33	41	45	47	56	67	71
120 I.M.	110		60				36		28	31	33	31	33	33	34
120 I.V.	88	24	24	22	20	24	27	25	29	29	36	38	45	56	64
140 I.M.*	80		72				33		21	23	23	25	26	28	28
140 I.V.	77	39	43	24	22	27	34	30	34	32	32	35	44	49	55
160 I.V.	74	48	46	43	27	24	31	27	36	39	36	37	42	43	41
174 I.V.*	83	56	35	32	25	19	18	20	24	26	28	29	30	29	28
Patient 2—Male:															
20 I.M.	111		86				65		56	50	54	72	77	83	80
20 I.V.	106	57	47	41	36	34	41	45	54	75	95	90	92	93	102
40 I.M.	104		84				50		43	43	43	47	52	59	65
40 I.V.	108	65	54	34	41	39	43	47	47	66	77	86	96	95	95
60 I.M.	88		64				41		36	41	45	43	50	43	47
60 I.V.	92	56	50	41	32	32	32	27	32	35	43	63	72	81	87
80 I.M.	98		70				39		41	50	48	52	47	45	48
80 I.V.†	97	56	45	38	31	32	36	32	32	38	46	55	61	75	83
100 I.M.†	101		70				43		41	39	36	41	36	38	38
100 I.V.	86	63	48	31	36	27	27	24	27	38	38	47	53	70	77
120 I.M.	95		54				42		38	36	36	29	25	38	39
120 I.V.	88	77	61	34	32	32	31	36	33	35	36	41	49	61	68
130 I.M.	96		61				45		35	33	29	29	24	31	35
130 I.V.	92	61	47	33	31	32	31	34	31	33	37	45	46	57	63
140 I.M.*	92		74				48		27	24	27	27	24	27	24
140 I.V.	102	72	66	59	45	34	34	32	31	34	38	42	48	52	57
160 I.V.	94	60	48	34	30	30	31	31	31	33	35	36	40	46	44
170 I.V.*	96	55	44	34	29	31	29	32	35	31	29	32	29	31	33
Patient 3—Male:															
20 I.M.	88		63				43		41	34	38	43	57	70	82
20 I.V.	75	32	27	25	25	27	29	27	34	55	63	75	83	80	79
40 I.M.	86		48				24		29	29	29	36	38	41	43
40 I.V.†	79	44	34	27	22	22	24	24	29	33	47	66	72	79	79
60 I.M.†	95		54				25		32	31	32	38	38	38	41
60 I.V.	92	32	28	24	19	19	22	27	25	30	43	54	63	74	88
80 I.M.	104		47				27		27	27	24	31	32	31	31
80 I.V.	95	36	29	29	19	19	19	25	24	24	29	36	47	68	74
86 I.M.	92		79				48		34	29	27	27	31	29	32
86 I.V.	89	45	31	30	22	21	20	22	23	23	26	37	46	57	69
92 I.M.*	97		60				29		27	27	27	25	27	29	27
92 I.V.	93	38	30	22	23	21	20	19	21	25	27	36	43	54	63
100 I.V.	101	36	32	24	24	24	19	19	20	22	27	36	39	47	59
110 I.V.	99	34	24	22	15	15	19	15	19	21	30	29	34	36	43
118 I.V.*	95	32	29	24	18	18	17	18	20	22	21	25	27	26	29

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TABLE II—(*contd.*).

The doses required to induce "sopor" are marked with †.
The doses required to induce coma are marked with an asterisk.
I.M. = intramuscular; I.V. = intravenous.

Units of insulin.	Fasting blood sugar.	Minutes after injection.													
		25.	30.	35.	40.	50.	60.	75.	90.	120.	150.	180.	210.	240.	270.
Patient 4—Female:															
20 I.M.	106		81				59		53	57	56	57	54	57	57
20 I.V.	108	72	48	36	34	31	31	45	47	66	86	90	93	95	98
40 I.M.	99		90				65		39	39	45	38	39	38	45
40 I.V.	95	45	32	29	20	15	20	22	22	48	54	68	75	75	83
60 I.M.	90		70				36		31	28	31	31	35	45	50
60 I.V.†	90	36	27	24	20	25	27	22	34	47	55	58	59	71	83
80 I.M.†	92		72				31		19	19	19	23	31	32	39
80 I.V.	88	57	39	32	24	22	24	25	25	26	34	41	54	70	75
90 I.M.	97		76				39		24	17	18	20	25	27	35
90 I.V.	93	43	35	34	29	26	26	32	30	29	34	36	41	49	56
98 I.M.*	88		60				31		20	18	18	20	22	20	19
98 I.V.	101	60	54	33	32	25	24	31	29	23	33	36	38	41	41
110 I.V.	96	54	40	32	29	25	23	24	25	23	26	28	34	37	39
118 I.V.*	86	65	54	39	32	22	18	14	15	15	17	15	16	18	—
Patient 5—Male:															
20 I.M.	106		94				79		75	79	85	92	96	98	101
20 I.V.	94	62	56	54	56	60	68	72	78	89	90	91	90	92	91
40 I.M.	92		78				68		58	62	67	71	75	83	89
40 I.V.	97	63	52	52	50	56	67	75	81	90	95	93	96	96	96
60 I.M.	93		84				67		57	65	66	68	70	74	77
60 I.V.	99	58	47	43	47	53	59	69	78	87	95	94	94	96	95
80 I.M.	104		63				63		61	54	57	59	59	63	67
80 I.V.	93	54	43	31	41	49	54	63	72	81	86	85	87	89	87
100 I.M.	92		72				34		43	50	48	56	56	59	61
100 I.V.†	95	48	33	27	35	39	43	55	56	64	76	89	93	97	97
120 I.M.†	95		60				46		43	40	54	54	54	55	57
120 I.V.	89	40	31	23	28	32	35	51	64	69	74	78	83	85	85
140 I.M.	97		57				36		34	36	41	41	39	41	42
140 I.V.	96	55	41	25	19	21	30	34	45	54	59	63	69	69	68
152 I.M.	92		71				39		31	34	28	34	36	34	32
152 I.V.	86	43	35	26	18	19	25	29	27	35	39	47	46	49	54
164 I.M.	90		62				32		27	25	25	27	26	24	26
164 I.V.	99	52	39	23	20	22	23	19	26	30	34	38	40	43	42
176 I.M.	98		59				28		22	18	20	21	23	25	24
176 I.V.	93	49	43	27	17	18	20	25	27	23	29	33	35	35	36
188 I.M.*	88		52				24		20	17	19	20	22	22	23
188 I.V.	95	47	35	25	21	19	24	27	29	33	26	30	33	31	30
200 I.V.	89	39	26	29	19	17	23	25	27	29	31	29	33	33	28
212 I.V.	93	45	28	24	21	20	22	23	25	26	24	23	25	23	24
220 I.V.*	87	66	44	30	19	17	18	20	22	21	19	21	23	23	21
Patient 6—Female:															
20 I.M.	92		86				65		39	41	39	50	45	47	47
20 I.V.	95	43	31	29	31	24	26	31	38	47	59	80	93	93	94
40 I.M.	99		83				45		25	27	27	31	29	29	29
40 I.V.	99	34	32	29	31	31	36	41	41	43	54	71	78	87	93
56 I.M.	120		74				45		31	31	31	27	20	24	31
56 I.V.†	97	27	24	23	17	20	25	32	33	34	37	37	41	56	67
68 I.M.†	122		74				34		27	31	29	29	19	25	29
68 I.V.	102	43	30	25	20	27	25	28	33	31	34	36	40	45	52
80 I.M.	96		56				32		27	24	24	23	24	27	29
80 I.V.	115	34	31	27	25	23	25	36	31	34	39	38	41	41	43
92 I.M.*	113		47				29		25	21	19	22	22	22	25
92 I.V.	97	39	34	—	20	31	27	31	31	25	32	30	31	33	37
104 I.V.	108	34	31	25	24	19	25	27	25	26	29	31	29	33	33
114 I.V.*	96	27	29	25	22	27	25	24	22	21	23	25	22	20	20

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TABLE II—(*contd.*).

The doses required to induce "sopor" are marked with †.
The doses required to induce coma are marked with an asterisk.
I.M. = intramuscular; I.V. = intravenous.

Units of insulin.	Fasting blood sugar.	Minutes after injection.												
		25.	30.	35.	40.	50.	60.	75.	90.	120.	150.	180.	210.	240.	270.
Patient 7—Male:															
20 I.M.	95		70				63		38	31	32	29	32	34	34
20 I.V.	108	48	39	25	32	27	32	33	36	43	50	74	87	93	97
40 I.M.	120		78				41		29	27	26	25	44	45	46
40 I.V.	106	57	45	39	27	29	24	25	27	31	61	72	83	95	92
60 I.M.	99		90				67		38	25	15	19	28	28	36
60 I.V.	106	50	39	29	29	29	27	31	24	34	52	63	75	89	94
80 I.M.	109		83				61		25	22	27	31	31	31	36
80 I.V.†	125	59	47	38	32	24	22	24	19	22	31	44	36	48	54
92 I.M.†	120		93				56		25	17	19	20	22	27	25
92 I.V.	111	48	31	24	24	19	15	20	20	27	36	32	36	36	43
100 I.M.*	119		81				39		22	20	19	20	19	21	23
100 I.V.	96	50	41	27	24	22	23	24	34	27	28	30	34	35	35
110 I.V.	112	43	29	25	29	31	25	22	25	32	29	32	34	29	29
118 I.V.*	101	45	20	19	19	17	20	19	19	20	22	25	24	28	30
Patient 8—Male:															
20 I.M.	98		74				34		36	27	27	37	38	39	50
20 I.V.	115	31	27	29	31	32	39	43	45	61	78	92	95	97	89
40 I.M.	95		72				36		32	32	29	38	32	36	38
40 I.V.†	100	29	23	24	23	24	22	18	25	41	43	50	65	72	87
52 I.M.†	93		56				32		29	29	31	27	33	35	34
52 I.V.	97	33	21	21	24	26	27	27	30	38	41	43	53	61	74
60 I.M.*	106		36				27		26	27	25	19	19	17	21
60 I.V.	95	34	19	24	25	32	29	27	25	35	38	41	45	49	54
68 I.V.	108	32	36	22	21	19	19	19	22	27	34	34	39	45	45
76 I.V.*	117	39	32	22	21	21	22	20	17	23	24	29	30	28	—
Patient 9—Male:															
20 I.M.	96		61				38		40	43	47	51	51	57	65
20 I.V.	94	56	39	32	33	35	39	45	46	57	73	81	87	88	87
40 I.M.	106		65				45		29	29	29	32	36	31	38
40 I.V.†	90	35	22	23	25	27	29	33	39	40	44	58	65	76	84
60 I.M.†	111		83				34		22	22	22	25	29	29	33
60 I.V.	99	31	21	19	19	23	26	27	30	36	42	51	55	61	67
72 I.M.	92		68				24		24	16	17	23	25	25	27
72 I.V.	98	37	21	18	19	23	21	25	25	29	35	41	46	55	59
80 I.M.*	95		66				18		18	17	15	17	17	20	21
80 I.V.	92	36	24	20	20	23	23	24	24	30	32	33	38	42	53
88 I.V.	98	32	22	18	19	18	22	24	25	27	30	31	35	35	33
96 I.V.	90	40	21	20	18	19	20	19	20	25	23	24	30	29	31
104 I.V.*	99	32	24	20	17	17	16	15	17	19	20	19	24	23	24
Patient 10—Male:															
20 I.M.	98		61				39		38	42	47	51	54	53	57
20 I.V.	93	33	27	30	31	34	37	40	42	57	72	82	88	89	88
40 I.M.	96		56				31		31	38	31	31	29	34	36
40 I.V.	92	34	29	27	29	32	29	31	32	41	67	77	84	84	86
60 I.M.	93		54				41		34	34	32	32	33	33	35
60 I.V.†	97	43	38	26	25	26	27	28	30	35	45	64	70	70	72
72 I.M.†	88		61				38		27	31	32	31	31	30	29
72 I.V.	100	39	29	25	22	20	29	29	29	24	34	43	54	63	69
84 I.M.	97		58				31		23	25	27	25	26	29	28
84 I.V.	90	43	32	25	27	29	26	19	22	24	28	32	41	53	56
94 I.M.*	92		54				25		20	19	23	20	19	21	20
94 I.V.	98	38	26	24	19	22	23	21	22	22	28	32	38	47	46
106 I.V.	93	32	22	22	19	22	24	22	24	20	26	26	35	36	38
114 I.V.*	100	52	33	32	31	19	20	23	23	24	22	22	21	23	26

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TABLE II—(*contd.*).

The doses required to induce "sopor" are marked with †.
The doses required to induce coma are marked with an asterisk.
I.M. = intramuscular; I.V. = intravenous.

Patient 11—*Female:*

Units of insulin.	Fasting blood sugar.	Minutes after injection.												
		25.	30.	35.	40.	50.	60.	75.	90.	120.	150.	180.	210.	240.	270.
20 I.M.	81		59				47		47	45	45	45	45	47	54
20 I.V.	79	45	36	25	31	36	36	41	47	60	72	74	75	74	76
40 I.M.	90		74				43		39	38	38	39	36	41	47
40 I.V.	86	25	19	27	27	27	33	36	40	45	54	63	63	72	81
60 I.M.	90		65				41		41	45	43	39	45	39	38
60 I.V.	93	59	41	36	31	41	38	52	47	46	45	48	59	68	74
80 I.M.	92		70				36		32	32	36	41	36	39	34
80 I.V.†	86	41	29	25	24	29	32	36	43	39	41	47	52	63	74
100 I.M.†	88		59				34		32	32	31	36	32	31	30
100 I.V.	86	43	34	29	24	32	34	32	36	37	41	50	51	52	63
120 I.M.	101		57				39		32	32	36	38	32	39	35
120 I.V.	90	52	38	31	30	27	32	32	32	34	38	43	45	49	54
132 I.M.	86		56				38		30	29	30	31	33	33	35
132 I.V.	93	41	32	27	29	30	31	33	32	30	36	38	39	41	45
144 I.M.*	86		43				29		27	24	24	27	25	29	30
144 I.V.	99	41	29	24	19	22	24	31	32	34	36	37	39	43	47
156 I.V.	90	39	34	31	25	22	28	30	30	31	33	35	34	38	43
168 I.V.*	91	38	31	26	22	22	24	24	24	27	29	27	31	29	33

Patient 12—*Female:*

20 I.M.	96		81				76		69	67	67	72	75	79	79
20 I.V.	91	65	49	38	44	58	64	65	64	67	77	89	91	89	90
40 I.M.	89		67				55		52	55	59	57	63	61	65
40 I.V.	82	69	26	22	27	36	38	38	49	53	67	73	81	81	83
60 I.M.	97		59				47		40	43	46	47	48	51	53
60 I.V.	92	38	32	36	32	29	34	43	45	47	52	52	63	72	71
80 I.M.	95		65				42		41	39	37	37	41	43	45
80 I.V.	83	45	34	29	24	30	39	39	39	41	43	49	57	65	65
100 I.M.	89		53				43		45	43	43	39	43	47	45
100 I.V.†	90	47	32	27	23	29	38	37	36	39	45	45	51	55	59
120 I.M.	95		67				38		37	39	38	40	43	41	41
120 I.V.	97	46	33	31	29	27	34	42	42	39	38	43	45	47	51
140 I.M.†	91		63				32		35	35	33	35	36	34	37
140 I.V.	101	47	36	25	23	24	31	35	37	42	39	37	41	45	47
160 I.M.	93		68				37		33	31	33	34	34	35	34
160 I.V.	96	37	32	21	23	21	27	33	33	35	39	41	43	43	45
172 I.M.	88		63				30		27	28	30	31	30	29	31
172 I.V.	93	36	28	23	21	24	25	25	27	31	35	31	33	34	37
184 I.M.	97		58				21		24	23	22	23	24	26	26
184 I.V.	95	40	27	25	23	22	22	25	28	30	33	36	34	33	35
196 I.M.*	93		54				22		19	17	16	20	22	21	21
196 I.V.	89	29	26	19	23	23	21	23	25	27	29	33	35	35	33
208 I.V.	91	36	24	20	21	24	22	23	23	21	*25	27	25	27	29
220 I.V.	83	31	27	23	17	19	20	23	23	25	26	24	25	26	27
232 I.V.*	96	32	28	21	19	17	20	19	18	21	20	19	21	21	22

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TABLE III.

Patient number.	Sex of patient.	Units of insulin required to produce— Initial sopor. I.M.	Initial sopor. I.V.	Sopor following sensitization. I.M.	Sopor following sensitization. I.V.	Initial coma. I.M.	Initial coma. I.V.	Coma following sensitization. I.M.	Coma following sensitization. I.V.
1	M.	100	80	74	62	140	174	98	130
2	M.	100	80	66	52	140	170	94	112
3	M.	60	40	42	30	92	118	70	88
4	F.	80	60	42	32	98	118	64	78
5	M.	120	100	92	78	188	220	150	166
6	F.	68	56	38	32	92	114	56	72
7	M.	92	80	—	—	100	118	—	—
8	M.	52	40	—	—	60	76	—	—
9	M.	60	40	—	—	80	104	—	—
10	M.	72	60	—	—	94	114	—	—
11	F.	100	80	—	—	144	168	—	—
12	F.	140	100	—	—	196	232	—	—

required to produce coma as compared with intramuscular insulin. Three hypotheses to explain the present findings suggest themselves as follows:

(1) *Excretion of intravenous insulin in the urine.*—The sudden injection of a large quantity of insulin directly into the blood stream might lead to some of the urine being excreted in the urine, and so have no effect upon the level of the blood sugar.

(2) *Destruction of the intravenous insulin by circulating substances in the blood.*—Substances circulating in the blood stream might neutralize part of the large amounts of insulin injected intravenously, and so reduce the efficacy of the insulin in maintaining the blood sugar at low levels for a sufficient period for coma to ensue.

(3) *Rapid but not prolonged action of intravenous insulin.*—Most drugs which can be given intravenously and subcutaneously or intramuscularly have a more rapid but less prolonged action when given by the former as compared with the latter routes. *A priori*, one would expect this to be true also of insulin, so that while it would be possible to produce the milder results of hypoglycaemia, such as perspiration, "sopor," etc., more rapidly with intravenous than with subcutaneous insulin, the action of the drug given intravenously would not be sufficiently prolonged to produce the much deeper hypoglycaemic state of coma with complete areflexia unless it was given in increased doses.

These hypotheses were then put to experimental proof:

(1) *Excretion of Intravenous Insulin in the Urine.*

The possibility that some of the insulin injected intravenously may be excreted quickly by the kidneys follows from the work of Fisher and Noble (1923), who were able to recover from a dog's urine 35 out of 40 units of insulin which had been given intravenously in divided doses of 10 units at hourly intervals under veronal anaesthesia. This work was confirmed by Bruger and Friedman (1938). Recordier and Andrac (1935) found that the hypoglycaemic action of insulin administered to dogs intravenously was consistently prolonged after bilateral nephrectomy. Goadby and Richardson (1940) injected 40 units of insulin into rabbits, and then injecting samples of blood withdrawn at varying intervals found that the blood-sugar level of the latter

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animals became depressed, and ascribed the hypoglycaemic effect to the insulin still in the blood of the first animal. Normally the hypoglycaemic effect could be induced if the blood were withdrawn within 90 minutes of the original injection, but if the kidneys were excluded from the circulation, the hypoglycaemic activity lasted considerably longer.

It would thus appear fairly certain that in animals insulin injected intravenously is partly excreted in the urine. The fact that it appears in the urine in a form capable of producing hypoglycaemia (Bruger and Friedman, 1935) indicates that it has been excreted before it has exercised its full hypoglycaemic effects, and it may therefore be that more insulin would be required to produce given results when administered intravenously than subcutaneously owing to its being excreted more rapidly when given by the former route.

The evidence for the excretion by the kidneys of insulin in normal and diabetic human subjects has been very conflicting. The literature is reviewed by Cutting (1942), who also devised a method by which 0·25 units insulin per 100 ml. urine, added *in vitro*, could be detected. She found that no insulin could be detected in normal urine, and that, if present, it must be there in amounts of less than 0·25 unit/100 ml.

Cutting's method consisted of adding 0·5 ml. of rabbit plasma to 100 ml. of urine which had been adjusted to a pH of 5·0 (isoelectric point of insulin). 32 gm. of crystalline ammonium sulphate was added to half-saturate the solution, and the mixture was stirred and kept in a warm place in order that the resulting precipitate which contained the insulin should flocculate. The precipitate was filtered out, dried and ground up in a mortar with 10 ml. of a borate buffer solution at pH 8·0. Some of the precipitate which did not dissolve was removed by centrifuge. The supernatant liquid which contained the insulin was then injected into test animals, and the blood-sugar curves estimated by the Hagedorn and Jenson method.

Dr. C. H. Gray kindly undertook the examination of the urine of 4 patients (2 male and 2 female) who were each given intravenous injections of 500, 750 and 1,000 units of insulin on successive days. The male patients were instructed to empty their bladders immediately before injection, and the female patients were catheterized. In order to ensure diuresis the patients were given 1 pint of plain water to drink immediately after the injection. Half an hour after injection the male patients emptied their bladders as far as possible spontaneously, while the female patients were catheterized. This was repeated one hour after the injection. Each patient was then given 250 c.c. of 33 per cent. glucose intravenously to abort or prevent the onset of hypoglycaemia, and this together with adequate sugar by mouth was found sufficient despite the large doses of insulin given.

The insulin was given in the large doses of 500, 750 and 1,000 units, because it was felt that if no insulin could be detected in the urine following such doses there was little point in attempting to find it using the usual doses necessary in Sakel's method (approximately 60–300 units).

Results.—Two specimens of urine, one at 30 minutes and the other at 60 minutes after the intravenous injection of 500, 750 and 1,000 units in each of 2 male and 2 female patients, were examined. All the tests were negative.

In view of the delicacy of the test by which insulin in the proportion of 0·25/100 ml. could be detected, the very large amounts of insulin injected, 500–1,000 units, and the unequivocal nature of the results, it must be concluded that no part of insulin injected intravenously in man is excreted in the urine.

(2) *Destruction of Intravenous Insulin by Circulating Substances in the Blood.*

The injection into the blood stream of the quantities of insulin given in the experiments (20–232 units) represents a very large increase over the minute quantity of insulin normally present, and it is possible that some of it may be neutralized by substances, such as adrenaline, which are already circulating in the blood. The large quantities injected make it unlikely that all the insulin would be destroyed in this way, but sufficient might be thus neutralized to account for the more temporary nature of the action of insulin administered intravenously, as compared with the more prolonged action of insulin given by the subcutaneous and intramuscular routes. To test whether this is so, the following experiment was carried out:

Experiment.—Four patients (2 male and 2 female) were selected and given no insulin for a fortnight. Each was then given 2 units of insulin daily for 24 days under the following conditions:

(*a*) On the first and succeeding *odd* days (1, 3, 5, etc.) 2 units of soluble insulin were given intravenously in the usual way and the blood-sugar levels charted during the following 150 minutes, by which time the blood sugar had returned to normal.

(*b*) On the second and succeeding *even* days (2, 4, 6, etc.) 100 c.c. of the patients' blood were removed from an ante-cubital vein, and to it were added 2 units of insulin, with very gentle mixing to ensure the even distribution of the insulin throughout the blood. The blood was then kept at 37° C. for 60 minutes and then injected into the patient intravenously. It was injected under pressure from a reversed Wolff's bottle, and the average time taken for the injection was 45–60 seconds. The blood-sugar level was then charted at intervals for the next 150 minutes. At the end of the 24 days there had been obtained for each of the 4

TABLE IV.

(A) 2 units of insulin intravenously.
(B) 2 units of insulin mixed with 100 c.c. of the patient's blood, kept at body heat for 1 hour and then injected intravenously.

	Fasting blood sugar.	Minutes after injection.											
		10.	15.	20.	25.	30.	35.	40.	50.	60.	75.	90.	120.	150.
Patient 1 (M.):														
(A)	99	75	70	61	62	55	57	61	67	73	80	88	94	95
(B)	94	74	63	60	56	53	55	60	70	75	81	88	94	99
Patient 2 (M.):														
(A)	94	76	72	69	66	62	63	69	77	82	87	91	94	94
(B)	95	76	71	69	66	63	65	69	78	85	86	93	94	95
Patient 3 (F.):														
(A)	91	73	66	58	48	49	51	58	64	71	76	85	90	90
(B)	92	73	65	57	50	49	51	56	64	71	76	84	90	91
Patient 4 (F.):														
(A)	89	66	59	52	46	46	47	53	58	68	76	82	88	89
(B)	92	67	59	52	46	44	46	53	60	75	75	82	88	90

TABLE V.—*Blood-sugar Values Following (A) the Intravenous Injection of 2 Units of Insulin and (B) Intravenous Injection of 2 Units of Insulin Mixed with 100 c.c. of the Subject's Blood and Kept at Body Heat for 60 Minutes.*

Day of experiment.	Fasting blood sugar.	Minutes after injection.											
		10.	15.	20.	25.	30.	35.	40.	50.	60.	75.	90.	120.	150.
Patient 1:														
1 (A)	97	70	63	54	54	57	61	65	67	68	76	81	95	96
2 (B)	101	75	68	57	53	45	53	62	71	73	79	83	98	99
3 (A)	93	72	66	61	56	56	57	59	65	68	73	79	91	94
4 (B)	97	70	61	59	52	55	57	61	67	72	77	85	99	98
5 (A)	92	74	69	63	56	54	57	65	67	74	77	82	88	90
6 (B)	89	69	63	56	55	53	59	63	69	77	75	81	89	92
7 (A)	97	75	65	61	56	57	59	68	70	73	76	80	91	93
8 (B)	93	79	69	63	59	57	61	61	68	69	77	83	92	89
9 (A)	89	74	66	61	66	66	61	65	75	79	86	89	88	89
10 (B)	99	72	65	64	59	59	59	61	73	75	77	81	95	96
11 (A)	98	76	66	64	57	59	57	63	75	81	89	95	99	99
12 (B)	91	71	52	57	52	51	49	55	67	77	85	87	89	86
13 (A)	99	82	76	70	65	52	56	53	66	72	83	93	96	96
14 (B)	87	78	68	59	57	57	56	62	69	81	87	89	89	89
15 (A)	91	75	70	63	52	52	54	54	59	66	79	87	89	89
16 (B)	96	76	67	62	58	55	57	65	69	76	81	89	94	95
17 (A)	102	75	68	59	58	57	58	61	70	76	81	93	99	101
18 (B)	93	73	61	63	55	53	57	63	67	71	75	87	92	93
19 (A)	108	76	68	64	61	59	59	56	68	75	87	99	104	104
20 (B)	97	77	63	67	59	53	54	61	71	77	81	95	96	94
21 (A)	91	71	61	56	52	45	54	61	65	78	84	89	90	90
22 (B)	95	75	68	55	54	44	49	57	67	82	87	97	96	91
23 (A)	92	74	65	55	49	45	54	52	56	63	72	85	93	93
24 (B)	95	71	65	59	56	49	47	49	59	73	79	93	93	96
Average blood-sugar levels:														
(A)	98	75	70	61	62	55	57	61	67	73	80	88	94	95
(B)	94	74	63	60	56	53	55	60	70	75	81	88	94	99
Patient 2:														
1 (A)	102	84	73	69	68	63	65	72	77	82	89	96	102	102
2 (B)	91	75	69	68	64	61	62	67	75	81	90	91	92	92
3 (A)	98	78	69	66	64	61	63	69	76	89	92	94	94	93
4 (B)	97	79	71	66	66	64	64	71	81	85	87	91	98	98
5 (A)	90	76	73	71	69	65	66	73	81	85	89	92	93	93
6 (B)	97	81	72	72	70	65	67	69	77	86	91	98	99	99
7 (A)	93	81	73	68	63	63	63	67	74	79	85	89	91	91
8 (B)	96	74	69	67	64	61	64	73	79	87	87	93	96	95
9 (A)	89	72	65	64	59	57	57	63	76	81	86	89	90	88
10 (B)	93	69	61	65	64	62	61	66	81	85	89	90	89	89
11 (A)	91	73	73	71	70	68	67	74	79	83	87	87	90	91
12 (B)	99	77	71	69	67	67	69	70	77	85	89	98	99	99
13 (A)	97	75	68	67	65	59	65	69	77	84	86	89	95	95
14 (B)	97	81	77	73	65	63	64	68	75	86	86	93	95	98
15 (A)	95	79	73	71	67	61	63	67	84	87	85	91	96	96
16 (B)	93	73	71	71	70	76	70	74	81	86	89	91	92	93
17 (A)	96	81	74	69	63	59	59	66	77	83	89	93	93	93
18 (B)	97	78	76	73	65	63	63	69	81	79	85	94	94	96
19 (A)	96	82	76	74	68	65	65	69	76	81	87	89	93	95
20 (B)	99	78	72	71	65	61	64	68	77	83	91	102	98	98
21 (A)	94	77	69	67	65	61	63	69	74	79	79	89	92	92
22 (B)	91	74	73	70	67	57	65	69	79	89	89	90	91	91
23 (A)	99	79	73	71	68	63	65	71	71	81	87	99	98	99
24 (B)	91	72	72	68	63	61	61	68	75	85	89	90	89	89
Average blood-sugar levels:														
(A)	94	76	72	69	66	62	63	69	77	82	87	91	94	94
(B)	95	76	71	69	66	63	65	69	78	85	86	93	94	95

TABLE V.—(*Contd.*)

Day of experiment.	Fasting blood sugar.	Minutes after injection.												
		10.	15.	20.	25.	30.	35.	40.	50.	60.	75.	90.	120.	150.
Patient 3:														
1 (A)	89	74	65	59	55	54	55	60	62	68	74	79	87	87
2 (B)	94	71	67	57	53	53	49	57	67	69	75	78	91	91
3 (A)	93	72	63	55	48	48	53	59	63	67	73	81	89	92
4 (B)	87	68	65	51	51	47	49	61	64	65	69	77	87	87
5 (A)	87	71	68	55	45	46	48	55	61	69	76	84	89	90
6 (B)	91	75	61	56	51	43	47	47	59	71	78	90	91	90
7 (A)	91	75	67	58	49	48	49	56	65	72	77	89	90	90
8 (B)	95	69	67	61	44	47	51	57	67	69	78	87	94	94
9 (A)	92	73	64	59	54	56	59	63	69	73	75	86	85	85
10 (B)	89	71	61	53	51	51	61	65	67	71	71	79	86	87
11 (A)	94	69	64	54	47	48	47	57	64	71	79	87	94	93
12 (B)	91	73	65	57	51	49	55	55	61	69	76	84	90	90
13 (A)	90	75	67	58	51	51	53	58	67	67	75	84	89	89
14 (B)	93	74	65	57	56	47	46	54	63	71	77	84	87	87
15 (A)	89	76	66	59	52	52	52	59	69	72	78	89	88	89
16 (B)	93	70	59	60	49	49	47	57	71	78	81	90	94	94
17 (A)	94	71	66	62	48	47	46	54	58	68	73	85	90	93
18 (B)	91	67	71	57	43	49	48	53	54	71	76	84	90	90
19 (A)	91	73	64	59	51	52	51	57	63	69	75	83	92	91
20 (B)	92	74	67	57	53	53	53	53	59	67	71	79	91	95
21 (A)	92	74	67	62	45	44	48	55	64	71	77	87	90	90
22 (B)	97	74	71	64	49	51	51	56	59	69	79	87	95	97
23 (A)	95	76	65	57	46	49	53	58	67	69	78	91	93	96
24 (B)	89	73	61	57	45	44	49	61	71	78	83	86	89	90
Average blood-sugar values:														
(A)	91	73	66	58	48	49	51	58	64	71	76	85	90	90
(B)	92	73	65	57	50	49	51	56	64	71	76	84	90	91
Patient 4:														
1 (A)	84	63	57	47	42	41	43	48	55	67	74	83	86	86
2 (B)	87	65	63	55	48	43	42	47	57	68	69	77	81	83
3 (A)	90	69	60	53	46	45	44	51	60	71	77	85	92	93
4 (B)	86	67	59	52	47	45	44	52	59	67	81	89	89	89
5 (A)	88	65	56	47	43	41	44	47	54	67	76	89	87	87
6 (B)	87	67	55	46	43	43	43	52	63	70	77	84	86	85
7 (A)	91	71	57	50	49	49	49	54	59	65	79	85	90	90
8 (B)	93	63	59	52	45	42	47	55	57	68	79	87	92	93
9 (A)	87	65	58	52	51	50	54	59	63	69	81	87	86	85
10 (B)	94	66	57	51	46	46	47	54	64	71	78	89	93	93
11 (A)	90	63	55	52	47	45	48	54	59	70	78	89	93	94
12 (B)	95	71	61	56	51	43	47	59	63	65	80	88	96	90
13 (A)	91	67	55	50	46	46	47	55	61	72	80	83	86	89
14 (B)	89	65	59	53	41	41	44	57	59	67	75	65	90	92
15 (A)	93	70	59	52	50	51	51	53	57	64	73	85	90	92
16 (B)	89	67	53	48	46	47	48	49	63	68	79	90	92	91
17 (A)	87	71	67	56	47	48	49	52	58	67	68	77	82	87
18 (B)	93	64	59	52	49	49	49	55	63	69	72	85	85	93
19 (A)	88	65	65	57	43	46	49	53	59	67	70	70	86	86
20 (B)	94	68	57	51	47	43	54	57	58	65	61	74	87	90
21 (A)	90	61	62	49	49	48	48	56	61	68	77	76	84	90
22 (B)	95	71	59	49	49	46	45	51	59	69	79	79	85	93
23 (A)	91	63	60	53	41	43	44	49	55	66	73	73	89	92
24 (B)	87	66	63	55	45	38	39	50	59	70	73	77	81	88
Average blood-sugar values:														
(A)	89	66	59	52	46	46	47	53	58	68	76	82	88	89
(B)	92	67	59	52	46	44	46	53	60	75	75	82	88	90

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patients 12 blood-sugar charts following the injection of 2 units of insulin which had been previously mixed with 100 c.c. of the patient's blood at body heat for one hour.

Results.—The results obtained are set out in detail in Table V, but the average readings of the blood-sugar levels obtained with the two kinds of injections may be summarized in Table IV.

It will be seen from Table IV that the blood-sugar values obtained in both groups, (A) and (B), are identical within the limits of the experiment. The effect on the blood sugar after 2 units of insulin have been incubated with 100 c.c. of the patient's blood at body heat for 60 minutes is of the same order as when this quantity of insulin is injected by itself. Taking the average blood volume in the adult to be 6 litres (Samson Wright, 1945), 2 units per 100 c.c. is equivalent to 120 units for the total blood volume, and were there any circulating substances in the blood ready to destroy injected insulin, it is probable that there would have been a definite neutralization of some at least of the insulin during the hour it was incubated with the blood at 37° C., with a consequent reduction of its effect upon the blood sugar following re-injection. No such diminution in activity could be found, however, as the blood-sugar values are practically identical with those obtained after the intravenous injection of 2 units of insulin in the usual way.

Conclusion.—It must, therefore, be concluded that the more temporary action of intravenous as compared with intramuscular insulin is not due to the neutralization of part of the intravenous insulin by substances already circulating in the blood stream. This conclusion, of course, does not exclude the possibility that, after insulin has been injected intravenously, a neutralizing substance might not then be poured into the blood stream to neutralize part of it, but it was not found possible in the time available to design experiments to test this possibility.

(3) *That a Portion of Intravenous Insulin is Used Up in Producing its Rapid Action on the Blood Sugar, so that Insufficient is Left to Prolong the Hypoglycaemia as is the Case with Intramuscular and Subcutaneous Insulin.*

It is well known that insulin given intravenously produces a more rapid fall in the blood sugar than when it is administered subcutaneously or intramuscularly. Sandison and McGregor (1942) also claim that patients become more easily sensitized to intravenous insulin, while several authors, e.g. Bardenat and Leonardon (1939), Reznikoff and Scott (1942) find that coma induced in this way is quieter than coma induced by the other parenteral routes. The question, therefore, arises whether there is any fundamental difference in the action of insulin when it is administered in different ways. Experiments were devised to see whether any such difference exists.

Experiment: Rate of absorption of insulin into the blood following injection.—One difference between intravenous and intramuscular injection is that by the first route all the insulin enters the blood stream almost instantaneously, whereas by the second route, a deposit of insulin is formed in the tissues, from which it is probably absorbed into the blood at a much slower rate. The

difference in action between intravenous and intramuscular insulin may, therefore, be entirely a question of *the rate at which the substance is absorbed into the blood stream.*

To test this hypothesis two patients were given insulin under the following conditions:

Increasing doses of insulin (20–132 units and 20–120 units) were added to three pints of isotonic saline and injected by intravenous drip over a period of 240 minutes. The injections were given at intervals of four days to avoid sensitization of the patient to the insulin, and blood-sugar estimations were made at 30, 60, 90, 120, 150, 180, 210, 240 and 270 minutes after the commencement of the intravenous drip. The blood-sugar results are set out in detail in Table VI, from which it will be seen that *although the insulin was given intravenously, the blood-sugar curve resembles that obtained after an intramuscular injection,* with the blood sugar reaching its lowest level in about 120 minutes after the commencement of the injection. This would seem to indicate that the apparent difference in the action of intravenous and intramuscular insulin is entirely due to the different rates at which the insulin enters the blood stream, since if insulin enters the blood by the intravenous route at a sufficiently slow rate, a blood-sugar curve of the intramuscular and not the intravenous type is produced.

To test the hypothesis further, each of three patients were then given 60, 40 and 20 units of insulin respectively as follows:

On the first morning the quantity of insulin (60, 40 or 20 units) was mixed with three pints of normal saline and given by intravenous drip over a period of 240 minutes. The patient given 60 units was therefore receiving insulin intravenously at the rate of 0·25 units per minute. The blood sugar was estimated at intervals of 15, 20, 25, 30, 35, 45, 60, 90, 120, 150, 180, 210, 240 and 270 minutes (Table VII). It was again found that although the insulin was given intravenously, the blood-sugar curve obtained was of the same type as that produced by intramuscular or subcutaneous insulin. The blood sugar reached its minimum level in 90 minutes as opposed to the usual 20–35 minutes,

TABLE VI.—*Blood-sugar Values Following Varying Doses of Insulin Given in Saline by Intravenous Drip Over 240 Minutes.*

Units of insulin.	Fasting blood sugar.	Minutes after commencement of intravenous drip.								
		30.	60.	90.	120.	150.	180.	210.	240.	270
Patient 1:										
20	76	65	56	54	38	37	39	38	38	36
40	79	48	42	36	36	36	39	39	36	39
60	81	65	43	32	34	27	29	32	32	36
80	90	43	38	29	27	25	27	27	27	27
100	101	61	39	36	27	31	29	26	26	25
120	90	55	27	31	27	26	27	31	29	27
132	92	47	31	29	22	24	20	19	20	24
Patient 2:										
20	92	81	74	68	63	59	54	57	54	50
40	86	65	61	59	55	52	36	31	39	48
60	98	74	60	58	56	45	34	28	28	36
80	88	72	56	54	48	45	32	27	25	29
100	92	74	57	43	32	32	27	25	27	34
120	90	72	54	38	32	29	27	29	30	31

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TABLE VII (A).—*Blood-sugar Values Following* 60 *Units of Insulin Given in Saline by Intravenous Drip Over Varying Periods of Time at Intervals of Four Days.*

Column (1): Length of time in minutes over which drip was given.
Column (2): Fasting blood sugar.

Column (1).	Column (2).	Minutes after commencement of intravenous drip.													
		15.	20.	25.	30.	35.	45.	60.	90.	120.	150.	180.	210.	240.	270.
240	98	84	80	77	72	68	63	52	26	24	24	29	25	25	32
210	95	77	75	70	68	64	60	46	37	27	30	29	25	27	39
195	92	73	69	63	58	56	49	38	38	32	29	29	22	25	41
180	93	75	67	54	62	58	50	34	31	31	31	31	33	36	59
150	92	71	68	62	58	55	49	34	33	32	32	32	32	42	57
120	88	70	65	58	52	48	42	29	31	33	34	34	43	59	70
90	86	70	66	59	49	52	45	31	27	29	43	50	52	66	70
60	88	69	63	53	52	48	40	24	27	31	36	43	59	68	81
45	86	61	54	46	38	34	28	17	22	31	43	63	74	79	75
35	84	57	50	43	34	28	26	24	29	29	39	52	70	79	83
20	88	62	53	54	37	32	28	29	41	49	59	63	72	79	83
15	92	63	55	49	35	31	29	34	34	47	57	67	77	83	89
7	92	62	53	47	39	34	28	29	31	41	50	61	74	79	83
3	96	66	57	50	38	31	32	32	34	50	52	65	68	78	86
0	98	67	59	51	34	34	32	32	32	42	53	59	72	74	81

TABLE VII (B).—*Blood-sugar Values Following* 40 *Units of Insulin Given in Saline by Intravenous Drip Over Varying Periods of Time at Intervals of Four Days.*

Column (1): Length of time in minutes over which drip was given.
Column (2): Fasting blood sugar.

Column (1).	Column (2).	Minutes after commencement of intravenous drip.											
		25.	30.	35.	45.	60.	90.	120.	150.	180.	210.	240.	270.
240	92		58			33	31	27	25	27	28	28	30
210	88		70			41	35	29	33	34	33	31	34
180	97		65			41	29	31	31	36	35	43	51
150	92		59			46	37	36	33	33	34	36	47
120	95		56			33	36	36	35	37	41	46	54
90	96		58			36	31	33	41	49	52	54	65
60	89		54			31	33	34	37	54	58	71	83
45	97		45			27	28	33	45	67	73	84	89
30	92	54	39	30	25	27	33	41	53	58	76	85	89
20	98	46	37	31	30	30	43	57	67	77	82	89	95
15	93	39	38	29	30	31	45	51	59	71	86	89	94
7	95	41	33	34	26	27	33	43	61	79	91	94	93
3	91	37	34	31	29	29	37	45	56	73	79	83	87
0	92	34	23	29	29	33	41	43	57	65	74	81	89

TABLE VII (C).—*Blood-sugar Values Following* 20 *Units of Insulin Given in Saline by Intravenous Drip Over Varying Periods of Time at Intervals of Four Days.*

Column (1): Length of time in minutes over which drip was given.
Column (2): Fasting blood sugar.

240	102		66			38	36	29	28	25	32	34	38
210	92		75			54	41	32	34	31	34	31	41
180	86		70			57	34	32	32	39	36	39	54
150	92		61			51	47	42	36	34	36	38	46
120	93		59			46	43	38	38	43	41	41	56
90	97		61			49	41	39	40	39	34	38	51
60	99		63			39	35	39	41	50	62	75	89
45	101		69			42	34	36	47	72	81	89	96
30	110	53	45	39	34	36	39	51	66	68	84	95	104
20	91	47	42	41	35	36	49	64	87	91	89	90	92
15	95	42	39	39	33	37	46	67	79	89	89	93	93
7	95	53	42	40	31	35	47	71	85	92	96	95	96
3	98	49	43	39	36	37	43	69	89	89	95	98	99
0	94	56	45	41	36	39	51	74	83	87	91	91	90

and this level was maintained until the intravenous drip was stopped after 240 minutes.

In order to minimize the effect of sensitization through daily injections of insulin, the patients were then rested for three days, and on the fourth day the experiment was repeated, but the insulin in saline was given over a period of 210 minutes. On succeeding fourth days the period over which the drip was given was progressively shortened through the following periods: 195, 180, 150, 120, 90, 60, 45, 35, 20, 15, 7, 3 and 0 minutes. At the same time the amount of normal saline with which the insulin was mixed was gradually reduced from three pints to *nil*, as the period over which it was given became progressively shorter. *It was found that as the period over which the insulin in saline was injected became shorter, so the character of the blood-sugar curve changed gradually from a typical subcutaneous curve to a typical intravenous curve.* The latter was found when 20 minutes or less were taken over the injection.

From the above results it appears that there is no fundamental difference in the action of insulin, whatever the parenteral route used to administer it. The character of the blood-sugar curve produced depends solely upon the rate at which the insulin enters the blood stream, since if intravenous insulin is given in small quantities over a long period (about 240 minutes) the blood-sugar curve is of the subcutaneous and not the intravenous type.

It remains to inquire into the mode of action of insulin injected rapidly by the intravenous route in the usual way. Why is it that intravenous insulin is unable to prolong the fall in the blood sugar, in the way that subcutaneous insulin does, so that, as we have seen, it is relatively inefficient in producing the signs of hypoglycaemia? Blood-sugar curves following intravenous insulin differ from those obtained with subcutaneous insulin mainly in the more rapid and profound fall in the blood sugar. Whereas with subcutaneous insulin the maximum fall in the blood sugar occurs about 90 minutes after the injection, with intravenous insulin the maximum fall is reached in 20–35 minutes, the exact time depending on the amount of insulin injected. In addition, the fall after intravenous insulin is always more profound than that after intramuscular insulin, although this fall cannot be maintained.

We have, therefore, to consider the relationship between the amount of insulin injected and (1) the *extent* of the fall in the blood sugar and (2) the *rate* of this fall.

If the curve of the graph of the relationship is a *rectangular hyperbole*, as shown below, then, since $xy = c$, small doses of insulin will cause a considerable initial fall in the blood sugar, but further decreases can only be achieved by the expenditure of increasingly large doses of insulin until a point is reached when further increases in the amount of insulin, no matter how large, are unable to reduce the blood sugar any further. Considerably more insulin will be required to produce the more intense falls in the blood sugar. *A portion at least of the insulin would be used up in producing the intense fall, and would be unavailable for prolonging the fall in the blood sugar which is necessary for the development of the more pronounced signs of hypoglycaemia, so that a greater quantity of insulin would be required to produce these pronounced effects than would be required by the intramuscular or subcutaneous route.*

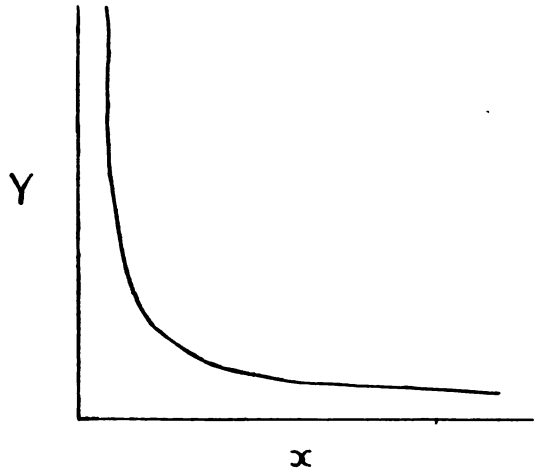
Experiments were then designed to find the relationship between the amount of insulin injected and the extent and rate of the fall in the blood sugar.

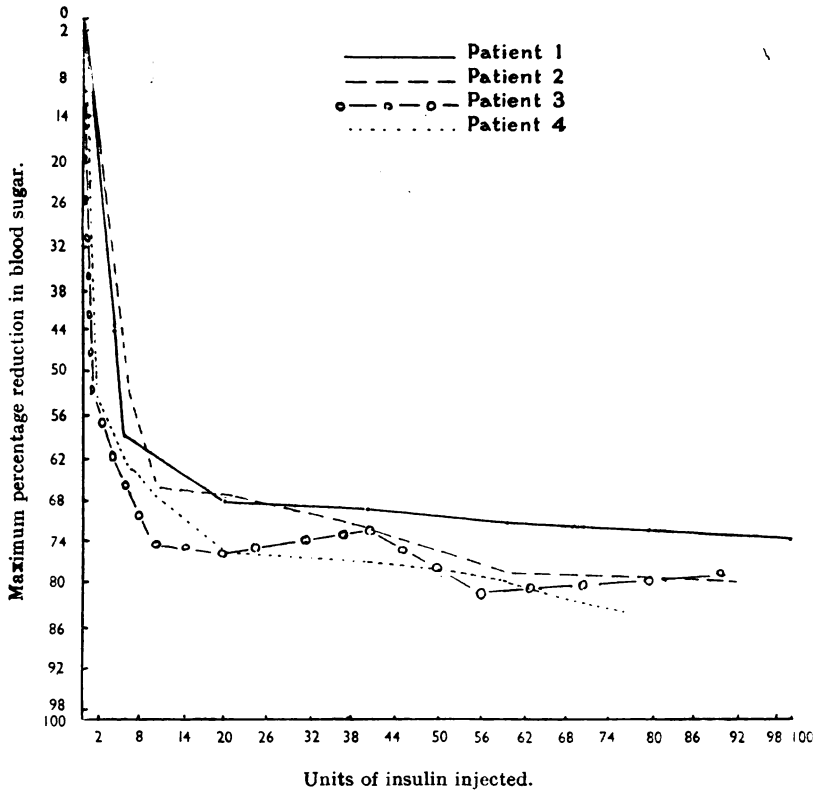
(1) *The Relationship Between the Amount of Insulin Injected and the Extent of the Consequent Fall in the Blood Sugar.*

Four patients were given increasing doses of insulin from 2–170 units at 4-day intervals to avoid sensitization, and the minimum blood value obtained with each dose was noted. From this value the percentage fall in the blood sugar was calculated. The results are given in detail in Table VIII, and from this a graph (Graph 1) was prepared for each patient in which the percentage fall in the blood sugar (ordinate (y)) was placed against the number of units of insulin injected (abscissa (x)). The graph has to be interpreted in the light of the conditions of the experiment, especially that of the patients' diet, which did not have a constant carbohydrate content as the patients ate as much as they wished (Himsworth, 1939). It will be seen, however, that the general form of the curves of the graph resembles that of a rectangular hyperbole. In Patient 4, for instance, 2 units of insulin produced an initial fall of 52 per cent. in the blood sugar, but 6 units (3 x) produced a fall of only 62 per cent. (1·2 x); 10 units (5 x), a fall of 67 per cent. (1·3 x); and 20 units (10 x), a fall of 75 per cent. (1·4 x). In general, the maximum fall of 70–80 per cent. was achieved by 10 units, after which the curve almost completely flattened out, so that high multiples of the original 2 units, which produced an initial fall of 52 per cent., were eventually required to produce a fall of a few milligrams per cent.

TABLE VIII.—*Minimum Blood-sugar Values Obtained with Increasing Doses of Intravenous Insulin.*

Units of insulin.	Fasting blood sugar.	Minimum blood sugar obtained.	Percentage reduction in blood sugar.	Units of insulin.	Fasting blood sugar.	Minimum blood sugar obtained.	Percentage reduction in blood sugar.
Patient 1:				*Patient* 2:			
2	97	54	44	2	94	63	33
6	101	41	59	6	89	42	55
10	95	36	62	10	91	31	66
20	106	34	68	20	75	25	67
40	108	34	69	40	79	22	72
60	92	27	71	60	92	19	79
80	97	27	72	80	95	19	80
100	99	27	73	86	89	21	76
120	88	23	74	92	93	19	80
140	102	28	73	100	101	19	81
160	94	25	73	110	99	15	85
170	96	25	74	118	95	17	82
Patient 3:				*Patient* 4:			
2	97	46	53	2	98	47	52
6	94	31	67	6	93	35	62
10	101	27	74	10	97	32	67
20	95	24	75	20	115	29	75
40	99	29	72	40	100	23	77
56	97	17	82	52	97	21	78
68	102	20	80	60	95	19	80
80	115	23	80	68	108	19	82
92	97	20	79	76	117	17	85
104	108	19	82	—	—	—	—
114	96	21	78	—	—	—	—





GRAPH 1.—Relationship between the amount of insulin injected and the extent of the fall in the blood sugar. (Compiled from Table VIII.)

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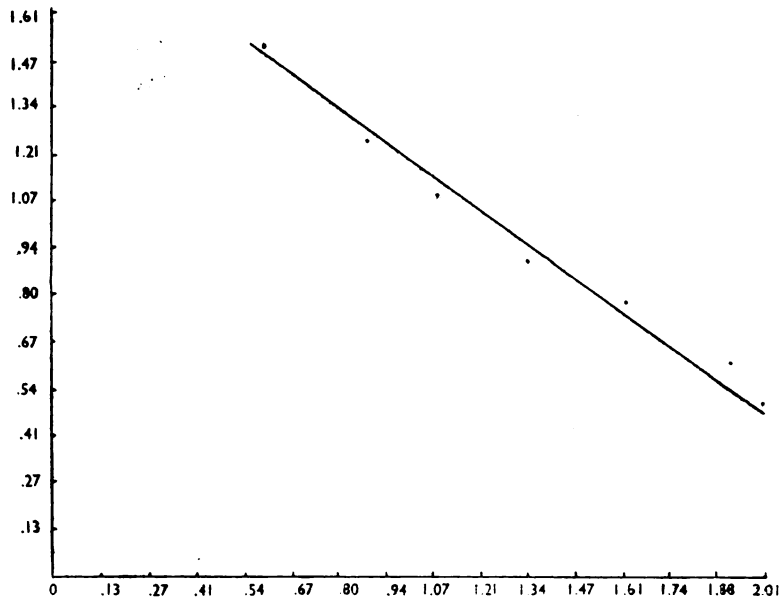

GRAPH 2.—Curve of the graph of log $(x + a)$ against log $(y - b)$.

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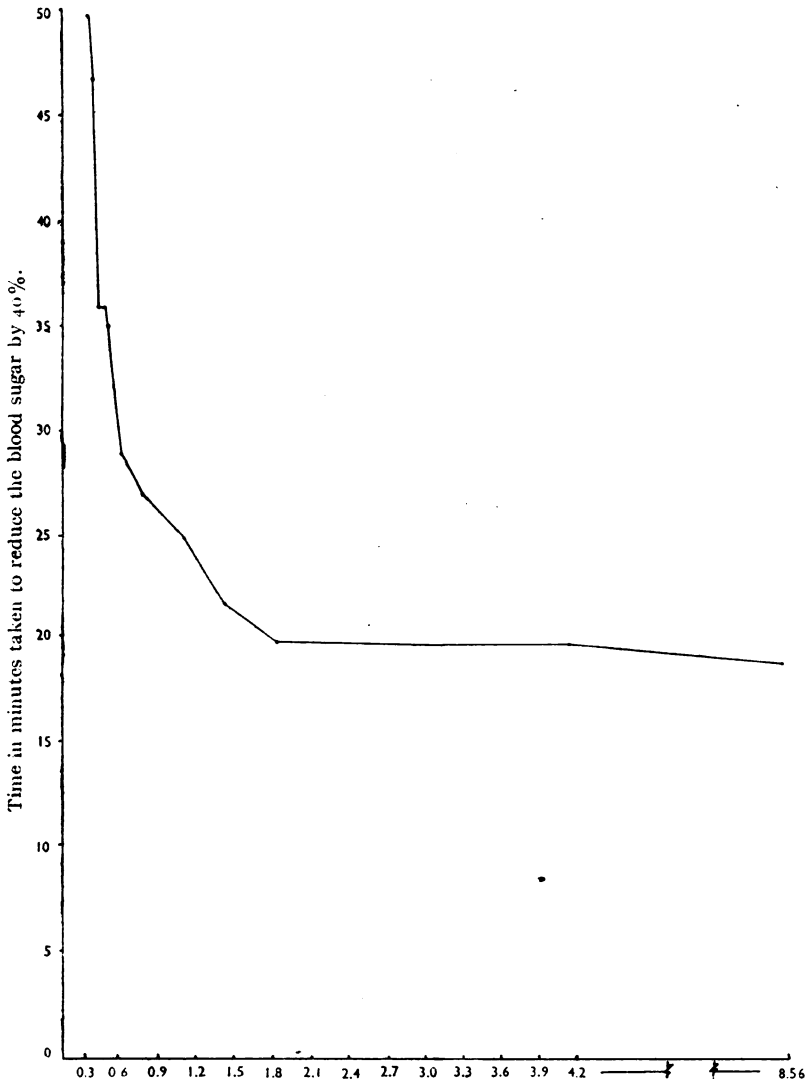

GRAPH 3.—Times taken by varying amounts of intravenous insulin to reduce the blood sugar by 40%. (Compiled from Table X.)

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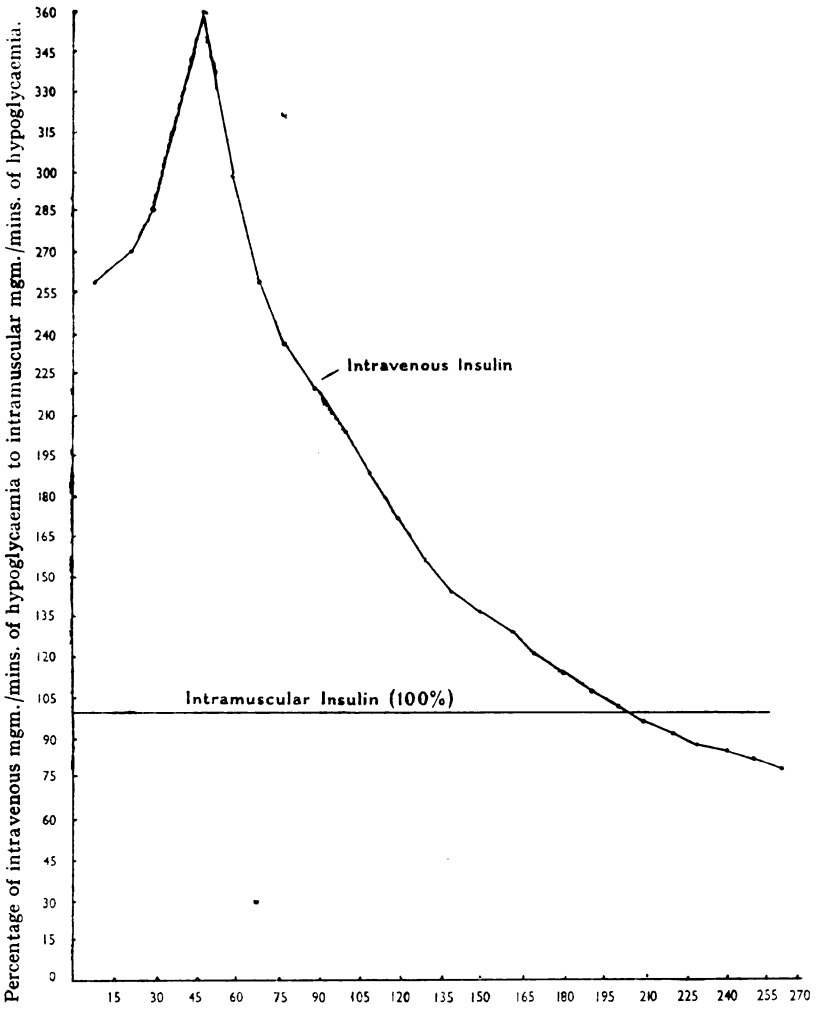

GRAPH 4.—Mgm./mins. of hypoglycaemia at varying times after intravenous injection of insulin expressed as the percentage of mgm./mins. of hypoglycaemia produced by intramuscular insulin at the same times after injection. (Compiled from Table XI.)

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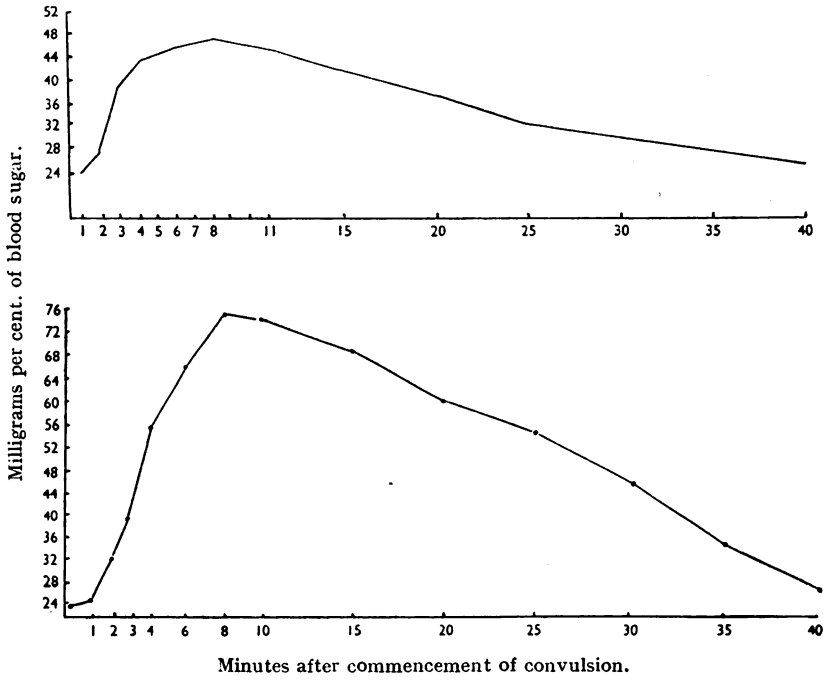

GRAPH 5.—The upper figure shows the behaviour of the blood sugar following a spontaneous insulin convulsion; the lower figure shows the behaviour of the blood sugar following a phrenazol convulsion induced during hypoglycaemia.

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Taking the curve of Patient 1 in detail, the following table can be constructed:

$x =$ 2	6	10	20	40	60	80	100
$y =$ 44	59	62	68	70	71	72	73

Changing y into 100-y so as to make both axes start at zero, we get—

$x =$ 2	6	10	20	40	60	80	100
$y =$ 56	41	38	32	30	29	28	27

$xy = c$ can also be rendered $\log (x + a) + \log (y - b) = C$. If there is any relationship of this latter form in the above table, i.e. if the original curve is a rectangular hyperbole, the curve of the graph of $\log (x + a)$ against $\log (y - b)$ would be a straight line.

For this particular curve it is reasonable to make $a = 2$ and $b = 24$. This leads to the table:

$x + 2 =$ 4	8	12	22	42	62	82	102
$y - 24 =$ 32	17	14	8	6	5	4	3

Expressing this table in logarithms we get:

$\log (x + 2) =$ ·60	·90	1·08	1·34	1·62	1·79	1·91	2·01
$\log (y - 24) =$ 1·51	1·23	1·15	·90	·78	·70	·60	·48

This is plotted in Graph 2 and the fit of the observed points to the line is good.

Owing to the difficulty in giving a biological meaning to the variables in the fitting of a hyperbolic curve, it is not claimed that the above curve shows anything more than consistency with the view that profound falls in the blood sugar can only be achieved by the use of disproportionately large doses of insulin *which are used up in producing the fall*. This result is in agreement with Himsworth's (1939) conception of the "head of pressure" nature of the blood sugar. The more profound the fall in the blood sugar, the more serious is the effect upon the metabolism of the tissues. A 10 per cent. fall from an already low blood sugar of 40 per cent. to 30 per cent. has much more serious effect on the tissues than an equal fall from 80 per cent. to 70 per cent. Therefore the more profound the fall the greater will be the activity of the anti-insulin mechanism to prevent any further fall, so that the more the blood sugar is reduced, the greater the amount of insulin required to reduce it still further.

(2) *The Relationship Between the Amount of Insulin Injected and the* RATE *of the Consequent Fall in the Blood Sugar.*

This relationship was deduced from the results obtained by injecting 60 units of insulin in saline over varying periods from 240–0 minutes (Table VII). Owing to the variation in the fasting blood levels, the blood-sugar values obtained in this experiment were recalculated as percentages of the fasting blood-sugar values, and these percentages are set out in Table IX. From this table was then calculated the *time*, in minutes, taken by increasing doses of insulin (0·25–8·56 units of insulin per minute) to reduce the fasting blood sugar

by the arbitrarily chosen amount of 40 per cent. The results of the calculation are given in Table X and in graph form in Graph 3. It will be seen that as with the relationship between the amount of insulin injected and the *extent* of the fall in the blood sugar, so the relationship between the amount of insulin and the *rate* of the fall in the blood sugar is of the rectangular hyperbole type. From the graph we find that 0·25 units of insulin will reduce the blood sugar by 40 per cent. in 50 minutes. To reduce it to this figure in 25 minutes (2 x) not 0·5 units, but 1·0 units (4 x) is required. To reduce it in 20 minutes (2·5 x), 1·71 units (7 x) are required. After 1·71 units per minute the curve flattens out, so that very large increases of insulin are required to reduce the blood sugar by 40 per cent. in 19 minutes (8·56 units per minute), after which further increases, however large, are unable to reduce the time beyond this minimum. It follows, therefore, that increase in the rate at which the blood sugar is reduced can only be achieved by the expenditure of *disproportionately large quantities of insulin which are used up in the production of the increased rate of fall.*

The relationship between the amount of insulin injected and the *extent* and *rate* of the consequent fall in the blood sugar have been considered separately, and the graphs of both relationships have been shown to be of the rectangular hyperbole type. In practice, of course, the relationships cannot be so separated, since the amount of insulin injected influences both the extent and rate of the fall in the blood sugar simultaneously ; but the fact that the graph of each relationship is of the rectangular hyperbole type indicates that when the extent and rate are influenced simultaneously, still more disproportionately large amounts of insulin will be required to, say, double the percentage fall in the blood sugar in half the time.

From the above experiments and calculations it follows that as a proportion of insulin injected intravenously is used up in producing the rapid, profound fall in the blood sugar which follows this mode of administration, insufficient insulin is left to prolong the hypoglycaemia at a sufficiently low level for coma to ensue. In this connection it may be pointed out that as long ago as 1930 Nordsted, Norgaard and Thaysen (1930) found a lag between the fall in the blood sugar and the development of even mild hypoglycaemia symptoms. Signs of hypoglycaemia could even develop as the blood sugar was returning to normal. This time lag is due, of course, to the fact that the tissues themselves have to be deprived of glucose before the signs of hypoglycaemia can develop, and this deprivation does not occur immediately the blood sugar falls, but some time afterwards. Freudenberg (1938) and Freudenberg and Fine (1940) pointed out that the blood sugar had to be maintained below 30 mgm. per cent. for about 90 minutes before unconsciousness would ensue, and for about 200 minutes before the corneal reflexes would disappear. In assessing the efficacy of any method of administering insulin in the production of hypoglycaemic symptoms it is necessary, therefore, to have regard as much to the time during which the level of the blood sugar can be depressed as to extent and rate of the initial fall in the blood sugar, since unless a profound and rapid initial fall can be maintained for a sufficient length of time, hypoglycaemic symptoms will be less than with a smaller, less rapid fall maintained for a longer period.

TABLE IX.—*Percentage Reduction in Blood Sugar Following 60 Units of Insulin Given in Saline by Intravenous Drip Over Varying Periods of Time at Intervals of Four Days. (Compiled from Table VII (A).)*

Column (1): Units of insulin injected per minute during intravenous drip.
Column (2): Length of time in minutes over which drip was given.
Column (3): Fasting blood sugar.

Column (1).	Column (2).	Column (3).	Minutes after commencement of intravenous drip.													
			15.	20.	25.	30.	35.	45.	60.	90.	120.	150.	180.	210.	240.	270.
0·25	240	98	16	18	21	26	30	35	47	73	75	75	70	74	74	67
0·29	210	95	19	23	26	28	33	37	51	61	71	68	69	73	71	59
0·31	195	92	21	25	31	37	39	47	58	58	65	68	68	76	73	55
0·33	180	93	19	28	31	32	38	46	63	67	67	67	67	65	61	37
0·40	150	92	23	26	32	37	40	47	63	64	65	65	65	65	54	38
0·50	120	88	20	26	34	41	46	52	67	65	63	61	61	51	33	20
0·67	90	86	18	23	31	46	40	48	64	69	66	50	42	39	23	19
1·00	60	88	22	28	39	41	45	55	73	69	65	59	51	33	23	8
1·33	45	86	29	37	47	56	61	67	80	74	64	50	27	14	8	13
1·71	35	84	32	40	49	60	67	69	71	66	66	54	38	15	6	1
3·00	20	88	29	40	39	58	64	68	67	53	44	33	28	18	10	5
4·00	15	92	31	40	47	62	66	68	63	63	49	39	27	16	10	3
8·56	7	92	32	42	48	58	63	70	68	66	55	46	34	20	14	10
20·00	3	96	31	41	48	60	68	67	67	65	48	46	33	29	20	10
60·00	0	98	32	31	48	65	65	67	67	67	47	46	40	27	24	17

TABLE X.—*Length of Time Taken by Varying Amounts of Insulin to Reduce the Blood Sugar by 40 mgm. per cent. Calculated from Table IX above.*

Column (1): Units of insulin injected per minute.
Column (2): Length of time taken by given amount of insulin to reduce the blood sugar by 40 mgm. per cent.

Column (1).	Column (2).	Column (1).	Column (2).
0·25	50	1·0	25
0·29	47	1·33	22
0·31	36	1·71	20
0·31	36	3·00	20
0·40	35	4·00	20
0·50	29	8·50	19
0·67	27	20·00	19

The hypothesis that a portion of insulin given intravenously is used up in producing the rapid and profound fall in the blood sugar indicated by the above experiments on the relationship between the amount of insulin injected and the extent and rate of the fall in the blood sugar would, therefore, be confirmed if it could be shown that the total amount of hypoglycaemia produced by a given quantity of intravenous insulin is less than that produced by the same quantity of intramuscular insulin.

It is necessary, therefore, to determine the power of intravenous and intramuscular insulin to produce hypoglycaemia in relation to the time over which it is produced, since the duration of the action is as important as its intensity. Unfortunately, there is no unit of "the degree x the duration of hypoglycaemia" available, and it is usual to express this quantity in terms of milligram/minutes of hypoglycaemia. If the same dose of insulin is injected first intramuscularly and then intravenously on separate occasions, from the blood-sugar curves obtained following the injection it is possible to calculate the milligram/minutes of hypoglycaemia produced over any desired period, and the two methods of injection can be compared with respect to the total milligram/minutes of hypoglycaemia produced before the blood sugar returns to normal.

Experiment.—The blood-sugar curves obtained from Patient 1 (Table II) following the injection of 20 units of insulin intramuscularly and intravenously were investigated and the total milligram/minutes of hypoglycaemia produced after 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260 and 270 minutes from the time of the injection was calculated. The results are set out in detail in Table XI, from which it will be seen that for some time after the injection, intravenous insulin produces very many more milligram/minutes of hypoglycaemia, but that later it fails to hold this lead, and ultimately is surpassed by the intramuscular insulin. For example, after 10 minutes intravenous insulin has produced 255 per cent. more milligram/minutes of hypoglycaemia than the intramuscular insulin. This preponderance reaches its highest level at 360 per cent. after 50 minutes, following which it steadily declines, so that each method has produced approximately the same number of milligram/minutes of hypoglycaemia after 210 minutes, and after 270 minutes the intramuscular insulin has actually produced 21 per cent. more than the intravenous. As Sakel's treatment is not usually given for longer periods than about five hours each day, the experiment was terminated at 270 minutes, before the blood sugar following intramuscular insulin has returned to normal. Had the experiment been continued until the intramuscular blood sugar had returned to normal, the superiority of intramuscular over intravenous insulin in terms of total milligram/minutes of hypoglycaemia would have been even more striking.

From the percentages of " intravenous milligram/minutes of hypoglycaemia to intramuscular milligram/minutes of hypoglycaemia " given in Table XIV, the graph of Graph 4 has been contructed. This brings out the conclusion noted above that intravenous insulin is more efficient for some time after the injection, but less efficient later on than intramuscular insulin in terms of production of milligram/minutes of hypoglycaemia. From this early superiority of intravenous insulin, it follows that insulin given in this way may be more efficient than intramuscular insulin in producing the milder degrees of hypoglycaemia, such as sweating, pallor, etc., but its later inferiority shows that it will be less efficient in producing the more pronounced degrees of hypoglycaemia, such as coma according to Wilson's (1937) standard. It has already been pointed out that different authors have varying standards of coma, and it is possible that some authors, e.g. Sandison and McGregor (1942), have found that a smaller dose of intravenous as compared with subcutaneous insulin would induce coma because their standard of coma has been a light one, whereas, had they adopted Wilson's (1937) standard of complete areflexia, they would have found that a larger dose was required. That this is probably so is shown by Table III, from which it will be seen that slightly smaller doses of intravenous than intramuscular insulin will induce " sopor " (unconsciousness), whereas considerably larger doses are required to produce coma with Babinski plantar responses and absent corneal reflexes.

The conclusions which may be drawn from the experimental work described so far will be summarized fully later. It may be stated briefly here that the value of intravenous insulin in Sakel's hypoglycaemic coma depends upon the depth of coma which the therapist wishes to produce. If it is desired only to

produce hypoglycaemic unconsciousness, the intravenous insulin is preferable to intramuscular as a smaller dose is required, and with the more rapid return of the blood sugar to normal the danger of post-hypoglycaemic coma developing is diminished. If, however, the considerably deeper hypoglycaemic state

TABLE XI.—*Milligram/Minutes of Hypoglycaemia Produced by* 20 *Units of Intramuscular and Intravenous Insulin.*

Blood-sugar curve (*Table II, Patient* 1) :

	Fasting blood sugar.	Minutes after injection.													
		25.	30.	35.	40.	50.	60.	75.	90.	120.	180.	10.	210.	240.	270.
I.M.	75		56				47		50	47	50	48	47	54	54
I.V.	83	38	29	31	25	30	38	45	53	66	72	81	81	83	83

Minutes after injection of insulin.	Total milligram/minutes of hypoglycaemia produced :— Intravenously.	Intramuscularly.	Percentage of intravenous mgm./mins. of hypoglycaemia to intramuscular mgm./mins. of hypoglycaemia.
10	88	35	262
20	361	133	272
30	810	280	289
40	1348	479	282
50	1864	516	360
60	2353	781	300
70	2781	1056	262
80	3158	1321	239
90	3486	1576	220
100	3762	1831	206
110	3986	2094	191
120	4074	2367	172
130	4132	2640	157
140	4271	2905	147
150	4389	3160	139
160	4481	3413	131
170	4544	3670	124
180	4577	3937	116
190	4597	4207	109
200	4617	4482	103
210	4637	4760	97
220	4654	5025	93
230	4665	5272	89
240	4668	5296	87
250	4668	5506	85
260	4668	5716	82
270	4668	5926	79

of coma with areflexia is required, then intravenous insulin has no advantage over intramuscular insulin, as a larger dose is required to maintain the blood sugar at a sufficiently low level for the long period necessary, and the possibility of prolonged coma developing remains the same. In view of this it was decided to determine whether any of the " prolonged " insulins, such as protamine insulin and protamine zinc insulin, had any advantage over ordinary soluble insulin when given intravenously.

Intravenous Protamine and Protamine Zinc Insulin.

Polatin and Spotnitz (1942*a*) found that there was less tendency for patients to develop after-shock on protamine zinc insulin intravenously than on ordinary soluble insulin given by the same route, and Hinko *et al.* (1941) found that intradermal sensitivity tests were less marked with protamine zinc insulin than with soluble insulin in a patient who had previously developed an anaphylactic shock following subcutaneous injection of soluble insulin. Longwell

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and Ravin (1936) in animal experiments could find no difference in the action of soluble insulin and protamine insulin when these were given intravenously. Protamine zinc insulin was used intravenously in Sakel's treatment by McGregor and Sandison (1940) and Sandison and McGregor (1942), who found that there was neither particular advantage nor particular danger in its use.

Protamine insulin and protamine zinc insulin have not been given intravenously more frequently, probably owing to the fact that they are suspensions and that, therefore, the possibility of embolism cannot be overlooked. Hagedorn *et al.* (1936) showed that protamine insulin is soluble in serum to the extent of 50 units per c.c. of serum, and attributed the solubility to the presence of protein. The solubility in water or salt solution is very much less—about 0·5 unit per c.c. The danger of embolism on intravenous use does not, therefore, arise. No work, however, appears to have been published on the solubility of protamine zinc insulin, and so before this type of insulin was given intravenously, the following experiment was carried out:

Experiment.—10 c.c. of blood were collected from each of six patients and 2 c.c. of the serum from each specimen were separated and placed in a test-tube. Protamine zinc insulin was then added to the serum and was found to dissolve in it. The upper limit of solution was about 50 units per c.c. of serum, beyond which a slight turbidity developed. It will be seen, therefore, that the solubility of protamine zinc insulin in serum is of the same order as that of protamine insulin. The exact chemistry of the solution of protamine insulin has not been worked out, but the chemistry of the solution of protamine zinc insulin is almost certainly the same, and is probably analogous to the protective effect of protein on colloidal suspensions (Trevan, 1941, 1946). As 50 units of protamine zinc insulin per c.c. of serum is roughly equivalent to 300,000 units for the 6 litres of total blood in the body, it is obvious that no danger of embolism is likely to arise from the doses usually used in Sakel's treatment.

In view of the results of the above experiments and of the work of Hagedorn *et al.* (1936), 6 of the patients who had previously been given comparative doses of intravenous and intramuscular insulin (Table II) were divided into two groups. The first 3 were given the same doses of protamine insulin intravenously as they had previously received of soluble insulin intravenously. In the case of the remaining 3 patients protamine zinc insulin was given under similar circumstances in place of the protamine insulin. The blood-sugar values obtained following the injections are set out in detail in Tables XII and XIII, from which it will be seen that both protamine and protamine zinc insulin have the same effect on the blood sugar as ordinary soluble intravenous insulin has. There was also no difference between the patients' clinical response to the various kinds of insulin. The delayed action insulins, therefore, do not appear to possess any advantage over soluble insulin when given intravenously.

Summary of Conclusions from Experimental Work.

(1) More intravenous insulin than intramuscular insulin is required to induce the profound hypoglycaemic state of coma with areflexia in Sakel's treatment.

TABLE XII.—*Blood-sugar Values Following (A) Increasing Doses of Soluble Insulin Intravenously and (B) Increasing Doses of Delay (Protamine) Insulin Intravenously to Test their Comparative Effects.*

Units of insulin.	Fasting blood sugar.	Minutes after injection.													
		25.	30.	35.	40.	50.	60.	75.	90.	120.	150.	180.	210.	240.	270.
Patient 1:															
20 (A)	83	38	29	31	25	30	38	45	43	66	72	81	81	83	83
20 (B)	90	51	42	30	30	29	40	47	57	67	75	85	87	87	88
40 (A)	90	34	30	32	29	32	33	35	39	48	59	70	78	79	79
40 (B)	86	47	34	33	30	30	30	34	41	46	57	70	79	79	78
60 (A)	78	42	37	35	32	37	38	42	47	54	64	66	76	78	78
60 (B)	88	36	31	30	33	35	40	40	41	49	63	70	77	75	74
80 (A)	88	39	31	31	25	24	29	32	39	37	56	72	83	85	87
80 (B)	91	51	43	43	32	32	28	29	30	43	57	68	75	83	84
100 (A)	92	35	27	23	23	22	29	31	33	41	45	47	56	67	71
100 (B)	87	32	32	26	27	27	25	34	34	38	38	38	49	62	68
120 (A)	88	24	22	22	20	24	27	25	29	29	36	38	45	56	64
120 (B)	91	39	21	19	22	26	26	26	30	29	29	36	47	60	69
140 (A)	77	39	43	24	22	27	34	30	34	32	32	35	44	49	55
140 (B)	83	51	34	22	23	23	24	24	37	39	39	41	41	47	58
160 (A)	78	44	46	43	27	24	31	27	36	39	36	37	42	43	41
160 (B)	85	36	36	32	19	25	27	27	33	35	36	38	40	41	41
174 (A)	83	56	35	32	25	19	18	20	24	26	28	29	30	29	28
174 (B)	81	39	31	23	23	20	18	21	25	25	23	26	26	27	27
Patient 2:															
20 (A)	106	57	47	41	36	34	41	45	54	75	95	90	92	93	102
20 (B)	98	47	41	37	34	35	38	46	55	73	88	94	94	94	96
40 (A)	108	65	54	34	41	39	43	47	47	66	77	86	96	95	95
40 (B)	99	45	44	31	37	41	41	43	45	61	69	84	89	90	90
60 (A)	92	56	50	41	32	32	32	37	32	35	43	63	72	81	87
60 (B)	97	75	63	34	34	33	34	32	32	31	38	65	75	83	90
80 (A)	97	56	45	38	31	32	36	32	32	38	46	55	61	75	83
80 (B)	102	61	34	42	36	33	33	39	39	41	48	48	59	63	76
100 (A)	86	63	48	31	36	27	27	24	27	38	38	47	53	70	77
100 (B)	93	47	45	33	31	30	30	30	30	21	32	39	49	61	72
120 (A)	88	77	61	34	32	32	31	36	33	35	36	41	49	61	68
120 (B)	95	56	45	31	33	35	35	37	35	35	35	35	39	54	54
140 (A)	102	72	66	59	45	34	34	32	31	34	38	42	48	58	64
140 (B)	95	56	47	45	43	31	35	35	36	37	37	37	45	61	67
160 (A)	94	60	48	34	30	30	31	31	31	33	35	36	40	46	44
160 (B)	98	70	55	49	31	28	28	30	35	34	33	35	39	39	47
170 (A)	96	55	44	34	29	31	29	32	25	31	29	32	29	31	33
170 (B)	97	47	32	20	19	17	28	28	32	31	27	25	20	27	28
Patient 3:															
20 (A)	75	32	27	25	25	27	29	27	34	55	63	75	83	80	79
20 (B)	81	56	35	29	30	27	30	33	37	49	59	79	80	84	86
40 (A)	79	44	34	27	22	22	24	24	29	33	47	66	72	79	79
40 (B)	83	49	41	33	25	21	21	21	30	31	39	54	69	76	76
60 (A)	92	32	28	24	19	19	22	27	25	30	43	54	63	74	88
60 (B)	88	35	33	22	20	18	19	25	23	25	39	57	57	67	79
80 (A)	95	36	29	29	19	19	19	25	24	24	29	36	47	68	74
80 (B)	87	45	20	25	22	22	27	29	32	32	32	32	44	59	69
86 (A)	89	45	31	30	22	21	20	22	23	23	26	27	46	57	69
86 (B)	92	51	35	35	27	29	30	29	29	30	36	45	54	61	72
92 (A)	93	38	30	22	23	21	20	19	21	25	27	26	43	54	63
92 (B)	92	41	29	21	19	18	23	24	22	23	23	31	39	57	—
100 (A)	101	36	32	24	24	24	19	19	20	22	27	36	39	47	59
100 (B)	95	33	27	21	21	25	23	23	23	23	24	29	38	49	54
110 (A)	99	34	24	22	15	15	19	15	19	21	30	29	34	36	43
110 (B)	98	43	31	23	20	19	17	19	21	23	27	27	26	39	47
118 (A)	95	32	29	24	18	18	17	18	20	22	21	25	27	26	29
118 (B)	97	31	35	21	20	18	17	20	23	24	24	23	23	27	31

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(2) Less intravenous insulin than intramuscular insulin is required to produce the milder hypoglycaemic symptoms, such as perspiration and unconsciousness.

(3) Insulin given intravenously in Sakel's treatment is—

(*a*) Not excreted by the kidneys.

(*b*) Not neutralized by circulating substances in the blood.

TABLE XIII.—*Blood-sugar Values Following* (*A*) *Increasing Doses of Soluble Insulin Intravenously and* (*B*) *Increasing Doses of Protamine Zinc Insulin to Test their Comparative Effects.*

Units of insulin.	Fasting blood sugar.	Minutes after injection.													
		25.	30.	35.	40.	50.	60.	75.	90.	120.	150.	180.	210.	240.	270.
Patient 1:															
20 (A)	108	72	48	36	34	31	31	45	47	66	86	90	93	95	98
20 (B)	98	67	51	34	33	32	34	46	51	67	79	88	94	98	99
40 (A)	95	45	32	29	20	15	20	22	22	48	54	68	75	75	83
40 (B)	97	51	34	32	22	19	22	23	24	44	57	71	79	86	86
60 (A)	90	36	27	24	20	25	27	22	34	47	55	58	59	71	83
60 (B)	93	43	31	26	21	23	23	24	29	41	56	56	60	72	79
80 (A)	88	57	39	32	24	22	24	25	25	26	24	41	54	70	75
80 (B)	91	51	40	28	25	22	26	28	30	31	31	38	51	67	72
90 (A)	93	43	35	34	29	26	26	32	30	29	34	36	41	49	56
90 (B)	95	55	50	30	28	24	23	24	31	34	36	38	38	52	59
98 (A)	101	60	54	33	32	25	24	31	29	23	33	36	38	41	41
98 (B)	94	43	42	28	29	28	27	32	34	34	36	36	38	45	44
110 (A)	96	54	40	32	29	25	23	24	25	23	26	28	34	37	39
110 (B)	96	50	32	29	27	26	26	27	24	24	27	27	31	36	41
118 (A)	86	65	54	39	32	22	18	14	15	15	17	15	16	18	—
118 (B)	93	55	41	27	27	24	20	18	21	17	18	19	17	17	17
Patient 2:															
20 (A)	95	43	31	29	31	24	26	31	38	47	59	80	93	93	94
20 (B)	93	56	44	31	29	26	28	33	41	46	57	73	81	85	89
40 (A)	99	34	32	29	31	31	36	41	41	43	54	71	78	82	93
40 (B)	91	43	37	30	28	28	41	45	45	49	56	69	77	77	87
56 (A)	97	27	24	23	17	20	25	32	33	34	37	37	41	56	67
56 (B)	98	39	22	24	20	26	19	27	27	36	39	40	47	63	65
68 (A)	102	43	30	25	20	27	25	28	33	31	34	36	40	45	52
68 (B)	97	51	41	29	27	23	29	31	35	39	41	43	51	51	49
80 (A)	115	34	31	27	25	23	25	36	31	34	39	38	41	41	43
80 (B)	98	37	29	26	27	25	25	29	29	35	36	37	38	38	39
92 (A)	97	39	34	—	26	31	27	31	31	25	32	30	31	33	37
92 (B)	100	51	41	27	26	24	23	23	29	36	29	28	28	33	35
104 (A)	108	34	31	35	24	19	25	27	25	26	29	31	29	33	33
104 (B)	94	76	34	23	18	18	24	23	27	27	27	27	32	35	36
114 (A)	96	27	29	25	22	27	25	24	22	21	23	25	22	20	20
114 (B)	97	41	28	20	19	18	17	23	25	24	23	23	23	21	22
Patient 3:															
20 (A)	108	48	39	25	32	27	32	33	36	43	50	74	87	93	97
20 (B)	101	72	41	23	25	26	34	35	38	45	46	67	77	81	93
40 (A)	106	57	45	39	27	29	24	25	27	31	51	72	83	95	92
40 (B)	103	49	43	38	30	24	26	29	32	39	55	69	79	93	93
60 (A)	106	50	39	29	29	29	27	31	24	34	52	63	75	89	94
60 (B)	99	51	37	27	26	25	33	35	34	37	49	65	73	87	91
80 (A)	105	59	47	38	32	24	22	24	19	22	31	44	36	48	54
80 (B)	106	44	34	31	39	27	27	25	23	23	29	39	47	51	56
92 (A)	111	48	31	24	24	19	15	20	20	27	36	32	36	36	43
92 (B)	98	61	35	21	33	20	21	21	24	25	34	37	37	39	41
100 (A)	96	50	41	27	24	22	23	24	34	27	28	30	34	35	35
100 (B)	104	46	27	26	20	23	25	27	27	29	29	33	33	33	37
110 (A)	112	43	29	25	29	31	25	22	25	32	29	32	34	29	29
110 (B)	107	72	33	31	23	23	23	27	25	26	27	35	37	37	34
118 (A)	101	45	20	19	19	17	20	19	19	20	22	25	24	28	30
118 (B)	105	51	31	21	23	19	16	17	17	23	24	24	23	24	26

(4) The varying efficiency of intravenous insulin in producing the different degrees of hypoglycaemia is due to the fact that the rapid, profound fall in the blood induced by intravenous insulin cannot be maintained, as the slower, less profound fall which follows the subcutaneous injection of insulin can be. A portion of insulin given intravenously is used up in producing the rapid, profound fall in the blood sugar, and so ultimately the total milligram/minutes of hypoglycaemia produced by intravenous insulin, following an early superiority, is less than that produced by intramuscular insulin.

(5) (*a*) The curve of the graph of the relationship between the amount of insulin injected and the *extent* of the consequent fall in the blood sugar is a rectangular hyperbole.

(*b*) The curve of the graph of the relationship between the amount of insulin injected and the *rate* of the consequent fall in the blood sugar is also a rectangular hyperbola.

Therefore the rapid, profound fall in the blood sugar following intravenous insulin can only be produced by the using up of a portion of the insulin, which is, therefore, unavailable for the maintenance of the blood sugar at the necessary low level for the required period of time for coma to be induced.

(6) The varying nature of the conclusions reached by previous workers on the relative efficiency of intravenous and intramuscular insulin in producing coma has been probably due to the different standards of coma adopted by the authors.

(7) There is no *a priori* reason, following the above experimental work, why intravenous insulin should reduce the incidence of post-hypoglycaemic encephalopathies in Sakel's treatment of the deeper hypoglycaemic states, such as coma with areflexia, are induced.

(8) If, however, only the milder effects of hypoglycaemia are required, intravenous insulin is preferable to intramuscular as less insulin is required intravenously for these effects, and there is consequently a greater likelihood of the patient spontaneously awakening.

Results Obtained During a Trial Period with Intravenous Insulin in Sakel's Treatment.

Fifteen patients were given a full course (approximately 50 comas) of Sakel's treatment using intravenous insulin. The standard of coma adopted was that of unconsciousness with Babinski plantar responses and absent corneal reflexes.

The following general conclusions were drawn at the end of this trial period :

(1) Differences found in Sakel's treatment using (*a*) intravenous and (*b*) intramuscular insulin are :

(i) More insulin is required intravenously than intramuscularly.

(ii) The total period of hypoglycaemia each day is about 20–30 minutes shorter with intravenous insulin, but this is not of practical importance, since the blood sugar has to remain below 30 mgm. per cent. with both forms of administration for about 200 minutes before coma with areflexia can be produced. It is this long period of low blood-sugar values which

produces post-hypoglycaemic phenomena, and not the short period of mild hypoglycaemia which precedes it and which is shortened by the use of intravenous insulin.

(iii) There is a greater tendency to the spontaneous development of major epileptiform convulsions with intravenous insulin.

(2) Apart from the above differences, the effects appear to be the same for the two forms of administration. Coma is no quieter, after-shock as common and " arousal from coma " times no shorter with intravenous than with intramuscular insulin. Of the 15 patients, one developed a definite post-hypoglycaemic coma. This incidence of prolonged coma of 1 in 15 with intravenous insulin compares with 4 cases out of 146 treated by the author with intramuscular insulin. While the comparison cannot be exact with a small series of 15 cases, the figures indicate that intravenous insulin is at least as likely to be followed by prolonged coma as is intramuscular insulin.

Two of the points mentioned above will now be dealt with more fully :

(1) The case of post-hypoglycaemic coma following intravenous insulin.

(2) The greater tendency to spontaneous major epileptiform convulsions with intravenous insulin.

(1) CASE REPORT.—Patient 5 ; female ; aged 31.

Condition on admission (Banstead L.C.C. Hospital).—The patient is a paranoid schizophrenic whose illness is of 9 months' duration. She is able to give a fair account of herself, but shows marked blockage of thought. She believes that some other women have conspired against her because she has not had a baby, although she has been married for four years. These women have combined to form an organization which has installed an electrical machine in the hospital grounds. This machine generates songs which play upon her day and night. She is aurally hallucinated, and hears accusatory voices coming over the wireless and from underneath the bed at night. There is some incongruity between thought and mood, but she

Course of Insulin Hypoglycaemic Therapy.

Day of treatment.	Dose of insulin.	Duration of sopor.	Duration of coma.	Interruption by—
1	20	—	—	Drank glucose
2	40	—	—	,, ,,
3	50	—	—	,, ,,
4	60	—	—	,, ,,
5	70	—	—	,, ,,
6	80	—	—	,, ,,
7	90	35 mins.	—	Nasal ,,
8	96	44 ,,	—	,, ,,
9	100	53 ,,	—	,, ,,
10	106	68 ,,	—	,, ,,
11	112	75 ,,	—	,, ,,
12	118	92 ,,	5 mins.	,, ,,
13	118	104 ,,	—	,, ,,
14	118	116 ,,	10 mins.	,, ,,
15	118	112 ,,	20 ,,	,, ,,
16	112	118 ,,	30 ,,	,, ,,
17	104	126 ,,	30 ,,	,, ,,
18	100	115 ,,	30 ,,	,, ,,
19	100	98 ,,	25 ,,	,, ,,
20	96	120 ,,	30 ,,	,, ,,
21	96	132 ,,	30 ,,	,, ,,
22	96	126 ,,	30 ,,	,, and I.V. glucose.

is occasionally impulsive in behaviour. Her personality is fairly well preserved, but she has no insight into her mental state. The statement that she has not had a baby is itself a delusion, as she has three children alive.

Response to insulin.—As will be seen from the above record, there was nothing remarkable about the patient's response to insulin. She had been in coma nine times before the coma which became prolonged occurred on the 22nd day of treatment. On each occasion she had awakened normally on interruption with nasal glucose. During the afternoon of the day of the prolonged coma her temperature rose to 103° F., she showed marked myotonic spasms, but these were controlled by intravenous hexobarbitone. Vitamin B_1 was given subcutaneously without effect, and on the evening of the first day she was given a transfusion of one pint of blood. Although the bloods had been cross-matched, she developed an intense rigor shortly after the transfusion had been completed. She became extremely collapsed, the pulse could not be obtained, and she appeared to be dying. Coramine was given and she slowly revived. Fortunately her general condition was good when the transfusion was started, otherwise a fatal outcome would have been almost certain. The patient was a multipara, and it is probable that she was an Rh-negative subject who was transfused with Rh-positive blood. She remained unconscious for a total period of 46 hours after the initial interruption of coma and in the course of a few days recovered completely physically. There was no change in her mental state as a result of the prolonged coma, and later the course of insulin therapy was completed with moderately beneficial results.

(2) *The Greater Tendency to Spontaneous Major Epileptiform Convulsions with Intravenous Insulin.*

As has been mentioned previously, the term "convulsion" has been used in the literature on Sakel's treatment to cover both the intense myotonic spasms which are frequently seen in the deeper stages of hypoglycaemia and the typical major epileptiform seizures which closely resemble those seen in idiopathic epilepsy, and which are frequently marked by an initial cry, followed by a typical tonic stage which passes into an equally typical clonic stage, the whole convulsion lasting about 40–50 seconds. This section refers only to convulsions of the latter kind.

Incidence of convulsions.—Seven of the 15 patients who were given the full course of treatment with intravenous insulin developed major epileptiform convulsions. This is a very high proportion, and although the series is a small one, the proportion is probably significant when compared with the 14 patients who developed such convulsions in the author's series of 146 patients treated with intramuscular insulin. This would seem to be confirmed by the experience of 2 of the 7 patients who developed convulsions with intravenous insulin. Both of these patients would have a fit after each dose of insulin if the dose exceeded 440 units in the one case and 190 in the other. If, however, these doses of insulin were given intramuscularly no fits resulted. Ventriglia (1939), Reznikoff and Scott (1942) and Mahoney and Herskovitz (1942) also found a greater tendency to convulsions with intravenous insulin, although Polatin, Spotnitz and Wiesel (1940) found the same incidence and Sherman, Mergener and Low (1941) a reduced one. The greater frequency of convulsions with intravenous insulin can probably be ascribed to the more rapid, profound fall in the blood sugar causing a greater disturbance of the equilibrium of the motor cortex of predisposed patients than is the case with the more slowly acting intramuscular insulin.

Finiefs (1938) regarded spontaneous epileptiform convulsions occurring in

Sakel's treatment as beneficial, and likely to enhance the value of the treatment. The chief disadvantage of their spontaneous development is that the number of fits cannot be controlled or the time of onset. They may appear at any stage of hypoglycaemia, and while convulsions early in the period of hypoglycaemia may have no adverse effect, they are certainly undesirable in the deeper stages of hypoglycaemia, when the patient's general condition may be such that it ought not to be subjected to the extra strain imposed by a severe convulsion. If convulsions are deemed desirable in Sakel's treatment it is much better to induce them under controlled conditions by electrical means or by cardiazol. This opinion is confirmed by the experience of one of the patients given intravenous insulin. Following a spontaneous convulsion he complained of pain in the back, and on being X-rayed was found to have a compression fracture of the 5th dorsal vertebra. Had this fit been induced by chemical or electrical means the fracture might have been avoided, since, as Furst (1940) has pointed out, the placing of a small pillow under the mid-thoracic vertebra so as to extend the spine will reduce the incidence of vertebral fractures in convulsive therapy. The convulsions in the present series occurred usually between 90–110 minutes after the injection of the insulin, the time incidence being remarkably constant for any given patient. One patient had a number of convulsions on different days after a period of approximately 200 minutes of hypoglycaemia.

Opportunity was afforded by the frequent occurrence of major convulsions after the injection of intravenous insulin to study the behaviour of the blood sugar during and after the fit, and to compare the results with those obtained during and after fits induced by cardiazol (phrenazol) during hypoglycaemia. The blood sugar had been previously estimated every 30 minutes after the injection of the insulin, and the level of the blood sugar at the previous estimation was taken to be the level at the time of the onset of the fit. The blood sugar was estimated at intervals of 1, 2, 3, 4, 5, 6, 8, 10, 15, 20, 25, 30, 35 and 40 minutes after the onset of the fit, and a word of thanks is due to the members of the nursing staff, whose watchfulness enabled these times to be adhered to. The behaviour of the blood sugar during and after 12 spontaneous and 12 phrenazol-induced convulsions is set out in the following charts and table. The convulsions occurred in 8 patients.

TABLE XIV.—(1) *Blood-sugar Values During and After Spontaneous Insulin Convulsions.*

Number of convulsion.	Minutes after commencement of convulsion.													
	0.	1.	2.	3.	4.	6.	8.	10.	15.	20.	25.	30.	35.	40.
1	24	24	27	38	43	45	47	46	41	37	32	28	25	25
2	28	28	31	39	46	50	50	48	42	37	31	27	26	26
3	27	28	32	41	52	50	50	49	44	40	33	28	29	28
4	24	25	29	37	37	46	47	45	41	35	30	26	25	24
5	24	24	27	37	43	43	48	44	38	34	34	28	27	28
6	25	24	26	35	42	45	47	42	38	33	27	24	24	22
7	29	29	32	40	41	45	48	47	42	38	33	28	28	28
8	31	32	34	44	47	51	53	51	45	39	33	33	32	33
9	26	26	29	37	43	48	49	48	44	40	40	32	28	28
10	27	29	32	38	44	49	52	51	46	41	36	28	27	27
11	26	25	27	34	44	46	49	45	40	36	30	25	24	20
12	28	28	31	41	46	49	51	47	41	36	37	29	30	30

(2) *Blood-sugar Values During and After Phrenazol-induced Convulsions During Hypoglycaemia.*

Number of convulsion.	Minutes after commencement of convulsion.													
	0.	1.	2.	3.	4.	6.	8.	10.	15.	20.	25.	30.	35.	40.
1	24	25	32	39	55	66	75	74	68	60	55	46	37	37
2	24	24	31	37	48	56	56	52	44	37	30	25	26	25
3	27	26	33	38	46	54	62	63	58	47	35	29	26	26
4	26	26	31	41	54	69	73	69	62	56	50	41	33	29
5	20	22	32	40	32	68	68	63	60	51	45	38	29	24
6	23	23	30	39	53	64	60	55	51	43	34	28	35	25
7	23	22	28	37	44	52	59	59	51	45	45	34	28	28
8	25	25	31	42	59	71	69	65	61	56	53	42	33	27
9	26	28	32	45	69	69	65	53	54	45	33	27	27	26
10	31	28	37	46	55	63	61	54	46	37	33	29	30	30
11	29	29	33	41	52	61	72	69	63	57	50	42	33	30
12	22	24	29	41	58	58	54	49	45	37	34	31	29	27

From the foregoing charts and table it will be seen that—

(1) *In Spontaneous Hypoglycaemic Convulsions*—

(*a*) All 12 convulsions occur when the blood sugar is between 20–30 mgm. per cent.

(*b*) The blood sugar starts to rise immediately the convulsion is over and reaches the highest point in 6–10 minutes, after which it begins to decline until it reaches the pre-convulsive level in about 40 minutes.

(2) *In Phrenazol-induced Convulsions During Hypoglycaemia*—

The post-convulsive increase in the blood sugar is not nearly as constant as it is after the spontaneous convulsions, varying as it does from 30–50 mgm. per cent. This is probably due to the fact that the patients were unlikely to be given the exact convulsive dose of phrenazol, and any additional phrenazol over the necessary minimum would result in a more severe convulsion with a greater increase in the blood sugar.

As an explanation of the post-convulsive behaviour of the blood sugar it is suggested that the convulsion results in the depletion of glycogen in the muscles, which is replaced by the formation of glucose from glycogen in the liver under the influence of adrenaline. The newly formed glucose raises the blood level as it travels from the liver to the muscles for reconversion into muscle glycogen.

Conclusion.

The following conclusions emerge from the experimental work described and from a study of the literature reviewed :

(1) *The Value of Intravenous Insulin in Reducing the Incidence of Post-hypoglycaemic Encephalopathies in Sakel's Hypoglycaemic Treatment.*

This depends entirely upon the depth of hypoglycaemic coma which it is desired to produce during the treatment.

(*a*) If the production only of unconsciousness is desired, intravenous insulin is of value as a smaller dose is required than that of intramuscular insulin, and the more rapid return of the blood sugar to normal with the doses of insulin

required to induce this state diminishes the possibility of the patient remaining sufficiently long in coma for post-hypoglycaemic encephalopathies to develop.

(*b*) If the considerably deeper state of unconsciousness with positive Babinski reflexes and absent corneal reflexes is desired, intravenous insulin has no advantage over intramuscular or subcutaneous insulin since a larger dose is required. The use of these larger doses, necessary to maintain the blood sugar at a sufficiently low level for the required period of time, prevents the blood sugar from spontaneously returning to normal until sufficient time has elapsed for post-hypoglycaemic encephalopathies to develop.

(2) *Disadvantages of Intravenous Insulin in Sakel's Treatment.*

(*a*) Greater frequency of uncontrolled spontaneous major epileptiform convulsions.

(*b*) The possibility of anaphylactoid shock occurring in patients sensitive to insulin.

(*c*) More insulin is required to induce the deeper hypoglycaemic states.

(3) *Advantages of Intravenous Insulin in Sakel's Treatment.*

(*a*) The time occupied by the treatment is reduced by about 30 minutes each day.

(*b*) The milder hypoglycaemic states can be induced with less insulin with a greater possibility of spontaneous awakening of the patient.

Reviewing the subject as a whole, it may therefore be said that intravenous insulin offers insufficient advantages over intramuscular insulin in Sakel's treatment to justify its use.

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