but their doses were lower.^{13 14} The most common side effect was dizziness; 11 of those taking the 60 mg/kg dose complained of this symptom compared with only one of those receiving a total dose of 30 mg/kg, which suggests that the symptom may be dose dependent. Abdominal pain and diarrhoea also occurred but were mild. Although these symptoms are common in patients with *S. mansoni* infection, they were probably caused, at least in part, by the drug since they occurred immediately after treatment.

Most (53) of the patients on a total dose of 60 mg/kg passed reddish urine on the second day of treatment. No other urinary abnormality was found, and a metabolite of the drug might have been responsible. I am unaware of any similar findings by other workers, but patients should be warned so that they do not become alarmed.

Eosinophilia has been reported after antichistosomal treatment with hycanthone.^{15 16} And the eosinophil count increased significantly in the patients in this study. This may represent an immunological response to the dying worms and release of antigens, as the peak increase had occurred by day 12. The only abnormality in liver function values was a transient rise in SGPT on the fifth and 12th days after treatment. Axton and Garnett¹⁷ noticed no significant changes in the SGPT in their patients after oxamniquine treatment, while Prata *et al*¹³ reported increases in both SGOT and SGPT. Our patients showed no significant change in SGOT, but oxamniquine was given orally, and the increase in SGOT in the trial of Prata *et al* might be explained by the use of intramuscular injections and resulting myositis. The rise in the SGPT in our patients may suggest either a transient hepatic toxicity caused by the drug, or a shift of worms to the liver. The role played by each factor is difficult to determine.

The fact that oxamniquine was also effective in reducing the egg count in patients who were not cured may prove useful in control programmes. The percentage reduction in the number of eggs was over 90% on the total dose of 60 mg/kg, and there was a smaller but still significant reduction in the number of

eggs on the 40 mg/kg and 30 mg/kg doses. These findings suggest that control programmes in developing countries can use lower doses, and so reduce costs, to effectively reduce transmission of *S. mansoni* infection, despite the lower cure rate.

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Autoimmunity in juvenile diabetics and their families

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Summary and conclusions

Pancreatic islet cell, thyroid, and gastric antibodies were studied in 116 young insulin-dependent diabetics and 257 relatives. Seventy-four per cent of the diabetics studied within three months of diagnosis had islet-cell antibodies but only 20% of those studied three years or more after diagnosis. Persistence of these antibodies was associated with a high prevalence of thyrogastric autoimmunity, which suggests that some cases have an aetiology similar

to that of "polyendocrine" autoimmune disease. Retinopathy or nephropathy, or both, was present in 10 diabetics, who were all members of "autoimmune" families, in which one or more members had organ-specific antibodies. Nine of the 10 healthy relatives with islet-cell antibodies and all families with more than one diabetic were also in this autoimmune group.

These data suggest that an autoimmune factor may contribute to juvenile diabetes and that such autoimmune diabetes has a tendency to run in families and may be more likely to cause complications.

Introduction

Autoantibodies to pancreatic islet cells were first described in patients with diabetes mellitus who also had polyendocrine autoimmune diseases.^{1 2} Islet-cell antibodies were subsequently found in 60-85% of newly diagnosed patients with juvenile diabetes.³ In these patients the antibodies are strongly associated with diabetes of short duration, and two to five years after diagnosis their prevalence has fallen to less than 20%.⁴⁻⁶ Whether an association exists between islet-cell and thyrogastric antibodies is unclear,⁴ and there are few data on thyrogastric

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autoantibodies in the families of juvenile diabetics^{7,8} and none on islet-cell antibodies. We have studied a series of young insulin-dependent diabetics and first-degree relatives to examine further the role of islet-cell and other organ-specific autoantibodies in juvenile diabetes.

Patients and methods

We took blood samples from three-quarters of the patients who were currently attending the paediatric diabetic clinic at the Radcliffe Infirmary, Oxford, a few patients from other diabetic clinics, and

TABLE 1—Prevalence of islet-cell antibodies in diabetic children according to duration of diabetes, in first-degree relatives, and in healthy controls

	No	% with islet-cell antibodies
Diabetics 1-3 months after diagnosis	27	74
Diabetics 4-12 months after diagnosis	16	75
Diabetics 13 months-3 years after diagnosis ..	27	41
Diabetics 3 years 1 month-16 years after diagnosis	46	20
First-degree relatives	257	4
Healthy controls	207	0.5

Relation of persistent islet-cell antibodies in juvenile diabetics to "polyendocrine auto-immunity."

TABLE II—Data on the seven families with more than one diabetic member

Family	Affected members	Age (y)	Duration of diabetes (y)	Treatment	Retinopathy	Nephropathy	ICA	Organ-specific antibodies	Organ-specific antibodies in unaffected members	No of non-diabetic members
1	Son Son Daughter Daughter	25 23 22 10	16 12 13 4	Insulin Insulin Insulin Insulin	+* +* +* —	— — — —	+ — — —	None None Thyroid None	Thyroid (mother) Thyroid (daughter) Gastric (daughter)	7
2	Father Son	41 12	22 <1	Insulin Insulin	+† —	+ —	— —	None None	Gastric (mother) Gastric (son)	3
3	Father Daughter Father's brother	37 8 39	30 2 18	Insulin Insulin Insulin	+† — +‡	+ — —	— + —	Gastric Thyroid None Gastric		3
4	Father Son	37 13	21 1	Insulin Insulin	+‡ —	+ —	— —	None None	Thyroid (mother)	2
5	Father Daughter	52 18	1 13	Oral agents Insulin	— —	— —	— —	Thyroid None	Gastric (mother)	3
6	Daughter Son	17 13	6 2	Insulin Insulin	— —	— —	— —	None Somatostatin cell	Gastric (mother)	2
7	Son Son	13 6	2 1	Insulin Insulin	— —	— —	— +	None None	Thyroid (mother) Gastric Thyroid (father)	4

*Extensive background and proliferative retinopathy.

†Severe proliferative retinopathy causing blindness.

‡Severe proliferative retinopathy.

ICA = Islet-cell antibodies.

three older diabetic siblings—a total of 116 patients (59 males and 57 females), aged 2-30 (mean 11) years. The time since diagnosis ranged from one week to 16 years. Where possible we obtained repeat samples (at two- to four-monthly intervals) from those who were positive for any of the autoantibodies we were studying. Three or more samples were taken from 27 patients.

We also took blood samples from as many as possible of the patients' first-degree relatives—in all 257 (150 parents, 105 siblings, and two uncles) representing 79 completed families. Those family members who had any of the autoantibodies were followed up in the same way as the probandi.

We obtained a detailed clinical history of the autoimmune disease from each family (usually from the mother) and, where possible, examined the hospital notes of the diabetics. The fundi of young diabetic patients and their relatives were examined under clinic conditions through a clear lens by one of the investigators (JIM or JDB). A diagnosis of retinopathy was, however, confirmed by an ophthalmologist in all cases.

Sera from 207 blood donors were also tested.

LABORATORY METHODS

Sera were tested while fresh or after storage at -20° for up to a year.

Immunofluorescence tests—The standard sandwich technique was applied with undiluted sera, and titres were established with serial dilutions to end-point.¹ Islet-cell antibodies were detected on fresh post-mortem blood group O human pancreas (unfixed 5 nm cryostat sections). Weak reactions were always confirmed on at least two different pancreatic substrates. Islet-cell antibodies react with all islet cells uniformly⁹ but some sera also stain discrete cells at the periphery of pancreatic islets; these contain either glucagon-cell antibodies or somatostatin-cell antibodies.¹⁰ To identify the cell type we applied a double immunofluorescence technique, using the respective hormone antisera raised in rabbits.¹¹ Gastric parietal cell antibodies were detected on group O human stomach obtained at partial gastrectomies. All screening tests were done with fluorescent sheep anti-human-Fab conjugate prepared in the laboratory. The double technique was performed with goat anti-human and anti-rabbit Ig conjugates.

Haemagglutination tests—Thyroglobulin and thyroid microsomal antibodies were estimated with commercial kits (Burroughs Wellcome and Fujizaki Ltd) of formalinised sheep red blood cells coated with human thyroglobulin (TGHA) and with thyroid microsomes (MCHA). The minimum titres we took as positive were 1/20 for TGHA and 1/100 for MCHA. The MCHA titre of 1/100 corresponds roughly to cytoplasmic immunofluorescence staining on undiluted serum and the method is highly specific for the thyroid.

We did not look for any other tissue antibodies in this series, though nuclear, smooth muscle, and mitochondrial antibodies were recognised when present on the pancreas and stomach sections.

Results and comment

DIABETIC CHILDREN

Our results confirmed that in children the prevalence of islet-cell antibodies is related to the duration of diabetes (table I). But only one of the 10 patients tested under the age of 6 years (seven being tested at the time of diagnosis) was positive.

Thyroid or gastric antibodies, or both, occurred in 21 of the 116 patients (11 of the 57 females and 10 of the 59 males) and in 13 out of 52 (25%) of those with islet-cell antibodies and seven out of 65 (10%) of those with no islet-cell antibodies. These differences are more striking in patients with persisting islet-cell antibodies (figure). A trend is apparent and the difference in prevalence of thyrogastric antibodies between the two groups becomes significant in the patients who had had diabetes for more than three years ($P < 0.001$).

Three of the patients had microaneurysms. One girl was diagnosed as being clinically hypothyroid at 15 months and became diabetic at 2½. Another child had a goitre, and a third showed a transient fall in thyroxine concentration to 60 nmol/l (4.7 µg/100 ml) and a concomitant rise in thyrotrophin (12 mU/l) at the time of diagnosis. They were all positive for thyrogastric antibodies. Glucagon- and somatostatin-cell antibodies are difficult to detect in the presence of islet-cell antibodies unless they happen to be of a different immunoglobulin class or a higher titre. One of the children with no islet-cell antibodies was positive for somatostatin-cell antibodies.

FIRST-DEGREE RELATIVES

Fifty-two of the 79 families investigated had at least one non-diabetic relative with organ-specific antibodies. Only four members of these "autoimmune" families had clinical autoimmune thyroid disease (two thyrotoxic and two hypothyroid), and none had diagnosed atrophic gastritis, pernicious anaemia, or Addison's disease. Of the 52 diabetic children in the autoimmune families, 14 had thyrogastric antibodies but only one of the 27 from "non-autoimmune" families ($P < 0.025 > 0.01$).

Seven families had more than one diabetic member and in one remarkable family four of the nine children were affected (table II). All seven families were "autoimmune." Seven of the diabetic members (aged 22-52 years) had retinopathy and three had nephropathy (one of these had nephrotic syndrome and the other two steadily increasing concentrations of blood urea). The diabetic members without complications were under 19, except for one father who had had diabetes for only one year.

The three children with evidence of thyroid malfunction were all members of the families with serological evidence of autoimmunity. In addition, two of the first-degree relatives had somatostatin-cell antibodies and one had glucagon-cell antibodies.

Ten of the healthy relatives had islet-cell antibodies and nine of these belonged to autoimmune families (table III). We retested eight

of these 10 within six months. The titre had risen in two and remained static in five others. Only one, a 10-year-old sister, had no antibodies in the second test; in this family none of the members, even the diabetic patient, had any organ-specific antibodies. None of the relatives with islet-cell antibodies had abnormal fasting blood glucose levels.

Non-organ-specific antibodies were not conspicuous. Nuclear antibodies were found in four diabetics and ten relatives.

Discussion

The data presented here confirm that there is a high prevalence of islet-cell antibodies in children at the time of diagnosis of insulin-dependent diabetes and that they tend to disappear with time.⁴⁻⁶

A striking association was apparent between persistence of these antibodies and evidence of autoimmunity to other endocrine glands. Even among children who did not have persisting islet-cell antibodies, 11% had organ-specific antibodies—far more than would be expected in normal children of comparable age (2-4%). This finding confirms the autoimmune association suggested by studies carried out before testing for islet-cell antibodies became possible. We and others^{8 12 17 18} have postulated that "polyendocrine" diabetes in adults might represent a primary autoimmune disorder comparable to cases of thyroiditis, gastritis, or adrenalitis in which ordinary virus infections cannot be incriminated. In this type of diabetes mellitus there is a prominent genetic predisposition to organ-specific autoimmunity and an association with tissue types HLA-B8, DW3, and DW4.¹⁹⁻²¹ Possibly some of the children with persistent islet-cell antibodies have an embryonic form of polyendocrine disease, with an increased prevalence of the same tissue types. HLA studies are under way in these families. Polyendocrine disease, whether clinically or serologically evident, is rare in children. But one of our young patients on developing diabetes suffered from myxoedema, another had a goitre, and a third had a short episode of hypothyroidism. All three had thyrogastric antibodies.

All the families with more than one diabetic showed some evidence of organ-specific autoimmunity. In these families there appeared to be a high frequency of vascular complications (though only one of the *propositi* had islet-cell antibodies persisting for more than three years). The high prevalence of complications among the relatives could be explained by the fact that they had had diabetes a long time. But complications are certainly not an inevitable result of long-standing diabetes and further studies are needed to resolve this problem. A slight

TABLE III—Data on the ten families having a non-diabetic member with islet-cell antibodies

Family	ICA-positive non-diabetic member				Diabetic member			Organ-specific antibodies in other members	No of other members
	Relationship to <i>propositus</i>	Age (y)	Change in titre on repeat test	Organ specific antibodies	Duration of diabetes (y)	ICA	Organ-specific antibodies		
1	Brother	12	Rise	Somatostatin cell Gastric	12	+	Thyroid Gastric	Thyroid (father) Thyroid (mother) Thyroid (sister)	5
2	Father	47	No change	None	11	+	Thyroid Gastric	Thyroid (mother) Gastric	2
3	Brother	13	Rise	Gastric	10	+	Thyroid Gastric	Thyroid (father) Gastric (mother) Gastric (brother)	4*
4	Mother	47	No change	None	1	+	None	Gastric (father)	2
5	Brother	19	No change	None	3	—	None	Gastric (mother)	4
6	Father	39	No change	Thyroid Gastric	4	—	None	Thyroid (mother) Gastric	2
7	Sister	17	Not repeated	None	<1	+	None	Somatostatin cell (mother)	2
8	Brother	24	Not repeated	None	<1	—	None	Thyroid (mother)	3*
9	Brother	16	No change	Thyroid	5	—	Thyroid	Thyroid (mother) Thyroid (sister)	3
10	Sister	10	Fall	None	6	—	None	None	3

*Including one sibling who was not tested.
ICA = Islet-cell antibodies.

correlation with vascular diseases has also been shown in adults, particularly women, with myxoedema and premixxoedema.^{22 23}

The other organ-specific pancreatic antibodies, glucagon- and somatostatin-cell antibodies, are sometimes found in diabetics together with islet-cell antibodies, and also in some non-diabetics with a family history of type I or insulin-dependent diabetes mellitus.²⁵ They tend to persist in the serum and might thus represent another marker of the genetic tendency to pancreatic autoimmunisation.

Healthy relatives with islet-cell antibodies also belonged to "autoimmune" families, and in at least three out of nine cases the diabetic member had had these antibodies for 10-12 years. Patients with polyendocrine autoimmune disease may develop islet-cell antibodies as long as ten years before clinical diabetes.^{12 24 26} This may also happen in people who have relatives with serological evidence of organ-specific autoimmunity. Follow-up studies are needed to confirm that islet-cell antibodies are a marker for potential diabetes. Our data suggest that any search for people with these antibodies should be concentrated in families with an autoimmune predisposition. Identifying such individuals will be particularly important if it ever becomes possible to prevent diabetes in those who are susceptible. The suggestion from our data that autoimmune diabetes may have a stronger tendency to run in families and be more likely to cause complications than in non-autoimmune families needs to be confirmed by further investigations.

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CONDENSED REPORT

Renal vein renin measurements in children with hypertension

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Summary and conclusions

Renal venous renin activity was measured in 50 children with hypertension. Main renal vein and segmental renal vein sampling was feasible in children as young as 15 months. In all cases in which there was a clear difference in renin secretion between the kidneys—that is, a main vein renin ratio above 1.5—surgery, when undertaken, successfully restored normal blood pressure. Most of the

children with main renal vein renin ratios below 1.5 had bilateral disease or apparently normal kidneys. Segmental renal vein sampling contributed useful information additional to that provided by main renal vein measurements and permitted identification of local sources of renin production.

In children with renal transplants who developed hypertension renal vein renin measurements helped in determining the cause and facilitating the management of the raised blood pressure.

Introduction

The use of renal vein renin measurements in identifying surgically curable forms of renal hypertension in adults is well established.¹⁻³ Nevertheless, only limited data are available on their use in evaluating hypertension in children. This is due to the large quantities of blood needed for plasma renin assays and the difficulties in taking samples from young children. Some reports indicate that renal vein renin measurements aid assess-

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