the use of the device. Hagenfeldt[1] reported a constant rate after the first 60 days, while Timonen[6] found a steady decline in the rate of loss. The regression equation we derived showed a decline in the rate of copper loss from all sizes of device throughout their use, which gradually became less dependent on the available copper surface area. If this equation is valid for longer periods of time we predict that a 200-mm^2 copper IUD would lose 0·046 μmol/day (2·9 μg/day) copper after one year of use, 0·027 μmol/day (1·7 μg/day) after two years, and 0·019 μmol/day (1·2 μg/day) after three years. Thus a device with 5400 mm^2 copper surface area would be required to obtain the reported release rate of 0·71 μmol/day (45 μg/day) after two years. These figures suggest that the long-term use of IUDs dependent on copper for their contraceptive action is of dubious value. Furthermore, a recent report[5] showed a significant increase in the failure rate of copper IUDs after two years' use, which could be prevented by replacing the device at that time.

The decrease in available copper was probably related to the appearance of the surface layer on the copper. In this short study we identified the early deposit as a protein layer, though long-term in-vivo studies show a calcareous deposit formed after extended use.[3] We could not determine the chemical composition of the protein layer, though albumin was probably one of the active constituents.

Investigations suggest that the presence of a copper-albumin surface complex on IUDs is important in the facilitation of copper removal.[7 11] We found that the low molecular-weight components of tissue culture medium were important in sustaining the release of copper, and that copper loss was inhibited by protein-containing solutions. The presence of albumin in the surrounding medium contributes to the copper release, as an equilibrium exists between the copper associated with the low molecular-weight components of the tissue culture medium and that which is bound to the albumin in solution. A similar dual location for the free copper probably exists in vivo, where a copper-amino-acid-albumin complex has been suggested as an intermediate step in the uptake of copper (fig 5).[12] The observed uptake of copper from IUDs probably occurs by this route, with the subsequent rapid excretion of this excess copper.[13]

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Acetylator phenotype in diabetic neuropathy

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Summary

The proportions of slow and fast acetylators in a group of diabetics with symptomatic peripheral neuropathy were compared with those in a group of diabetics who had had the disease for at least 10 years without developing neuropathy. There was a significantly higher proportion of fast acetylators in the group of diabetics without neuropathy than in those with neuropathy or in the normal population.

Hence genetic factors separate from the diabetic diathesis may determine the development of neuropathy in any particular diabetic.

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Introduction

The exact pathogenesis of the complications of diabetes is unknown but they are thought to be secondary to the metabolic abnormality, and they increase with the duration of the disease and poor control.[1] Only a few patients, however, develop complications regardless of the duration of their diabetes. Thus the overall prevalence of symptomatic peripheral neuropathy is about 20%,[2] yet in a group who had had diabetes for more than 40 years the prevalence of neuropathy was only 15%.[3] Why only this small proportion of patients develop neuropathy in the presence of a presumably common metabolic abnormality is unknown, but possibly there is a genetic susceptibility to complications.

The rate of acetylation of certain drugs, including the antituberculosis drug isoniazid and sulphonamides, is genetically determined, and the population may be divided into slow and fast acetylators.[4] Slow acetylators are more likely to develop neuropathy when treated with isoniazid.[5] Because a similar genetic dimorphism might influence the development of neuropathy in diabetes we decided to determine the acetylator phenotypes of diabetics with and without neuropathy.

TABLE I—*Details of patients in groups 1 and 2. (Percentages given in parentheses)*

	Age in years ± 1 SE	Sex		Type of diabetes		Years of treatment ± 1 SE	Type of treatment	
		M	F	Juvenile	Maturity		Insulin	Diet ± OHA
Group 1 (n = 66)	64 ± 12	24 (36)	42 (64)	24 (36)	42 (64)	18·5 ± 2·1	43 (65)	23 (35)
Group 2 (n = 64)	56 ± 6	26 (41)	38 (59)	25 (39)	39 (61)	10·9 ± 3·9	37 (58)	27 (42)
	P < 0·01	NS		NS		P < 0·001	NS	

NS = Not significant. OHA = Oral hypoglycaemic agents.

TABLE II—*Percentage acetylation of serum sulphadimidine six hours after ingestion in 49 patients*

% Acetylation	10–	17·5–	25–	32·5–	40–	47·5–	55–	62·5–	70–	77·5–85	Total
No of patients	4	5	8	7				7	10	8	49

TABLE III—*Percentage acetylation of urinary sulphadimidine five hours after ingestion in 81 patients*

% Acetylation	19–	26·7–	34·4–	42·1–	49·8–	57·5–	65·2–	72·91–	80·6 –	88·3–96	Total
No of patients	4	12	21			5	10	14	8	7	81

Patients and methods

Informed consent was obtained from suitable White patients attending diabetic clinics in Sheffield and Leicester. No patient had a history of sulphonamide sensitivity.

Group 1 comprised 66 patients who had had diabetes for more than 10 years and had no clinical evidence of peripheral or autonomic neuropathy except for loss of vibration sense at the ankle in those over 65.

Group 2 comprised 64 patients with diabetes of any duration who had signs of peripheral neuropathy or amyotrophy. Symmetrical peripheral neuropathy was defined as loss of light touch or pain sensation or both in the legs in a stocking distribution combined with absent ankle jerks. Amyotrophy was defined as proximal weakness, pain, and wasting in the hip flexors and quadriceps with reduced or absent knee jerks. Autonomic neuropathy was defined as the combination of typical symptoms—for example, impotence or diarrhoea—with at least one objective sign, such as postural hypotension or abnormal response to the Valsalva manoeuvre. Only patients with unequivocal clinically detectable signs were included in group 2, but no attempt was made to grade the severity of the neuropathy because of the lack of objective measurement. Loss of ankle jerks and vibration sense was not sufficient for inclusion in the group. Patients with a blood urea concentration exceeding 12 mmol/l (72 mg/100 ml) were excluded to preclude the possibility of impaired renal function affecting the test.

Group 3 consisted of normal people culled from the data of Evans.[6]

Six normal volunteers were given a single 100-mg dose of chlorpropamide to see whether this drug could be measured with the assay procedures. Causes of peripheral neuropathy other than diabetes were eliminated by careful questioning, but serum vitamin B_{12}, folic acid, and the Wassermann reaction were noted in all cases. Acetylator status was determined according to the method of Evans.[6] Sulphadimidine 750 mg was given in the fasting state, and the concentrations of free (F) and total (T) sulphadimidine were measured either in serum collected six hours after ingestion or in an aliquot of urine five hours after ingestion. The percentage of sulphadimidine acetylated was calculated as $(T-F)/T$. Statistical significance was determined with use of the t test or χ^2 test, as appropriate, with Yates's correction in a 2 × 2 contingency table.

Results

Groups 1 and 2 were comparable in sex distribution, type of diabetes, and type of treatment. Those without neuropathy (group 1), however, were significantly older and had been treated significantly longer than those with neuropathy (table I). In group 2 the preponderant lesion was symmetrical peripheral neuropathy (43 cases). Of the remaining patients, nine had autonomic and peripheral neuropathy, six amyotrophy, and six amyotrophy and peripheral neuropathy. No patient in either group had abnormal serum vitamin B_{12} or folate concentrations. The Wassermann reaction was negative in all cases.

Table II shows the frequency distribution of the percentage acetylation of sulphadimidine in the 49 patients assessed by serum analysis. There was a clear separation ($P < 0·01$) between slow acetylation (mean 26·5 ± 1 SE of mean 2·2%) and fast acetylation (74·0 ± 1·6%). Eighty-one patients were assessed by urine analysis (table III), and again there was a clear separation ($P < 0·01$) between slow and fast acetylation (mean values 36·7 ± 5·7% and 78·4 ± 9·9% respectively). The distribution of serum and urine tests in groups 1 and 2 was similar. In four normal volunteers given chlorpropamide no sulphonamide was detected in the serum, nor in two was any found in the urine.

Table IV shows the distribution of acetylator phenotypes in the two groups of patients compared with the results of Evans[6] for a control population (group 3). There was a significantly lower proportion of slow acetylators in group 1 than in the normal population ($\chi^2 = 6·71$; $P < 0·01$) or group 2 ($\chi^2 = 5·17$; $P < 0·05$). Group 2 did not differ significantly from the controls. When groups 1 and 2 were combined, however, the overall prevalence of slow acetylators was 47%, which, though lower than in the control series, was not significantly so ($P > 0·1$).

TABLE IV—*Distribution of acetylator phenotypes in groups 1-3*

Acetylator status	Group 1	Group 2	Group 3
Slow	24 (36%)	37 (58%)	35 (61%)
Fast	42 (64%)	27 (42%)	22 (39%)
Total	66	64	57

When the distribution of juvenile- and maturity-onset diabetes was compared in patients with fast and slow acetylator phenotypes (table V) there was no significant difference.

TABLE V—*Distribution of juvenile- and maturity-onset diabetes in fast and slow acetylators*

	Fast	Slow	Overall
Juvenile-onset ..	27 (39%)	22 (36%)	49 (38%)
Maturity-onset ..	42 (61%)	39 (64%)	81 (62%)
Total	69	61	130

Discussion

Although we used two methods to determine acetylator status, Evans[6] had shown that these gave identical separation. We also felt that it was valid to compare our data with his population survey data. In our series slow acetylators were less common among diabetics who had had the disease for at least 10 years without developing neuropathy than among those with neuropathy or the normal population. An increased proportion of fast acetylators was reported[7] in a series of unselected diabetics, but in our series the preponderance of fast acetylators was seen only in the group without neuropathy. The difference between the two groups of diabetics makes it unlikely that this preponderance was due merely to linkage between acetylator and putative diabetic genes. Nor could there be a relation with the histocompatibility genes, since there was a similar distribution of acetylator phenotypes between patients with juvenile-onset and maturity-onset diabetes, yet HLA-B8, BW15, and BW18 are increased in frequency only in juvenile-onset diabetes.[8]

The association between freedom from neuropathy and fast acetylator phenotype was similar to that found in patients taking isoniazid.[5] In isoniazid neuropathy, however, axonal degeneration is the main pathological lesion,[9] whereas in diabetes segmental demyelination is usually seen.[10] Hence the two neuropathies are unlikely to have a common aetiology, such as pyridoxine deficiency. Recently, however, axonal degeneration was reported in experimental diabetic neuropathy.[11]

Our findings suggest that genetic factors unrelated to the diabetic diathesis may interact with the metabolic abnormality of diabetes to determine whether a patient develops a neuropathy. Clearly the impaired ability to acetylate may have aetiological significance.

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BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life

Final report to the Medical Research Council

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Summary

The Medical Research Council's trial of BCG and vole bacillus vaccines in the prevention of tuberculosis in Great Britain has ended after 20 years' follow-up of the 54 239 participants, who were aged 14 to 15 years when they entered the trial in 1950-2. Participants who were tuberculin positive on entry were left unvaccinated; those who were tuberculin negative were allocated at random to an unvaccinated or to a vaccinated group.

The protective efficacy of each of the two vaccines, among those initially tuberculin negative, was 84% during the first five years, and gradually decreased, averaging 77% for each vaccine over the whole period. The incidence of tuberculosis decreased substantially in all groups during the trial, however, and of the total of 610 cases of tuberculosis only 27 developed between 15 and 20 years. Thus we cannot make a reliable assessment of efficacy during this final period.

The prevalence and incidence of tuberculosis in Great Britain have decreased radically since this trial began. The expected benefit from large-scale BCG-vaccination of children is now far less, and may decrease further if the incidence of tuberculosis continues to decline.

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Introduction

In 1950 the Medical Research Council started a controlled clinical trial of the effects of BCG and vole bacillus vaccines during adolescence and early adult life. Over 50 000 children of both sexes, nearly all aged 14 to 15½ years on entry, participated. All were initially free from both active tuberculosis and known contact with the disease at home and originally lived in urban or suburban areas in or near north London, Birmingham, and Manchester. Those with negative reactions to tuberculin on entry were vaccinated with BCG or vole bacillus vaccine or left unvaccinated, according to a method of random allocation. All the participants, including those who initially had positive reactions to tuberculin, were followed up to discover the cases of tuberculosis that occurred among them.

The four reports already published[1-4] gave further details of the trial and showed that the two vaccines conferred substantial protection against tuberculosis for 15 years after vaccination. This paper is intended only as a supplement to those reports; it extends the information on protection up to 20 years after vaccination, at which stage the trial ended.