they will again be made available and will be more widely employed in place of x rays.

Thorium X has not, in my hands, been of much value. It will pale, but not clear, a port-wine stain, though it is the only measure that may be effective in that rare dermatosis, parapsoriasis. Theoretically thorium X, as a source of alpha particles, should be a useful and safe measure in the treatment of superficial affections, but it has proved disappointing.

General Treatment

My previous remarks indicate the stress I would place upon the general approach to and investigation and understanding of the dermatological problem as a part of treatment. I would equally stress the importance of general as against local treatment, and general treatment may include the administration of drugs.

I have time for only a word or two upon a few of the drugs more recently introduced, most of them dangerous drugs about which we still have much to learn. They should be used with caution and only where the character, gravity, or intractability of the affection justifies it, and patients so treated should be kept under close clinical observation.

I have mentioned the sulphonamides, which can help considerably in the control of pyogenic affections and in some other ills, such as dermatitis herpetiformis, where the effect would appear to be along some other channel than the combating of infection.

Penicillin is of limited value in dermatology, but will sometimes clear or relieve cases of chronic or recurrent erysipelas or chronic lymphangitis and elephantiasis. One of the distressing effects of penicillin therapy—viz., pruritus and urticaria—may be controlled by another type of drug, the antihistamines. These again are of more interest from the laboratory and experimental point of view than the clinical, but they may be helpful in cases of allergic reaction of known cause and limited course. We cannot feel entirely happy, however, in introducing agents into the system which counteract so essential a metabolite as histamine.

I must say a word about the use of calciferol in massive dosage as employed in the treatment of lupus vulgaris. As a vitamin it may be regarded as harmless, but in this dosage it is dangerous and should not be employed over any long period in the treatment of trivial affections. The effects in lupus vulgaris and in sarcoidosis may be quite remarkable, but a careful watch has to be kept upon the blood chemistry and particularly upon renal function.

The general treatment of disorders of function calls for a careful assessment of the patient as a whole and his adjustment to life and his environment. That assessment must be appreciated and understood by the patient if treatment is to achieve success. I have already referred to this.

Symptomatic treatment will often assist and encourage the patient in his efforts, but it must be sustained and be employed as a help and not as a direct or specific therapy to be prescribed for a limited period. In ideal circumstances the patient employs such symptomatic remedies as the doctor suggests in the light of his understanding of his problem and of the purpose of those remedies. Again, it is important that the patient shall find benefit from and not be disturbed by such measures. They may serve as a supplement to the diet, a substitute for a holiday, an antidote to overwork, worry, or fatigue, or even to counter the stress of an unsuitable climate. They are not of themselves cures for a disease but rather comforts for the patient, and should be recognized as such, and should be employed in a very individual manner and with proper understanding.

GLOBIN INSULIN: A CLINICAL STUDY

BY

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Globin insulin (G.I.) was introduced in 1943 as a slow-acting insulin intermediate in duration of action between protamine-zinc insulin (P.Z.I.) and soluble insulin (S.I.). It is in many respects similar in action to Hagedorn's original protamine or delay insulin. It has been slow to gain recognition in this country, but from the patient's point of view offers the obvious advantage of simplicity, and now that the management of diabetes has become the inculcation of a *modus vivendi* rather than a *regimen valetudinis* it is important to eliminate time-consuming or fussy procedures so far as is possible.

Material

This survey is based on the records of 366 ambulant patients under regular observation who have been taking globin insulin for one to four years. They are drawn from the diabetic clinics of the Royal Sussex County Hospital and the New Sussex Hospital, Brighton, and from private practice. At the present time 68% of those attending one clinic and 66% of those attending the other are on globin insulin. The majority of the patients already attending the clinics were balanced on a combination of P.Z.I. and S.I. given before breakfast. It was recognized that in order to obtain the expected action of S.I. it must not be mixed in the syringe with P.Z.I. (Wauchope, 1940; Peck, 1943), and most of the patients had been taught either to inject one kind of insulin immediately after the other through the same needle or to give two injections. When patients mixed the two kinds of insulin in the syringe the dose of S.I. was equal to or greater than that of P.Z.I. and was difficult to assess owing to variations in the amount of mixing (Wauchope, 1940). A few patients were satisfactorily balanced on one dose of P.Z.I., and a few older people of regular habits remained satisfied with two doses of S.I. a day.

At the time globin insulin was introduced the war was in its fourth year, air raids were frequent, and almost all the diabetics attending the clinics were in full work in factories, civil employment, household duties, etc. Many were air-raid wardens in addition. Their hours were irregular, their sleep interrupted, and the insulin had often to be given in poor light. In these circumstances from late 1943 onwards new patients were started on a single dose of globin insulin, usually before breakfast: they were balanced as out-patients unless their illness was first recognized by the onset of coma.

The diet utilized the protein and fat allowed by the Ministry of Food, which, together with the bacon and egg rations, supplied about 1,400 calories: C., 120; P., 280; F., 1,035 (C., 30 g.; P., 70 g.; F., 115 g.). The rest of the calories required were made up mainly of carbohydrate and such protein on "points" as was available. A start was made with 200 g. of carbohydrate, which was added to according to the needs of the patient. In practice very few eat the whole of the fat ration and many have at least one meal a day at a canteen or restaurant.

The results were unexpectedly successful, and gradually G.I. became the insulin of choice. Many patients who had been on P.Z.I. and S.I. and who for one reason or another needed readjustment were changed to G.I.

The times of the clinics allow for a routine blood-sugar estimation about four hours after insulin and breakfast; the patients test their own morning and evening specimens of urine and bring a chart or notebook for inspection.

The criteria for a satisfactory balance are: (1) the comfort and well-being of the patient; (2) the attainment and maintenance of a reasonable weight; (3) absence of thirst or polyuria at any time during the 24 hours; (4) absence of ketosis; (5) absence of insulin reactions; (6) a normal blood sugar before the midday meal; and (7) small amounts of sugar in the morning and evening specimens (green reaction to Benedict's solution). Points 1 to 4 have been almost universally maintained in the absence of complications; points 5 to 7 naturally vary from time to time.

Age

The patients may be considered under three categories according to the age at which they came under observation: (1) the young, who range from $2\frac{1}{2}$ to 20; (2) the active working population, from 21 to 64; and (3) the old, from 65 onwards. The numbers of patients in each category and the dosage of insulin are set out in Table I.

The Young (under 20).—It was expected that these would do well on G.I.; Hagedorn's delay insulin had often been found useful for those whose last meal was at 5 or 6 p.m. and who were therefore prone to insulin reactions at night on P.Z.I.

TABLE I

Age	Dosage of Globin Insulin in Units						Total No. of Cases	Under 40 Units	Over 40 Units
	0-20	21-40	41-60	61-80	81-100	100+			
Under 20	3	7	11	4	2	0	27	37%	63%
Active workers 21-64	90	84	52	10	0	2	238	73%	27%
Retired persons over 65	52	32	9	5	0	3	101	83%	17%
Total	145	123	72	19	2	5	366	73%	27%

The buffer substance, of which 1 ml. was put into each bottle of delay insulin, had occasioned difficulties, first because the amount was not always accurately measured and there was not enough for the last bottle of insulin, and secondly because each issue of insulin had to be in multiples of six bottles, which did not accord with the times of the visits. Moreover, soluble insulin had often been combined with the delay insulin so that two kinds were used. Globin insulin given alone was therefore a great advance in simplicity, and was welcomed by the mothers and by the children and young people themselves.

Active Workers (21-64).—The great majority (65%) are in this group; their occupations do not differ from those of the non-diabetic population, and include professions and trades, indoor and outdoor employment, clerks and farm labourers. There is even one serving soldier. Most of those who worked in factories during the war are now in other employment not involving night shifts. Many of the women are housewives responsible for families; there are school teachers, nursing sisters, nurses in training, typists, shop assistants, and domestic servants. Their lives are not without incident, but they have been remarkably free from severe reactions.

Retired Persons (over 65).—Many are of the stable type of diabetic who would do well on any kind of insulin. Some are too fat, but most are normal in health and weight. As would be expected, the majority (83%) are on small or moderate doses (under 40 units).

Dosage

It will be observed from Table I that the majority of patients of all ages (73%) are taking less than 40 units of insulin; this is, of course, not peculiar to globin insulin.

It has been suggested (Malins, 1945) that globin insulin has a limited use for patients on small or moderate doses; it is pertinent, therefore, to consider those on the larger doses. In this series the only category in which the majority are taking over 40 units is that of the young people; the dosage is, however, not high, only two patients taking over 80 units (88 in each case).

One is an overgrown thin lad, now 18, who came under observation in 1941 at the age of 10. He was difficult to

balance, having a low renal threshold, and for five years was first on P.Z.I. and S.I. and latterly on a combination of P.Z.I., delay insulin, and S.I. (total dosage 88 units) in an attempt to avoid reactions. He began G.I. in January, 1946, and has been much steadier on 80 to 88 units; he has left school and is working as a newsagent.

The other patient is the daughter of a farm labourer in a remote country district where supervision and a satisfactory diet have been impossible; she came under observation in 1942 at the age of 10 and during the next two years was often admitted to hospital for rebalancing after insulin reactions or ketosis. She has been on globin insulin since January, 1944, and has had no reactions beyond an occasional shakiness before meals. She has just left school at 16 and is working as a daily domestic.

The largest individual doses in this survey are taken by patients in the category of active workers—two women on 156 and 176 units.

One is an example of the case whose needs rise steadily. She is an energetic housewife, now aged 53, and has had no illness or reactions. The only complication is benign vascular hypertension. From 1936 to the end of 1941 she was on two doses of S.I.; the total was raised from 48 to 100 units to balance blood-sugar readings of over 300 mg. per 100 ml. From January, 1942, to August, 1944, she was on P.Z.I. and S.I., which was raised from 96 to 120 units, the blood sugar being again over 300 mg. per 100 ml. on many occasions. From September, 1945, till the present time she has been on G.I.: starting with 120 units, she reached a maximum of 180 units in 1946, and is now on 156 units. The blood-sugar estimations have been more reasonable, 218 mg. per 100 ml. being the maximum in 1947, with a minimum of 87 mg. Her weight, 9 st. 6 lb. (59.9 kg.) in 1936, is now 10 st. (63.5 kg.).

The other is a stout hard-working ward maid now taking 176 units. Her blood sugar is usually in the region of 175 mg. and her needs have been high from the outset in 1946. She began with 80 units of G.I. and was raised fairly quickly to 170 to 180 units, on which she has remained steady.

Of the old people 83% are taking less than 40 units, but it is surprising to find three women on doses of over 100 units.

The first is a thin old person of 78 who has been on 120 units for the last two years and who comes to the clinic from a neighbouring town 10 miles away. The second, on 156 units, is now 64. She has had diabetes for over 20 years and came under observation 16 months ago with thirst, loss of weight, and lassitude. She was on 60 units of S.I. in the morning only, and her blood sugar four hours afterwards was 300 mg. per 100 ml. She was balanced on G.I., and has taken 112 to 120 units since September, 1947, with excellent control. The third, a woman of 65, was an in-patient at the National Hospital for Nervous Diseases for the investigation of a cerebral lesion when glycosuria was discovered in 1946. She returned home, and her diabetes was balanced on 100 units of G.I. She has been fairly stable on 104 to 108 units since early in 1947.

The patients on the larger doses of globin insulin do as well as those on moderate or small doses. There is no clinical difference, and none in this series are of the unstable type of case. They are not subject to reactions, and apart from the third case, just mentioned, have no complications. It will be seen that in Case 13 (Table II) 124 units of G.I. gave a steady level throughout the day; the patient was sent home on 128 units.

Insulin Reactions

Among 150 patients whose notes are well documented over several years, 40 (27%) reported reactions and 110 did not. Most of those who reported any reactions have had many during the years of observation. Eleven who were formerly on a different insulin have had reactions on both: in two cases they were severe on P.Z.I. and S.I. but slight on G.I. In addition six reported reactions on other insulins

and none on G.I. Of the whole number of reactions reported, only three were severe. These cases were (1) a corporation labourer who mistook the strength of insulin supplied, injected a double dose, and was brought to hospital in coma; (2) a man driving a car who omitted his mid-morning lunch, was summoned and deprived of his driving licence; (3) a woman on G.I. since 1944, reported being taken home incapable in a police car at tea-time: she has always been subject to reactions, and when on P.Z.I. and S.I. had many severe attacks, in one of which she was admitted to hospital in coma.

The incidence of reactions is not related to the age of the patient nor to the dosage of insulin; the young people have had few and the old have not been free. The third patient just mentioned, who had more reactions than any in the series, is a married woman of 53 taking about 40 units—one would suppose a moderate case. It is generally difficult to relate the reactions to the carelessness of the patient.

The Time of Reactions.—The times of 126 reactions on globin insulin taken before breakfast, as reported by the patients, are: midnight to 7 a.m., 12; 10.30 a.m. to 1 p.m., 75; 3 to 6 p.m., 30; 7 to 10 p.m., 9. It is perhaps surprising, in view of the reputed slow action of globin insulin, to find that by far the greatest number of reactions occurred from 2½ to 5 hours after taking it. A mid-morning lunch is as necessary with G.I. as with P.Z.I. and S.I. The next common time is in the afternoon about tea-time, so that it is a mistake to omit or be late for tea. A few reactions have occurred between midnight and breakfast, but in most cases it is unnecessary to take a late buffer meal. The fewest reactions were reported in the late evening before and after supper, and this is the time of day when the blood sugar is usually at its highest.

Patients appear to dread nocturnal reactions, though to an observer it would seem to be a safer and more convenient time than when out and about. Many have spoken of the relief from this dread afforded by globin insulin. Local reactions have been inconspicuous and mainly due to error in the technique of injection; a few patients complain of more stinging than with other kinds of insulin.

Examples of Satisfactory Control

It is difficult to demonstrate by figures the success or otherwise of insulin control. A few clinical examples of satisfactory balance are given.

The Ordinary Case.—A cowman aged 45 came under observation in 1944; his symptoms had been present for one month. He was tall and thin and weighed 11 st. 7 lb. (73 kg.). No physical signs of disease were found. A radiograph of the chest revealed fine fibrosis at the base of the left lung but no evidence of pulmonary tuberculosis. There was moderate hypochromic anaemia. His blood sugar was 240 mg. per 100 ml., and there was heavy glycosuria with traces of ketones in the urine. He lives in a village 18 miles away from the hospital, and continued at work. He was balanced in a few weeks, and has remained on G.I. 54 to 56 units since November, 1945. He has had no reactions and the range of blood-sugar estimations has been from 100 to 150 mg. per 100 ml. He now weighs 12 st. 6 lb. (78.9 kg.). His work is extremely hard; he rises in the dark in winter to milk and works till sunset in the harvest. His appetite is enormous, and he eats mountains of bread and potatoes.

The Man Working on Shifts.—A police constable aged 35 came under observation in November, 1944. His symptoms were of 10 days' duration: thirst, polyuria, loss of weight, lassitude, inability to run upstairs. He was 6 ft. 2 in. (1.85 m.) in height and weighed 10 st. (65.3 kg.). No physical signs of disease were found. There was heavy glycosuria, but no ketosis, although the blood sugar was 660 mg. per 100 ml. He was off work for three weeks, and was balanced as an out-

patient on G.I. 54 units. Since January, 1945, his insulin needs have varied between G.I. 50 and 56 units. The blood sugar, taken at intervals of one to two months, has been twice above normal limits—250 and 220 mg.—and has otherwise varied between 115 and 180 mg.; he has had no reactions; his weight is now 11 st. 9 lb. (73.9 kg.). His only sick leave was on account of a Colles's fracture sustained in the course of his duties. His shifts vary from week to week: (a) 6 a.m. to 2 p.m.; (b) 2 to 10 p.m.; (c) 10 p.m. to 6 a.m.; the time of taking insulin is varied accordingly.

Various Types of Insulin.—A girl who came under observation in 1927 at the age of 19 was balanced in hospital on S.I. three times a day. She remained on this system from December, 1927, to December, 1939. The diet was 2,000 calories, with about 60 g. of carbohydrate. Her weight increased from 8 st. 8 lb. to 11 st. (54.4 to 69.8 kg.). There was persistent glycosuria, and her blood sugar varied from 275 to 480 mg. per 100 ml., except for an isolated occasion when it was 150 mg. She was admitted in pre-coma in 1928 and 1932, and appendicectomy for acute purulent appendicitis was performed in 1932. In 1936 radium was applied for menorrhagia, and after this she began to have bad insulin reactions on S.I. 70–80 units a day, in three doses. Blood-sugar estimations of from 77 to 350 mg. were recorded during the years 1936 to 1939 inclusive. In December, 1939, a mixture of P.Z.I. and S.I. was given in the morning with, at first, S.I. in the evening, the total dosage varying from 75 to 88 units. The carbohydrate of the diet was increased to 150 g. She continued to have many reactions; the blood sugar ranged from 71 to 283 mg. per 100 ml. and she was admitted in insulin coma in 1941. In 1942 and 1943 she was rather more steady. In 1944 she underwent hysterectomy for menorrhagia due to fibroids. After this she began globin insulin, and, apart from one admission in diabetic pre-coma owing to an intercurrent illness, has been much steadier and has reduced the dose from 72 units to 34. She has had no reactions, is taking 250 g. of carbohydrate, weighs 10 st. 6 lb. (66.2 kg.), and is in full work as a housekeeper.

This remarkable case, which has been in the hands of many physicians and surgeons, is noteworthy for four reasons. First, the long duration; secondly, the persistence of hyperglycaemia during the first 12 years of the patient's diabetic career; thirdly, the successful weathering of two major operations; and, finally, the present well-being, reduction of insulin needs, and hard-working capacity at the age of 40.

A Child.—John D. came under observation in 1942 at the age of 5. He was balanced as an in-patient on 14 units of delay and 14 units of soluble insulin. His weight was 3 st. ½ lb. (19.3 kg.). He went to school and was inclined to have reactions on the way home, so that the soluble insulin was gradually eliminated, but it was again found necessary in 1943. At the end of 1943 his weight was 3 st. 7 lb. (22.2 kg.), he was on D.I. 20 and S.I. 10 units, and his blood sugar had varied during 1943 from 268 to 507 mg. per 100 ml., while reactions at tea-time were reported. In January, 1944, he began globin insulin and has continued satisfactorily. He is now 11, is 4 ft. 7 in. (1.4 m.) in height, and weighs 5 st. 2½ lb. (32.8 kg.). He has had no reactions for a year. This case illustrates the difficulties of insulin treatment of a child in a large family and the relief afforded by a simple procedure. He is the sixth in a family of seven; his father is a working-man who gives the insulin (G.I. 40 units: 80 units to the ml.) at 7.15 a.m. before he goes to work. His mother prepares breakfast for the father, two youths at work, and five children for school. It may be supposed that John's diet is free; he has dinner at school and comes home to tea at 5 p.m.

Control Throughout the Day

In order to obtain a view of the control during the day the records of patients who have been in hospital for some complication and whose blood sugar has been estimated before leaving are shown in Table II. It will be seen that in most cases the blood sugar rises in the evening, falls during the night, and is lowest before midday dinner; this is consistent with the experience of out-patients in the times

TABLE II

Case No.	Age	Globin Insulin in Units	Blood Sugar in Mg. per 100 ml.			
			6 a.m.	Noon	6 p.m.	10 p.m.
1	37	32	175	125	200	
2	30	60	116	—	131	
3	7	38	75	256	118	
4	16	120	112	85	225	
5	65	16	162	—	150	
6	57	60	156	131	93	
7	51	16	150	—	193	
8	50	32	137	143	100	
9	70	40	106	112	243	
10	70	20	106	187	87	
11	55	12	100	131	181	
12	61	42	168	212	137	
13	68	124	181	231	187	
14	63	32	62	93	181	
15	12	28	112	112	125	
16	42	24	106	225	106	
17	19	36	193	100	200	
18	36	32	131	234	156	
19	64	12	112	162	212	
20	21	68	112	140	131	
21	21	68	474	137	200	394

of their reactions. The control was reasonably good, though in some of the cases a readjustment of the dosage or the times of the meals was made before the patient left hospital—e.g., cases 3, 13, 14.

Failures

In a few cases there is an escape of control in the late evening, sometimes lasting all night and causing nocturnal polyuria. Often a redistribution of the times and amount of food rectified it, or a temporary evening dose of 8–12 units of soluble insulin while the globin is being adjusted is indicated; this can be left off gradually after a week or two. Case 21 (Table II) shows this escape—Case 20 is the same patient after readjustment.

In those few cases in which the blood sugar is low at noon and the evening dose remains necessary a transfer to P.Z.I. alone may solve the difficulty. This has been successful in the cases of two boys.

Discussion and Conclusions

It has been questioned whether, since P.Z.I. and S.I. in various combinations give good results, there is need for a third type of insulin. Rabinowitch *et al.* (1947) discuss this, and after careful studies of ambulant patients on P.Z.I. or G.I. alone, P.Z.I. and S.I. in separate syringes, or S.I. twice a day found that the fasting blood sugar was lower with P.Z.I. alone than with G.I. alone, but the postprandial level was lower with G.I.; they obtained the best control with G.I. in the morning and P.Z.I. in the evening. Roberts and Yater (1947) in a survey of 97 cases recorded a better control with G.I. than with P.Z.I. in 70. Malins (1945), in a clinical study of 36 cases, considered that globin insulin has a limited place in the treatment of mild and moderately severe cases.

My impression has been—and a survey of the notes confirms it—that all types of patient do as well on a single dose of globin insulin each day as on other kinds of insulin, singly or in combination. From the doctor's point of view it is easier to adjust the dose than with the varying combinations of P.Z.I. and S.I. even when they are given separately; when they are mixed in the syringe a stable balance is always difficult.

The speed and efficiency of the clinic is increased. The opportunities for mistakes and confusion in measuring the dose are greatly lessened, as is the time consumed in teaching the patient self-administration. P.Z.I. given alone has the same advantages, but, owing to the longer time which elapses before it begins to act and the prolonged duration of the action, is of limited application.

Nearly all patients who have transferred from another type of insulin to G.I. prefer it on account of its simplicity

Many who, for one reason or another—e.g., being admitted to other hospitals—have been rebalanced on P.Z.I. and S.I. have asked to return to G.I. They say that they feel safer from reactions and that it is much easier and quicker to take.

Globin insulin is, I believe, likely to become the insulin of choice in ambulant uncomplicated cases. It achieves the maximum degree of simplicity so far attainable—one dose of one kind of insulin once a day. Soluble insulin remains the type for use in all emergencies.

Summary

The notes of 366 diabetic cases treated as out-patients with globin insulin are reviewed; the dosage of insulin in different age groups and the incidence and times of reactions are recorded, and an attempt is made to assess the degree of control obtained.

The opinion is put forward that globin insulin alone is the best type of insulin available at present for uncomplicated ambulant cases of diabetes.

It is a pleasure to thank Dr. Prowse and the other physicians and surgeons of the Royal Sussex County Hospital, and those of the New Sussex Hospital, for the use of notes of cases seen by them before they came under my care.

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RENAL COMPLICATIONS IN DIABETES MELLITUS

WITH SPECIAL REFERENCE TO THE KIMMELSTIEL-WILSON LESION

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In the prolonged observation of patients under treatment for diabetes mellitus one of us has been impressed with the relatively frequent occurrence of albuminuria. In a number of these cases clinical and laboratory evidence of progressive renal failure was observed, and the condition was often complicated by retinal changes and hypertension. These changes were earlier interpreted as evidence of progressive vascular degeneration in most instances, but the observation made by Kimmelstiel and Wilson in 1936—that a pathological change in the glomeruli of the kidney seemed to be a typical finding in diabetes—suggested a review of this problem.

Kimmelstiel and Wilson (1936) observed hyalinization of intercapillary connective tissue in the kidney in eight patients, all of whom except one had suffered from diabetes and in whom, terminally, oedema and renal failure had occurred. They named this condition intercapillary glomerulosclerosis. Following on this observation several workers contributed further examples from both the pathological and the clinical aspect. Anson (1938) found six diabetic cases with similar lesions. Derow, Altschule, and Schlesinger (1939) reported a further example, and in the same year Newburger and