Drug Treatment of Disease**TREATMENT OF DIABETES MELLITUS*****2. INSULIN PREPARATIONS AND THERAPEUTIC USES**

BY

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There are now no fewer than seven insulin preparations available for the treatment of diabetes. They are all put up in strengths of 40 and 80 units per ml. (U40 and U80), but soluble insulin is also obtainable in a strength of 20 units per ml. (U20), and, on special application to the manufacturers, of 320 units per ml. (U320).

The characteristic appearance and approximate duration and intensity of activity of these insulin preparations are summarized in the Table; suitable times for testing urine are also included. It should be remembered that the larger the dose of insulin the longer its action; this fact is of great importance in respect of testing urine, arrangement of diet, and the likely incidence of hypoglycaemia.

Certain rules should be followed in the mixing of insulin preparations. Soluble insulin can be mixed with P.Z.I., globin, and isophane, but not with the lente insulins. If soluble insulin is mixed with P.Z.I. in the same syringe, allowance must be made for the conversion of a certain amount of soluble into P.Z.I.; for this reason, as a rule, the dose of soluble should exceed that of P.Z.I. When soluble is mixed with isophane insulin (N.P.H.) no such conversion takes place. It is wise never to mix more than two insulin preparations in the same syringe. Lastly, all insulin suspensions should be well shaken before use.

Local reactions may occur with any preparation, but are more common with P.Z.I. than with soluble or the lente insulins.

There is a wide range of choice in insulin therapy, and it may be possible to achieve the same degree of control in more than one way; the following remarks on the indications for the use of individual insulins or mixtures of insulins should not therefore be regarded as hard-and-fast rules, but rather as guiding principles based on the experience and prejudices of the author.

Soluble Insulin

In all diabetic emergency states, such as acute infections, precoma, and coma, soluble insulin should always be used alone and at short intervals. In such conditions dosage will depend on a number of factors such as age, previous insulin requirement, and the severity of ketosis, but Lawrence's suggestion that the number of units should be one-tenth of the blood-sugar value in milligrams per 100 ml. is a sound guide, especially if, for blood sugars of 500 mg. or less, the fasting value of 100 mg. is subtracted before the calculation is made.

In maintenance therapy, injection of soluble insulin morning and evening is the oldest and still probably the best way of controlling severe diabetes. Apart from

the inconvenience of two injections, the chief drawback of this otherwise simple and adaptable method of treatment is the tendency for very insulin-sensitive patients to relapse into heavy glycosuria and ketonuria during the last few hours before the next injection. This tendency is most marked before the morning injection and can be prevented by adding a small dose, 4 to 12 units, of P.Z.I. to the evening injection of soluble insulin, and giving it before tea instead of before the evening meal. This modification of two injections of soluble insulin is of special value in the treatment of young diabetics and in the management of the pregnant diabetic woman. It is probably true to say that the majority of children over the age of 10 are best treated with morning and evening injections of soluble insulin, for single-injection methods are less efficient and more apt to give rise to ketosis, hypoglycaemia, and late complications of the disease. It is often a good plan to start treatment in the very young diabetic with a single injection of a long-acting preparation, such as lente insulin, but it is always wise to warn the parents that, when the child approaches puberty, two injections will probably be required to keep the diabetes in good control.

Protamine Zinc Insulin

This is the oldest available long-acting insulin, and, though its action covers a period of 24 hours or longer,

Preparations of Insulin; Times for Testing Urine

	Appearance and Labelling	Duration of Action in Hours	Intensity of Action	Times for Testing Urine
Soluble insulin	Clear U20 cream label U40 blue label U80 green label	6-8	Strong	A.M. dose before mid-day meal or tea P.M. dose on waking
P.Z.I.	Cloudy U40 blue and pink U80 green and pink	24	Weak	Before breakfast
Globin	Clear U40 blue and orange U80 green and orange	8-12	Moderate	Before tea or evening meal whichever is better
Isophane (N.P.H.)	Cloudy U40 blue and white U80 green and white	8-12	"	" "
I.Z.S. amorphous (semi-lente)	Cloudy U40 blue and red U80 green and red	8-12	"	" "
I.Z.S. crystalline (ultra-lente)	Cloudy U40 blue and yellow U80 green and yellow	24	Weak	Before breakfast
I.Z.S. (lente)	Cloudy U40 blue and magenta U80 green and magenta	24	Moderate (short) Weak (long)	As for semi- and ultra-lente

N.B. (1) The duration of action stated is for moderate doses of 40 units or less; larger doses have a more prolonged action. (2) The bladder should be emptied half to one hour before all tests except that made on the waking specimen.

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it is weak and delayed in onset. For these reasons it has to a large extent been replaced as a single-injection method of treatment by the more efficient lente insulin, which contains both relatively fast- and long-acting components. P.Z.I. has, however, the convenient property, not shared by the lente insulins, that it can be administered with soluble insulin. Given together in this way, they provide a single-injection method of treatment which may prove successful in those cases in which lente insulin alone fails to control the blood-sugar level between breakfast and lunch. In small doses P.Z.I. may also prove useful in prolonging the action of soluble insulin. It should, however, be remembered that, when P.Z.I. is mixed with soluble insulin in the same syringe a certain amount of the latter is converted into P.Z.I.; for practical purposes this may be taken as equal to half the number of units of P.Z.I. used.

Globin Insulin

This insulin may be regarded as having an action intermediate in intensity and duration between that of soluble and P.Z.I. It resembles in this respect both semi-lente and isophane (N.P.H.) insulin, and, as these are now in more general use, will not be considered in more detail.

Isophane Insulin (N.P.H.)

This intermediate preparation contains soluble insulin and protamine in proportions which combine so as to leave no excess of either in the end-product. In large doses of 40 or more units it may act for as long as 24 hours, but in smaller doses it often fails to control the fasting blood-sugar level. It is best given as morning and evening injections in those insulin-sensitive cases in which the action of soluble insulin is too strong and not sufficiently prolonged to prevent relapse before the next injection. It can also be given in the same way as P.Z.I. to prolong the action of soluble insulin, but, in the author's experience, is more likely to give rise to hypoglycaemia six to eight hours after the injection.

The Lente Insulins (Insulin Zinc Suspensions)

These consist of semi-lente (I.Z.S. amorphous), ultra-lente (I.Z.S. crystalline), and lente (I.Z.S.).

Semi-lente insulin closely resembles isophane (N.P.H.) in action but differs from it in not being miscible with soluble insulin. It can, however, be mixed with ultra-lente without any change in the individual actions of the two insulins.

Ultra-lente insulin has a very similar action to that of P.Z.I., but again cannot be mixed with soluble insulin.

Lente insulin is a 3:7 mixture of semi- and ultra-lente insulins and is probably the most suitable available preparation for treatment with a single morning injection. It gives good control in almost all mild and most moderately severe cases, the usual range of dosage being from 16 to 48 units. In more severe diabetics higher dosage is required, and control is apt to be more variable and uncertain. It is the author's practice not to exceed a dose of 60 units; if this fails to control the diabetes it is usually better to use two injections of S.I. or possibly a mixed dose of S.I. and P.Z.I. One of the chief disadvantages of lente insulin is that it fails to prevent relapse due to infection or other causes.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Hydrenox (Boots).

NaClex (Glaxo)

These are preparations of hydroflumethiazide, which is another diuretic compound derived from chlorothiazide ("To-day's Drugs," February 28, p. 582). Its structure is similar to that of hydrochlorothiazide ("To-day's Drugs," May 9, p. 1238), but the chlorine atom is replaced by a trifluoromethyl (CF_3) radicle. It was developed in Copenhagen under the trade-name "rontyl."¹⁻³

Qualitatively the diuretic effect of hydroflumethiazide is similar to, and probably identical with, that of chlorothiazide and hydrochlorothiazide. Quantitatively on a weight basis it is more potent than chlorothiazide, and equal to or slightly less potent than hydrochlorothiazide.

The indications for treatment with hydroflumethiazide are the same as for other diuretics. The dosage range is 50 to 200 mg. daily. Because of the liability to induce depletion of potassium, the drug should be given on alternate days or for only three to four days each week, and a potassium supplement must be added if treatment is continued for more than a few days.

N.H.S. basic price: hydrenox and nalex, tabs. 50 mg., 100 for 24s.

REFERENCES

- ¹ Kobinger, W. and Lund, F., *Ugeskr. Læg.*, 1958, 120, 1583.
- ² Hobolth, N., Thomsen, K., Hansen, P. F., Hagensen, N. R., and Oprešnik, J., *ibid.*, 1958, 120, 1585.
- ³ Sele, V., *ibid.*, 1958, 120, 1592.

"So far as the ordinary practitioner is concerned, education in preventive medicine and public health is an entirely good thing and in any event touches him personally at few points and then only lightly at worst. Education in disease, however, is a different matter. So far as a number of our patients are concerned, we believe we are quite safe in asserting that most of what they are told goes in one ear and out the other. But there are a minority, and often an extremely awkward minority, who are passionately interested in their bodies and the diseases they may acquire, sometimes so much as to rank as obsessives or neurotics. To them a little knowledge is a most dangerous thing. They question the doctor and often argue with him. They waste his time and sometimes pester him. Their half-baked notions are often ludicrous, and unhappily, though it should be one of the first things every doctor learns, no more than anybody else has he the capacity to suffer fools gladly. Small wonder then that when irritated by one of these individuals he damns disease education and all those engaged in it heartily and to all eternity. . . . What between the 'hints' of the Ministry, the stunts of the politicians, the 'education' of the television authorities, and the frank intimidation of the patent medicine vendors, the modern Englishman will soon surpass the popular conception of his American equivalent, living from pep-pill in the morning to enable him to earn a living, to his tranquillizer at night to soothe the nameless terrors that beset him. Such, it seems, is progress and the good life!"—From an Editorial, *Medical Press*, May 13, 1959, p. 418.