CONVENTIONAL insulins contain several impurities such as proinsulin, C-peptide, polymers of insulin (Steiner et al, 1968) and other pancreatic peptides (Bloom et al, 1976). All are immunogenic (Schlichtkrull et al, 1972) and may lead to the development of insulin-binding antibodies in patients using insulin preparations containing them. As a result, some patients develop local skin sensitivity, lipoatrophy or lipohypertrophy at the site of insulin injection. A few develop resistance to insulin and require very large daily doses of insulin to control their diabetes.

Highly purified insulin preparations are now available (Montgomery, 1977). They contain less impurities and have been reported to cause less complications (Bruni et al, 1973). In order to assess their effectiveness, two groups of patients have been studied. Thirty-seven patients were changed electively from conventional beef insulin to highly purified pork insulin, and 16 patients with juvenile onset diabetes were treated with highly purified pork insulin from the time of diagnosis.

PATIENTS

The patients all attend the Diabetes Clinic of the Royal Victoria Hospital, Belfast. Those transferred to highly purified pork insulin were selected because of poor control of their diabetes, high dose of beef insulin, early microvascular changes or evidence of local reactions to beef insulin such as skin sensitivity, lipoatrophy or lipohypertrophy.

At intervals during the six months before transfer to highly purified insulin, daily insulin dose, 2 to 3 hour post-prandial plasma glucose, body weight and dietary intake were recorded for each patient. These continued to be recorded during the follow-up period of 6 to 12 months. The patients were asked to report any hypoglycaemic attacks which occurred during the period of study. All were admitted to hospital initially because of reported concern about severe hypoglycaemic reactions following transfer to highly purified insulin (Asplin and Hartog, 1976). They were changed either to Leo Neutral and Leo Retard (Nordisk) or to Actrapid MC and Monotard MC (Novo). These patients were divided into three sub-groups depending on their mean daily dose of insulin during the six months before changeover (Table 1).

The patients treated with highly purified insulin from the time of diagnosis had daily insulin dose, 2 to 3 hour post-prandial plasma glucose and body weight recorded during a follow-up period of six months. These were compared with the results for a similar group of patients, started on conventional insulin five years ago, who were matched for age, sex, body weight and dietary intake.
TABLE 1: PATIENTS CHANGED FROM CONVENTIONAL BEEF INSULIN TO HIGHLY PURIFIED PORK INSULIN WITH SUB-GROUPS ACCORDING TO THEIR MEAN DAILY DOSE OF INSULIN.

| Sub-Group | Changeover | Number of patients | Mean daily insulin dose prior to changeover | Mean Number of years diabetes ± S.E.M. | Mean Number of years diabetes ± S.E.M. |
|-----------|------------|--------------------|-------------------------------------------|----------------------------------------|----------------------------------------|
| A         | 40 units or less | 10                 | 47.7 ± 5.1                                | 17.4 ± 3.5                             |
| B         | 41-80 units    | 17                 | 39.2 ± 5.2                                | 8.9 ± 1.6                              |
| C         | More than 80 units | 10                | 28.7 ± 4.7                                | 11.8 ± 3.1                             |

RESULTS

The effect on daily insulin dose of changing to highly purified pork insulin is shown in Fig. 1. There were marked variations within each sub-group. In sub-group A seven patients showed changes of less than 10 per cent in daily insulin dose after transfer to highly purified insulin. The other three patients showed a rise of more than 10 per cent. In sub-group B eight patients showed a change of less than 10 per cent, four an increase of more than 10 per cent, and five a decrease of more than 10 per cent. In sub-group C four patients showed a change of less than 10 per cent, one an increase of more than 10 per cent, and five a decrease of more than 10 per cent. One patient in this sub-group showed a decrease of 79 per cent in daily insulin dose one month after changing to highly purified insulin. This was maintained during the follow-up period.

![Graph showing mean ± S.E.M. daily insulin dose before and after changeover to highly purified insulin.](image)

**Figure 1:** MEAN ± S.E.M. DAILY INSULIN DOSE BEFORE AND AFTER CHANGEOVER TO HIGHLY PURIFIED INSULIN (\(^*\)P<0.05). NUMBERS IN COLUMNS INDICATE NUMBER OF PATIENTS REPRESENTED.
No significant change in dietary intake occurred in any of the sub-groups, which is reflected by the absence of any major change in body weight (Fig. 2). Degree of diabetic control is difficult to assess. Figure 3 shows mean 2 to 3 hour post-prandial plasma glucose of the three sub-groups. These were in the 10-15 mmol/l range before transfer and are disappointingly high, but despite increased efforts to improve control after changing to highly purified insulin, plasma glucose levels did not change significantly in sub-groups A and C. There was a transient improvement in sub-group B which was not associated with any significant change in insulin dose. No increase in clinical hypoglycaemia attacks occurred after changeover to highly purified insulin. Three patients in this group with local skin sensitivity to conventional insulin showed no sensitivity with highly purified insulin. Six other patients with lipoatrophy or lipohypertrophy showed improvement when changed to a purified preparation.

![Figure 2: Mean ±S.E.M. Body weight before and after changeover to highly purified insulin. Numbers in columns indicate number of patients represented.](image)

The daily insulin dose in the patients started on highly purified insulin at the time of diagnosis was slightly higher but not significantly different from that in the patients on conventional insulin. However, only those on highly purified insulin showed a fall in daily insulin dose during the follow-up period (Table 2). Dietary intake and body weight showed no change in either group. There was a significant fall in 2 hour post-prandial plasma glucose in the group on highly purified insulin but not in those on conventional insulin.
**FIGURE 3:** Mean ±S.E.M. 2 to 3 hour post-prandial plasma glucose before and after changeover to highly purified insulin (*p < 0.05). Numbers in columns indicate number of patients represented.

**TABLE 2:** Mean ±S.E.M. daily insulin dose in units (purified and conventional) in patients with juvenile onset diabetes (*p < 0.05).

| Type of insulin | One month after starting | Three months after starting | Six months after starting |
|-----------------|---------------------------|-----------------------------|---------------------------|
| Highly purified | 40.8 ± 4.0                | 35.5 ± 3.2*                 | 31.1 ± 3.2*               |
| Conventional    | 31.6 ± 2.6                | 32.8 ± 3.3                  | 34.0 ± 4.2                |

**DISCUSSION**

With the advent of highly purified insulins it has become important to decide which patients should receive them. These results are similar to those from many other centres in showing that patients with local skin sensitivity, lipoatrophy or lipohypertrophy on conventional insulin are much improved on highly purified insulin. Patients on very high doses of conventional insulin, usually due to the presence of high titres of insulin-binding antibodies, also benefit by getting a substantial reduction in daily insulin dose. However, for the majority of patients there is either no reduction or only a modest reduction in insulin dosage. Further-
more, no improvement in their diabetic control was observed so that it is unlikely that the diabetic who is well or moderately controlled on conventional insulin will gain any therapeutic benefit from changing to a highly purified preparation. Insulins from both Danish manufacturers were used in this study and no important differences were observed between them.

The group of juvenile onset diabetics started on conventional insulin showed no change in insulin dose after six months. However, after five years, nine of the patients, in whom comparison was valid, showed a very marked rise from a mean of 31.8 to 50 units/day in the absence of change in weight, dietary intake or 2 to 3 hour post-prandial plasma glucose. Information on long-term follow-up of the patients on highly purified insulin is not available, but Andreani et al (1974) showed that there was no increase in insulin dose up to two years with these less immunogenic preparations. It would therefore seem reasonable to use these insulins in patients receiving treatment for the first time. Whether this will result in any improvement in the long-term complications of diabetes remains to be seen.

SUMMARY

Clinical experience with the new insulins in two groups of patients is described. In a group of 37 patients, changed electively from conventional beef insulin to highly purified pork insulin, only those on more than 80 units/day of beef insulin showed a marked fall in insulin dosage after changeover. This fall was not maintained up to one year in the majority of patients. There was no improvement in diabetic control after changeover, but marked improvement in local reactions to insulin did occur. Sixteen patients with juvenile onset diabetes were treated with highly purified pork insulin from the time of diagnosis. There was no significant difference in insulin dosage during the first six months of treatment compared with that in a similar group of patients started on conventional insulin five years ago. Those on conventional insulin showed a marked rise in insulin dosage after five years. Information on long-term follow-up of those on highly purified insulin is not available. Indications for the use of the new insulins are discussed.

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REFERENCES

Andreani, D., Iavicoli, M., Tamburrano, G. and Menzinger, G. (1974). Comparative trials with monocomponent (MC) and monospecies (MS) pork insulins in the treatment of diabetes mellitus. Influence on antibody levels, on insulin requirement and on some complications. Hormone and Metabolic Research, 6, 447.

Asplin, C. M. and Hartog, M. (1976). Hazards of monocomponent insulins. British Medical Journal, 1, 1146.

Bloom, S. R., Adrian, T. E., Mitchell, S. J., Barnes, A. J. and Kohner, E. M. (1976). Dirty insulin, a stimulant to autoimmunity. Diabetologia, 12, 381.
Bruni, B., D'Alberto, M., Osenda, M., Ricci, C. and Turco, G. L. (1973). Clinical trial with monocomponent lente insulins. Diabetologia, 9, 492.

Montgomery, D. A. D. (1977). Modern insulin and insulin therapy in diabetes mellitus. Ulster Medical Journal, 47, 39.

Schlichtkrull, J., Brange, J., Christiansen, A. H., Hallund, O., Hedting, L. G., and Jorgensen, K. H. (1972). Clinical aspects of insulin—antigenicity. Diabetes, 21, 649.

Steiner, D. F., Hallund, O., Rubenstein, A., Cho, S. and Bayliss, C. (1968). Isolation and properties of proinsulin, intermediate forms and other minor components from crystalline bovine insulin. Diabetes, 17, 725.