

# Diabetes today — a review and update (Part IV)

— L I Robertson



## Summary

*This is the fourth and last part of a practical approach to the understanding of diabetes mellitus, its terminology, diagnosis and etiology as well as clear guidelines to the management of the diabetic patient in general practice. Part 4 deals in particular with complications and newer research findings world-wide.*

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**KEYWORDS:** Diabetes Mellitus; Insulin; Self Assessment; Self Medication; Patient Education; Compliance.

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There are two minor complications which result, not from the diabetes, but from the subcutaneous injection of exogenous insulin. These are insulin lipo-atrophy and lipodystrophy.

### INSULIN LIPO-ATROPHY

This complication results from localised immune complexes formed in the subcutaneous fat due to impurities in the insulin preparations, but is rarely seen these days. Full thickness atrophy of subcutaneous fat occurs, leaving scalloped areas of varying size right down to the fascia. As our modern insulin preparations are free from these impurities, the complication is rare unless the insulin has been stored under abnormal conditions such as when accidental freezing has occurred.

Modern purification methods allow for a high degree of purity and freedom from other protein contaminants such as were common in older preparations. Some of our modern insulins are purified by single

chromatography (for example SP-insulin (Lilly), CR- and CS-insulins (Hoechst) and Mono-pic insulin (Organon).) Others are doubly chromatographed like monocomponent (MC) insulin (Novo), single-component (SC) insulin (Lilly) and porcine RI insulin (Nordisk).

### Treatment

These (often hideously deforming) atrophic areas can be made to fill up, thus restoring the normal contours by the simple expedient of using purified insulin (e.g. monocomponent) directly into the atrophic areas for a short while, and we have seen filling up and reversion to normal contour in as little as two weeks. We have recently seen a young lady who had been an insulin dependant diabetic for three years who developed atrophy while on monocomponent insulin which had been exposed to near freezing temperatures while she was on an ocean-going liner. She had five or six deep lipo-atrophic areas which were clearly visible through her tight-fitting blue

jeans. These were no longer visible after three weeks of injecting from a new vial of the same mono-component insulin directly into the affected areas.

### INSULIN LIPODYSTROPHY

This is a far commoner complication, and it would appear that the incidence depends on how carefully one examines the injection sites of IDDM patients. We found, in a survey in our clinic, that some 50 % of our IDDM patients had one or more lipodystrophic areas. They result from the use of repeated injections of insulin into the same circumscribed region resulting in fatty hypertrophy. It is likely that the successful treatment of insulin lipo-atrophy as described

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### *Deforming atrophic areas could be restored by changing the way of injecting the insulin.*

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above depends on this tendency to fatty hypertrophy if injections are constantly given in the same subcutaneous areas. On switching sites the hypertrophic areas gradually disappear. Again, patients have to be educated in the rotation of injection sites.

### INSULIN MICRO-ABSCESSSES

This disorder results from injecting insulin too superficially, and almost intradermally. Pigmented acneiform lesions result and may take years to disappear. Modern insulin syringes have fixed micro-fine needles which are short enough to permit for injections being given virtually at right angles to the skin instead of the oft-recommended 45°, as most patients, except the very thin, have a sufficient depth of subcutaneous tissue.

### THE DIAGNOSTIC "GREY AREA" OF DIABETES MELLITUS

The first two parts of this update may have left the impression that the diagnosis (of IDDM or NIDDM) is always clearcut. In practice, however, there are many instances where one cannot be sure whether a particular patient requires exogenous insulin or not. These are usually middle-aged patients who have had a fairly acute onset of symptoms with some weight-loss, polydipsia and polyuria. Ideally, it would be useful to be able to check C-peptide secretion with or without stimulation using glucagon, but in practice one generally tries the effect of oral hypoglycaemic agents first.

Of course, the presence of ketonuria and/or severe weight loss is generally a clue that we are dealing with a patient who requires exogenous insulin. An even commoner dilemma is to decide when a patient (hitherto regarded as NIDDM and treated as such) is running out of beta-cell reserve (and requires insulin). The problem is compounded by the fact that even when the decision to use insulin is made these patients have so much peripheral insulin resistance

that enormous doses of insulin are required to achieve even mediocre control. And if they are obese, as they may well be, they may continue to gain weight while remaining hyperglycaemic.

It was thus exciting to hear from Augustin-Pascal and his co-workers at the recent Madrid meeting of the International Diabetic Federation (IDF) that in 50 % of their NIDDM patients with secondary failure to oral hypoglycaemic agents, a ten-day period of tight glycaemic control using IV insulin infusion restored the efficacy of the oral hypoglycaemic drugs and that this respite lasted for at least a year. We are at present repeating this research in some of our NIDDM patients with secondary oral failure.

To end this review and update, I should like to discuss some of the newer methods of insulin delivery and take a brief glimpse into the future of diabetes management.

### CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII).

CSII, using an insulin pump, has been used for the past decade or more. These devices allow for a more physiological replacement of insulin, which, when combined with other elements of optimal diabetic monitoring and care, may result in near-normalisation of blood-glucose and the other hormonal and metabolic and functional abnormalities. Unfortunately it is exorbitantly expensive and time-consuming and not without risk. We have, for example, noted with increasing concern the number of reports of the acceleration of previously existing diabetic proliferative retinopathy. (In fairness, it should be emphasised that this is more a reflection on the fact that this optimization has been started too late which is responsible, rather than the method itself). Except for pregnancy, however, the long-term benefits of CSII have not yet been clearly demonstrated. It may be employed in highly motivated patients who are likely to adhere to the instructions for its use and the careful monitoring necessary to ensure that good control results from CSII. In fact, it must be admitted that most of the IDDM patients who fall into this well-motivated category could be as satisfactorily managed with the use of one or other of the intensified insulin regimens.

### INTENSIFIED INSULIN REGIMENS

These regimens, involving three to four daily insulin injections are being increasingly used and with gratifying success. One of these regimens was discussed in Part II, namely the four injection regime using a night-time basal delivery insulin ("Ultratard HM") and three pre-prandial injections of a short-acting insulin ("Actrapid HM") which was conveniently given with a pen injector device ("Novopen"). It offers accurate, virtually painless delivery in an easily transportable form. We have observed, way past the three-month trial period, continued decreases in HbA<sub>1c</sub> levels, as well as patients who glorify in their

new-found freedom from the tyranny of fixed meal-times and those everlasting "snacks" which made weight control so difficult for the fashion conscious. The success of this sort of regime can be easily imitated by employing a single daily dose of an intermediate acting insulin and two or three pre-prandial injections of a short-acting soluble insulin. Initially, these patients should be encouraged to test their blood sugar before each meal and learn how much to give in order to avoid both hypo- and hyper-glycaemic excursions.

Another line of research has been into methods of administering insulin in ways which avoid pain, the benefits of which will be obvious, particularly in the young child on a multiple injection regime. Thus we have seen the development of devices which enable mixtures of insulin to be given in the form of a painless jet. Intranasal aerosolised insulin is also

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### *Thousands of diabetics are dying for the want of elementary medication.*

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being extensively investigated but the delivery of insulin in this form is still very much in the realm of the research centre. Yagi and his Japanese co-workers have also been investigating insulin delivery per rectum using suppositories containing insulin with emamine derivatives and sodium salicylate as adjuvants and promoters, with very encouraging results.

For some time now researchers have been involved in trying to produce an artificial endocrine pancreas. The principle drawback was a means of monitoring glucose excursions which was small enough to be portable (unlike the "Biostator", which meant the patient was tethered to his hospital ward much as the patient who has had an artificial pump-driven heart).

Shichiri and his team have come closest to the completely portable artificial endocrine pancreas with the development of their needle type glucose sensor. They developed a telemetry glucose monitoring system utilizing such a needle type sensor. This is coupled to a computer which works out the amounts of insulin and/or glucagon necessary to maintain glucose homeostasis and sends a signal to a double pump system which delivers the required amount of these two hormones. And all of this is a little larger than a couple of 30-packs of cigarettes and fits round the patient's waist, permitting exercise.

Prof A Michael Albisser of Toronto Children's Hospital has also done extensive original research into these artificial endocrine pancreas systems but it is interesting that he is far more keen to enthuse over his latest brainchild which – if you have followed this review – would seem both a retrograde step as well as an anachronism. He has used a small Hewlett Packard calculator with an extra "chip"

and, using algorithms based on *urine tests* (1), enabled the calculator to give to its young IDDM operators an accurate readout of the doses and mixtures of insulin which were necessary for optimal control. And when I expressed my scepticism he was able to convince me that to judge by their lowered HbA1c levels, these child diabetics were doing very well (and without daily finger-pricks) thanks to this novel method of management.

David Sutherland at Minneapolis and many other workers in Europe and Japan have been performing pancreatic transplants for some time now. These are either done at the same time as renal transplantation or, more recently, in diabetics who are not in renal failure. There are at present some 250 patients alive after pancreatic transplantation, and, allowing for the drawbacks associated with the need for immunosuppressive therapy, these diabetics are doing well in that they have reverted to complete euglycaemia and reversal of the other metabolic disorders.

There is also a great deal of experimental work being carried out in many centres worldwide into the transplantation of islet-cells. At the recent International Symposium on Diabetic Complications at the Hague, A. Taunton-Rigby reported on a novel method of encapsulating islet-cells in a way which may obviate the need for any immunosuppressive therapy at all. The use of this method in human diabetics is awaited with interest.

Finally, there is some tremendously exciting work being done using cyclosporin in recent-onset IDDM. As discussed in a previous section, there is little doubt that IDDM has auto-immune components to its aetiology and pathogenesis. There is also little doubt that T-cells are involved and they have been found in the insulinitis which predates the severe beta-cell destruction. Cyclosporin is T-cell specific. Bach and his co-workers in France are at present conducting a randomised trial into the use of cyclosporin in recent onset IDDM patients. The initial results are promising indeed. Their first two patients have been followed for 26 months now and not only has it been possible to reduce the dose of cyclosporin but there has been no need for insulin, except for a very short while in one patient who had a successful pregnancy while on the trial. The fact that cyclosporin carries both the risk of renal toxicity as well as long-term risks of lymphoma production have of course to be considered before recommending this form of semi-prophylactic therapy.

All of these new research methods are exciting and promise well for the diabetics of the future, but we would do well to remember that while all this esoteric research is being carried out in the affluent first world, there are still thousands of diabetics who are dying for the want of insulin or for the lack of even the most elementary means of monitoring their glycaemic control.

And many of these are fellow South Africans.