Survey of the human acetylator polymorphism in spontaneous disorders

D A PRICE EVANS

From the Department of Medicine, Riyadh Armed Forces Hospital, PO Box 7897, Riyadh 11159, Kingdom of Saudi Arabia.

SUMMARY There is ample evidence that the human acetylator phenotypes are associated with drug induced phenomena. It is principally the slow acetylators who exhibit toxic adverse effects because of their relative inability to detoxify the original drug compounds. In rare instances, however, it is the rapid acetylators who are at a disadvantage.

In the matter of association of spontaneous disease with either acetylator phenotype, there are two groups of disorders to consider. First, disorders in which carcinogenic amines are known to be an aetiological factor. This is because these amines are substrates for the polymorphic N-acetyltransferase activity and hence there is a possible rational basis for searching for an association. Secondly, other disorders where searches for associations are based more on hunches.

In the first group there is a definite statistical association between cancer of the bladder and the slow acetylator phenotype. In prevalence studies the slow phenotype is 39% more associated with bladder cancer than is the rapid phenotype. On the basis of the evidence now available it is not possible to say whether this association is because slow acetylators develop the disease more frequently or whether they survive longer. In the second group the relevant studies show (1) a greatly increased prevalence of slow acetylators in Gilbert's disease; (2) a confirmed association between the rapid acetylator phenotype and diabetes; (3) a possible association between the rapid acetylator phenotype and breast cancer; (4) a possible association between the slow acetylator phenotype and leprosy in Chinese patients; (5) an earlier age of onset of thyrotoxicosis (Graves' disease) in slow acetylators than in rapid acetylators; (6) no evidence of an association between either phenotype and spontaneous systemic lupus erythematosus.

There are many published studies on the relationship of the acetylator polymorphism to drug induced disorders. Slow acetylators exhibit toxic reactions to the original unchanged drug compound more frequently than rapid acetylators. In a few clinical situations, however, rapid acetylators fare worse than slow acetylators. A number of publications describe surveys of the acetylator phenotypes in patients with spontaneous disorders. The objective of this article is to evaluate these studies.

Methods

POINTS WHICH HAVE TO BE CONSIDERED IN STUDIES OF ASSOCIATIONS BETWEEN THE ACETYLATOR POLYMORPHISM PHENOTYPES AND SPONTANEOUS DISORDERS

(1) Was the disease entity being investigated adequately defined?

On the whole it is preferable to have the disease

entity defined by some internationally accepted criterion, for example, systemic lupus erythematosus (SLE) as defined by the American Rheumatological Association.¹ There was very little value in, for example, publishing the phenotypes of 100 patients with various lung disorders without providing details of the diagnoses.²

(2) Was the ethnic composition of both patient and control groups defined?

It is essential to know the ethnic composition of the patient and control groups. For example, in the otherwise excellent paper of Zacest and Koch-Weser,³ the ethnic composition of the group of 20 hypertensives studied in Boston, Massachusetts is not stated. Sometimes an arbitrary assumption with regard to ethnic group seems warranted, for example, presumably Lawson *et al*⁴ were studying SLE and rheumatoid arthritis in white Glasgow citizens.

Received for publication 30 September 1983.
Accepted for publication 23 November 1983.

(3) *Was the patient sample a stratum (that is, derived from a selected group within the population)?*

It is preferable to have as unselected a sample of the disorder being investigated as possible. Sometimes, however, a selection is inevitable, for example, it is possible that a particularly severely afflicted group is studied simply because they attend a special hospital clinic for the disorder under consideration.

(4) *Was the phenotyping test performed in a technically satisfactory manner, that is, was the phenotype definition satisfactory?*

It is clear that ambiguous results (subjects with 'intermediate' results) are best avoided by rigorous attention to detail. For example, when using the sulphamethazine test of Evans,⁵ some investigators omit the collection of the blood sample and rely solely on the urine specimen. Obviously the same confidence cannot be placed in the results as if both specimens were collected and their results demonstrated to be in agreement with each other in the form of a scattergram. The separation between the two phenotypes must be clear. When a diagram is constructed from the data in Godeau *et al.*,⁶ for example, it is not possible to assess the phenotype frequency in their systemic lupus erythematosus patients, so this study is not considered further.

(5) *Did the disease condition being investigated interfere with the phenotyping test?*

Since the sulphadiazine phenotyping test of Evans⁵ depends upon renal and hepatic function, disorders of the kidney and liver could interfere with the results obtained.

Fine and Sumner,⁷ who studied 10 uraemic patients, state that there is a relatively greater retention of acetyl sulphadiazine in uraemia. This could influence the phenotyping procedure by producing an increased ratio of acetylated drug in the blood and a diminished ratio in the urine. Furthermore, the acetylation process is induced in severe and prolonged uraemia. Hall,⁸ however, gives evidence from phenotyping 57 patients with varying degrees of diminished creatinine clearance, and his scattergram shows two distinct groups, viz slow and rapid acetylators. (There is a difference between absolute values and the overall pattern, and it is the latter which gives the phenotyping.)

With regard to liver disorders, Levi *et al.*⁹ showed in 29 subjects with serum bilirubin concentrations less than 2 mg/100 ml that isoniazid half life distributions show a clear bimodal curve enabling phenotype recognition as in healthy subjects. In 39 subjects with serum bilirubin concentrations greater than 2 mg/100 ml the antinode is so blurred that phenotype recognition is not possible.

A group of patients with potential liver damage is alcoholics. Lester¹⁰ showed isoniazid half life data on 28 alcoholics (without ethanol in their blood) and the distribution would appear to be bimodal as in healthy subjects. However, he found that maintenance of 0.02 to 0.04% ethanol in the blood before and during the determination of the half lives resulted in a 30% decrease in the half lives in both groups of subjects. Similarly, Olsen and Morland¹¹ showed that the presence of about 1 g/l of ethanol in the blood decreased the apparent half life of sulphadiazine by about 20% in both acetylator phenotypes. Olsen and Morland¹² showed that ethanol causes a significant reduction in the plasma half life of procainamide with an increase in total clearance. This effect occurs in both phenotypes. The volume of distribution was unaffected.

The position and activity of the subjects being phenotyped may be of importance. For example, Levi *et al.*⁹ point out that isoniazid half lives in patients with liver disease are increased by about 20% by the change from lying to walking. On the other hand, pretreatment with other drugs (mainly with barbiturates) has no effect on the distribution curve of isoniazid half lives in normal subjects.

An increased acetylation of sulphadiazine of six undernourished as compared with six well nourished subjects was demonstrated by Shastri and Krishnaswamy.¹³ In a further investigation,¹⁴ however, undernutrition was found not to alter the acetylator phenotype of male adults. Similarly, malnutrition does not seem to have affected the results of phenotyping numerous series of tuberculous patients.¹⁵

Complete Freund's adjuvant and hydrocortisone administration result in 'induction' of acetylation of sulphadiazine (syn:sulfamethazine) in the rabbit.¹⁶ It is not clear whether this effect is mediated via the reticuloendothelial system or via hepatocytes. The effects of such processes on phenotyping human patients is at present unknown.

Considering neoplastic disease, Bulovskaya *et al.*¹⁷ describe not only an increased frequency of the rapid acetylator phenotype, but also increased acetylating activity within both phenotypes in carcinoma of the breast. The present author knows of no other published series of acetylator phenotyped breast cancer patients. Lavigne *et al.*¹⁸ report an increased acetylation of para-amino-salicylate (PAS) in patients with lymphosarcoma and acute and chronic leukaemia. It is known that PAS is monomorphically and not polymorphically acetylated in man. Nevertheless, the possibility exists that there may be a general enhancement of acetylating capability in some neoplastic disorders. It is clear,

however, that the presence of a bronchial carcinoma does not affect the phenotyping test result (unpublished results).

(6) Satisfactory control series for comparison

Satisfactory control series are required (as mentioned above) before any association between phenotype and disorder can be assessed. This is probably the most difficult point of all. It is generally considered that unaffected sibs constitute the most satisfactory control group for studies of associations between disorders and genetic phenotypes.¹⁹ Other possible controls which may be used are unrelated domiciliary controls²⁰ or general population controls. Using other patients who do not suffer from the disease being investigated is generally not considered a good idea because their afflictions may have some relationship to the polymorphism in question. A considerable body of data is required to rule out such a possibility.

(7) Reproducibility of the statistical association

Because of the difficulties outlined above, credence increases when similar results have been obtained by different investigators in widely different locations. For example, the highly significant association between bladder cancer and slow acetylator status shows no statistical heterogeneity between five series.²¹

Results

There is a clear cut association between the slow

acetylator phenotype and presence of bladder cancer. This phenotype is 39% more frequently associated with this disease than it should be by chance. There is no heterogeneity between different series (table 1).

In one series,²⁸ studied with great care, there is a highly significant association between the slow acetylator phenotype and Gilbert's disease (table 2).

In a study of Graves' disease,²⁹ it was found that the phenotype frequencies did not differ from those in the general population. However, slow acetylators did develop the disease at a significantly younger mean age than rapid acetylators (29.5 years as compared with 39.5 years).

TABLE 2 The acetylator phenotypes in Gilbert's syndrome.²⁸

	Slow acetylator	Fast acetylator	Total
Reference population	39	37	76
Gilbert's syndrome	21	6	27
Total	60	43	103

$$\chi^2_1 = 5.73, p < 0.02.$$

TABLE 3 Breast cancer data.¹⁷

	Slow acetylators	Rapid acetylators	Total
Breast cancer	13	28	41
Controls	24	14	38
Total	37	42	79

$$\chi^2_1 = 7.83, p < 0.01.$$

TABLE 1 Test of association between bladder cancer and acetylator phenotype. Modification by Haldane²² of the method of Woolf.²³

	No of subjects				Approximate relative risk x	$\log_e x$ $= y$	Sampling variance V	Weight $\frac{1}{V} = w$	Significance of difference from zero wy^2
	Bladder cancer		Controls						
	Slow	Rapid	Slow	Rapid					
Lower <i>et al</i> ²⁴ Danish*	46	25	38	36	1.7288	0.5474	0.1124	8.8963	2.6657
Lower <i>et al</i> ²⁴ Swedish*	80	35	79	39	1.1267	0.1193	0.0776	12.8827	0.1834
Cartwright <i>et al</i> ²⁵ †	74	37	118	89	1.4921	0.4002	0.0592	16.9016	2.7054
Woodhouse <i>et al</i> ²⁶ ‡	21	9	16	13	1.8517	0.6161	0.2757	3.6270	1.3767
Liverpool series ²¹	66	34	510§	342	1.2932	0.2571	0.0484	10.6748	1.3666

$$\text{Weighted mean value of } y = Y = \frac{\sum wy}{\sum w} = \frac{20.7208}{62.9824} = 0.3290.$$

$$\text{SE of } Y = (\sum w)^{-\frac{1}{2}} = 0.1260.$$

$$95\% \text{ fiducial limits of } Y = Y \pm 1.96 \cdot \text{SE}(Y) = Y \pm (2.78 \times 0.126) = 0.6793 \text{ and } -0.0213.$$

$$\text{Antilog of } Y = X = \text{combined estimate of values of } x = 1.389.$$

$$\text{The equivalent } X \text{ values to the } 95\% \text{ fiducial limits of } Y \text{ are } 1.9725 \text{ and } 0.9789.$$

$$\text{Significance of difference of } X \text{ from unity} = \chi^2_1 = \frac{(\sum wy)^2}{\sum w} = 6.8170 (p < 0.01).$$

$$\text{Heterogeneity expression is tested by } \chi^2_{k-1} = \sum wy^2 - \frac{(\sum wy)^2}{\sum w} = 1.4824 (p > 0.10).$$

*Technique of phenotyping: Weber and Brenner.²⁷ †Technique of phenotyping: monoacetyl dapsone/dapsone ratio in plasma.

‡Technique of phenotyping: plasma isoniazid half life. §Pooled Liverpool control data: see first part of table 5.

From: Evans *et al*.²¹

A surprising finding¹⁷ was both an increased frequency of the rapid acetylator phenotype and also an increased acetylating capacity within both phenotypes of patients with breast cancer (table 3).

Following an initial small study by Mattila and Tiitinen,³⁰ subsequent reports show an association of the rapid acetylator phenotype with diabetes mellitus

(see tables 4, 5, and 6). The criticism could be made that diabetics of different types are pooled in table 4. Unfortunately, each UK diabetic series was not accompanied by its own control series, and so a Woolf²³/Haldane²² analysis is only possible for diabetes using pooled UK data.

Shenfield *et al*³⁴ suggest the possibility that a high

TABLE 4 *Diabetes mellitus.*

Reference	Type of diabetes	Location where study conducted	Ethnic group	Technique of phenotyping	Total No of patients	No of slow acetylators	q	SE (q)	Upper confidence limit	Lower confidence limit
30	Juvenile	Helsinki	Finns	Serum isoniazid half life	9	2	0.4714	0.1470	0.7654	0.1744
31	Adult	"	"	"	19	13	0.8272	0.0645	0.9561	0.6982
	Random outpatient clinic patients	Oxford	Not stated	5	47	18	0.6189	0.0573	0.7334	0.5043
	Inpatients, poor control, "many juvenile diabetics"	"	"	"	38	19	0.7071	0.0574	0.8218	0.5924
32	Juvenile	Sheffield, Leicester	'Whites'	5	49	22	0.6701	0.0530	0.7761	0.5640
33	Maturity onset	"	"	"	81	39	0.6937	0.0400	0.7739	0.6139
	Insulin dependent without complications	South-east England	Caucasian	5	18	10	0.7454	0.0786	0.9025	0.5882
	Insulin dependent with complications	"	"	"	37	18	0.6975	0.0589	0.8153	0.5797
34	Type 1	Perth,	Causasoids	36	47	12	0.5053	0.0629	0.6312	0.3794
	Type 2	W Australia	of European descent		69	27	0.6255	0.0470	0.7195	0.5316
	Normal control subjects				112	58	0.7196	0.0328	0.7852	0.6540
35	Juvenile onset	Madrid	Presumably	5	32	17	0.7289	0.0605	0.8499	0.6078
	Maturity onset		Spanish		87	50	0.7581	0.0350	0.8281	0.6882
	Controls		Caucasians		157	90	0.7571	0.0261	0.8093	0.7050

TABLE 5 *Details of UK control series (all Caucasian).*

Reference	Health status	Technique of phenotyping	Total No of subjects	No of slow acetylators	q	SE (q)	Upper confidence limit	Lower confidence limit
Liverpool series								
37	Healthy	% urinary sulphamethazine acetylated	58	29	0.7071	0.0464	0.8000	0.6143
38	Tuberculous	INH T _{1/2}	101	67	0.8145	0.0289	0.8722	0.7567
39	Healthy	% urinary sulphamethazine acetylated	119	62	0.7218	0.0317	0.7853	0.6584
40	Non-schizophrenic	"	122	71	0.7628	0.0293	0.8214	0.7043
5	Healthy + tuberculous	% sulphamethazine acetylated in serum and urine	135	84	0.7888	0.0264	0.8417	0.7359
41	Tuberculous	"	95	63	0.8143	0.0298	0.8739	0.7548
42	Healthy	"	44	26	0.7687	0.0482	0.8651	0.6723
43	Healthy	% acetylation of sulphapyridine and sulphamethazine in serum and urine	50	28	0.7483	0.0469	0.8421	0.6545
44	Healthy	5, method 2	27	15	0.7454	0.0642	0.8737	0.6171
45	Healthy	Serum and urine acetylsulphapyridine: total sulphapyridine	26	17	0.8086	0.0577	0.9240	0.6932
46	Healthy	Ratio of acetylisoniazid: isoniazid in urine and plasma	49	30	0.7825	0.0445	0.8714	0.6935
47	Healthy	5, method 2	26	18	0.8321	0.0544	0.9408	0.7233
Total			852	510	0.7737	0.0109	0.7954	0.7520
Non-Liverpool UK controls (additional data to form a UK control series)								
7	Healthy	% sulphamethazine acetylated in blood and urine	25	14	0.7843	0.0663	0.8810	0.6157
4	Healthy	% urinary sulphamethazine acetylated	25	16	0.8000	0.0600	0.9200	0.6800
26	Healthy	INH T _{1/2}	29	16	0.7428	0.0622	0.8671	0.6185
Grand total			931	556	0.7728	0.0104	0.7936	0.7520

INH T_{1/2} = plasma isoniazid half life.

TABLE 6 *Test of association between diabetes and acetylator phenotype. Modification by Haldane²² of the method of Woolf.²³*

Source	No of subjects				Relative incidence x	$\log_e x$ y	Sampling variance	Weight $\frac{1}{V} = w$	Significance of difference from zero wy^2
	Diabetes		Controls						
	Slow	Rapid	Slow	Rapid					
Pooled UK data	126	144	556	375	1.6929	0.5264	0.0192	52.0143	14.4155
34	39	77	58	54	2.1060	0.7448	0.0730	13.7077	7.6041
35	67	52	90	67	1.0428	0.0419	0.0593	16.8723	0.0296

Weighted mean value of $y = Y = \frac{\sum wy}{\sum w} = \frac{38.2994}{82.5944} = 0.4637$.

SD of $Y = (\sum w)^{-\frac{1}{2}} = 0.1100$

95% fiducial limits = $Y \pm 1.96 \text{ SD} = -0.0098$ and 0.9372 .

Antilog $Y = X = 1.5900$.

The equivalent X values to the 95% fiducial limits of Y are 0.9905 and 2.545.

Significance of the difference of X from unity = $\chi^2_1 = \frac{(\sum wy)^2}{\sum w} = 17.7596$.

Homogeneity estimate = $\chi^2_{N-1} = \sum wy^2 - \frac{(\sum wy)^2}{\sum w} = 22.0493 - 17.7596 = 4.2897$.

TABLE 7 *Miscellaneous disorders.*

Reference	Disease category	Locations survey conducted	Ethnic group	Technique of phenotyping	No of patients	No of slow acetylators	q	$SE(q)$	Upper confidence limit	Lower confidence limit
Mental disorders										
49	Chronic schizophrenics on neuroleptics	Helsinki	Finns	INH $T\frac{1}{2}$	29	21	0.851	0.049	0.948	0.753
40	Schizophrenic	Liverpool	British whites	% urinary sulphadimidine acetylated	78	51	0.809	0.033	0.875	0.742
50	Neurotic depression	Newcastle	British whites	INH $T\frac{1}{2}$	25	16	0.8000	0.0600	0.9200	0.6800
	Endogenous depression	"	"	"	25	17	0.8246	0.0566	0.9378	0.7115
51	Neurotic depression	"	"	36	29	19	0.809	0.055	0.918	0.700
	Neurotic anxiety states	"	"	"	28	17	0.779	0.059	0.898	0.661
52	Phobic anxiety states	"	"	"	23	15	0.808	0.061	0.931	0.685
	Neurotic depression	Glasgow	Pre- sumably British whites	5	27	12	0.6667	0.0717	0.8101	0.523
53	Neurotic depression	Glasgow	British whites	5	97	51	0.725	0.034	0.795	0.655
54	Mongolism	Helsinki	Finns	INH $T\frac{1}{2}$	61	41	0.820	0.037	0.893	0.747
Gastrointestinal disorders										
55	Duodenal ulcer	Liverpool	British whites	37	50	28	0.748	0.046	0.842	0.655
56	Postgastrectomy syndrome	Oulu and Helsinki	Finns	INH $T\frac{1}{2}$	13	8	0.784	0.086	0.956	0.612
45	Ulcerative colitis (17), Crohn's disease of ileum and colon (2)	Liverpool	British whites	Serum and urine acetylsulphapyridine: total sulphapyridine	19	11	0.7609	0.0744	0.9098	0.6120
57	Ulcerative colitis (84), Crohn's disease (38)	Edinburgh	British whites	5 and salicyl-azo-sulphapyridine metabolites	122	87	0.844	0.024	0.893	0.796
58	Crohn's disease (14), ulcerative colitis (10), undifferentiated CIBD (4)	Saskatoon, Saskatchewan	Canadian	Serum ratio acetylsulphapyridine: total sulphapyridine	28	19	0.8238	0.0536	0.9309	0.7166
59	Ulcerative colitis (20), Crohn's disease (25)	Buffalo, NY	Not stated	Sulphasalazine metabolism as given in ref 57	45	28	0.7888	0.0458	0.8804	0.6972

TABLE 7—continued.

60	Ulcerative colitis	Oxford	White British	Acetylation of sulphapyridine derived from salicylazo-sulphapyridine	181	112	0.7866	0.0229	0.8325	0.7407
61	Colitis on sulphasalazine	Israel	Israeli (derivation not stated)	Serum ratio acetylsulphapyridine: total sulphapyridine	63	30	0.6901	0.0456	0.7812	0.5989
62	Ulcerative colitis, Crohn's disease	Stuttgart	Not stated	„	65	40	0.7847	0.0384	0.8614	0.7075
Leprosy										
63	Leprosy	Malawi	Malawis	MADDS	17	8	0.686	0.088	0.862	0.510
64	Leprosy	Malaysia	Chinese	DDS	3	1	0.8165	0.0589	0.9344	0.6986
65	Relapsed leprosy	„	„	Isoniazid acetylation	21	15				
	Dapsone-resistant leprosy	Sungei Buloh, Selangor, Malaysia	Malaysian Chinese	„	40	16	0.632	0.061	0.755	0.510
	Non-dapsone resistant leprosy	„	„	„	44	12	0.522	0.064	0.651	0.394
Dermatitis herpetiformis										
66	Dermatitis herpetiformis	London	British whites	5 and MADDS	10	7	0.837	0.087	1.010	0.663
67	„	Helsinki	Finns	DDS	50	28	0.748	0.046	0.842	0.655
68	„	London	British whites	Sulphamethazine similar to ref 37	28	19	0.809	0.054	0.916	0.702
Hypertension										
69	Hypertension (24 accelerated)	St Louis, Missouri	Caucasian Negro	MADDS	37	18	0.816	0.056	0.928	0.705
3	Hypertension	Boston, Massachusetts	Not stated	DDS	30	15	0.707	0.065	0.836	0.578
					37	13	0.806	0.066	0.939	0.674
70	Hypertension	Helsinki	Finns	Sulphamethazine similar to ref 37	23	12	0.722	0.072	0.867	0.578
71	Hypertension	Turku	Finns	5	21	9	0.655	0.0825	0.8195	0.4898
8	Hypertension	Vasteras	Swedes	5	57	30	0.725	0.046	0.817	0.634
72	Hypertension	London	Caucasian Black Indian	5	123	62	0.7100	0.0372	0.7735	0.6465
				Schedule 2	30	16	0.7303	0.0624	0.8550	0.6056
					10	8	0.8944	0.0707	1.0358	0.7531
Cardiac										
73	Ventricular premature beats	Odense	Danes	„	18	12	0.816	0.068	0.953	0.680
74	Cardiac and/or renal disease	Linköping	Swedes	Sulphapyridine also INH T _{1/2}	21	17	0.900	0.048	0.995	0.804
75	Myocardial infarction	Glasgow	Pre-sumably British whites	5	19	12	0.7947	0.0696	0.9339	0.6555
Renal										
76	Uraemia before dialysis	Cardiff	Pre-sumably British whites	Urinary sulphadimidine concentration	10	6	0.775	0.100	0.975	0.575
7	Uraemia on haemodialysis	Glasgow	British whites	Metabolic clearance of sulphadimidine	10	6	0.755	0.100	0.975	0.575
Rheumatology										
4	Rheumatoid arthritis	Glasgow	Pre-sumably British whites	36	25	18	0.8485	0.0529	0.9544	0.7427
77	„	Jyväskylä, Pre-Finland	Pre-sumably Finns	INH T _{1/2}	39	16	0.6405	0.0615	0.7635	0.5175
78	„	Philadelphia	Not stated	81	25	19	0.8718	0.0490	0.9698	0.7738

TABLE 7—continued.

79	„	Jerusalem	Israelis of heterogeneous origin	MADDS DDS	43	28	0.8069	0.0450	0.8969	0.7169
Hepatic										
80	Porphyria cutanea tarda	Madrid	Presumably Spanish	5	51	33	0.8044	0.0416	0.8876	0.7212

INH $T_{\frac{1}{2}}$ = plasma isoniazid half life.MADDS = ratio $\frac{\text{mono acetyl diamino diphenyl sulphone}}{\text{diamino diphenyl sulphone}}$ in urine.

CIBD = chronic inflammatory bowel disease.

TABLE 8 Chinese control subjects.

Reference	Disease category	Location survey conducted	Technique of phenotyping	No of subjects	No of slow acetylators	q	SE (q)	Upper confidence limit	Lower confidence limit
86	Healthy	Taiwan	Plasma INH concentration	121	27	0.4724	0.0401	0.5525	0.3923
87	Tuberculous	Singapore, Hong Kong	Sulphadimidine and INH	386	83	0.4637	0.0225	0.5088	0.4186
				184	40	0.4663	0.0326	0.5315	0.4010
88	Healthy	Liverpool	Plasma INH concentration	59	13	0.4694	0.0575	0.5844	0.3544

INH = isoniazid.

plasma glucose concentration causes greater acetylation in diabetics. They show neither a histogram nor a scattergram of their data. The division between the phenotypes would be expected to be blurred if variably raised plasma glucose was contributing a further component of variance to the distribution of both phenotypes. This would not appear to be so in the scattergram of Bodansky *et al.*³³ Furthermore,

Mattila and Tiitinen³⁰ present a histogram of isoniazid half lives which show a clear bimodality, and the mean isoniazid half life in both phenotypes in diabetics closely resembled those found in non-diabetics. These findings are not at variance with those of Thom *et al.*⁴⁸ whose experimental non-diabetic normal subjects showed shortened isoniazid half lives following large glucose doses.

For many miscellaneous conditions the data available do not suggest any significant association with either acetylator phenotype (table 7).

With regard to leprosy, there is no reliable comparison group for the Malawi patients.⁸²⁻⁸⁵ For the Chinese patients, the pooled estimate is $q = 0.6383$, $SE(q) = 0.0370$ (table 7). The three available Chinese control groups (table 8) give very consistent estimates and when they are pooled $q = 0.4662$, $SE(q) = 0.0162$. This suggests that in Chinese the

TABLE 9 Acetylator phenotypes in Chinese leprosy patients and controls.

	Acetylator phenotype		Total
	Slow	Rapid	
Leprosy patients	44	64	108
Control subjects	163	587	750
Total	207	651	858

 $\chi^2_1 = 17.6$.

TABLE 10 Acetylator phenotyping of hydralazine induced systemic lupus erythematosus patients.

Reference	Location where study conducted	Ethnic group	Technique of phenotyping	Total No of patients	No of slow acetylators
69	St Louis and La Jolla	Caucasian	37	12	12
89	Stockholm and Lulea	Presumably Caucasian	Isoniazid half life	30*	29
90	London, Stoke-on-Trent, and Leicester	Presumably Caucasian	15	26	25
72	London	Caucasian	5	12	11
and Harland SJ, personal communication, 1982		Black Indian	Method 2	1	1
				—	—

*One patient of uncertain status omitted.

TABLE 11 *Systemic lupus erythematosus patients and controls.*

Reference	Disease category	Location survey conducted	Ethnic group	Technique of phenotyping	No of patients	No of slow acetylators	q	SE(q)	Upper confidence limit	Lower confidence limit
91	Spontaneous SLE	Philadelphia	Not stated	MADDS DDS	13	10 definite, 1 probable	0.9199	0.0544	1.0287	0.8111
" 4	Healthy Spontaneous SLE	" Glasgow	" Presumably British white	INH T _{1/2} 36	21 22	10 16	0.6901 0.8528	0.0790 0.0557	0.8480 0.9641	0.5321 0.7415
" 92	Normal Spontaneous SLE	" Linköping	" Presumably Swedes	" INH T _{1/2}	25 15	16 13	0.8000 0.9309	0.0600 0.0471	0.9200 1.0252	0.6800 0.8367
93	"	Mexico	Presumably Mexicans	6 hour acetylated and free INH in plasma and urine	25	24	0.9798	0.0200	1.0198	0.9398
94	"	Cincinnati	US whites, US blacks	41	13 white 12 black 11 white 7 black	10 7 8	0.8771 0.7638 0.6667	0.0666 0.0932 0.0878	1.0103 0.9501 0.8423	0.7438 0.5774 0.4910
95	"	Nashville	"	MADDS DDS						
" 96	Normal Spontaneous SLE	" Denver	Not stated US white, US black, Mexican-American	"	20 15 white 4 black 8 Mexican-American	9 7 2 1	0.6708 0.6831 0.7071 0.3536	0.829 0.0943 0.1768 0.1654	0.8367 0.8717 1.0607 0.6843	0.5050 0.4946 0.3536 0.0228
61	"	New York City	Not stated	"	21	14	0.8165	0.0630	0.9425	0.6905
97	"	Israel Helsinki	Presumably Finns	INH T _{1/2} Sulphamethazine, 100	29 42	16 29	0.7428 0.8309	0.0622 0.0429	0.8671 0.9168	0.6185 0.7451
"	Non-SLE pts, had drug eruptions etc	"	"	"	19	16	0.9177	0.0456	1.0088	0.8265
98	Spontaneous SLE	Tokyo, Fukuoka	Japanese	INH T _{1/2}	19	3	0.3974	0.1053	0.6079	0.1868
"	Healthy subjects	"	"	"	19	2	0.3244	0.1085	0.5414	0.1074
78	Spontaneous SLE	Philadelphia	Not stated	81	10	5	0.7071	0.1118	0.9307	0.4835

SLE = systemic lupus erythematosus.

T_{1/2} = half life.

INH = isoniazid.

MADDS = mono acetyl diamino diphenyl sulphone.

DDS = diamino diphenyl sulphone.

slow acetylators may be more prone than rapid acetylators to develop leprosy (table 9).

Another disorder which merits special consideration is spontaneous systemic lupus erythematosus (SLE). There is a strong association between the slow acetylator phenotype and hydralazine induced SLE (table 10). The idea was therefore promulgated that spontaneous SLE might also be associated with the slow acetylator phenotype. Sufficient information is now available from different ethnographic groups to show that this idea is not tenable (table 11).

Discussion

The interpretation of the association between bladder cancer and the slow acetylator phenotype rests upon the knowledge that carcinogenic amines are polymorphically acetylated.⁹⁰ Since it is usually survivors undergoing regular cystoscopic examina-

tions who are studied, the acetylator phenotype may be considered either to predispose to the development of the disease or to be a factor leading to enhanced survival (as compared with rapid acetylators). Neither the first nor the second of these explanations can be discounted on the evidence at present available.

With regard to the other associations described with (1) Gilbert's disease, (2) diabetes mellitus, (3) breast cancer, (4) leprosy, and (5) age at onset of Graves' disease, logical interpretation is much more difficult. The natural substrates for the polymorphic N-acetyl-transferase enzyme are unknown. It may be speculated that acetyl accepting molecules, for example aromatic amines or amino-methyl-uracils, may be involved in some way in the production of these four disorders. This present survey may stimulate researchers to investigate such possibilities.

References

- ¹ Rabbam NB, Minkin W. Criteria for classification of systemic lupus erythematosus. *JAMA* 1975;**231**:846.
- ² Walstad RA. Inaktivering av medikamenter ved acetylering. *Tidsskr Nor Laegeforen* 1975;**2**:100-3.
- ³ Zacest R, Koch-Weser J. Relation of hydralazine plasma concentration to dosage and hypotensive action. *Clin Pharmacol Ther* 1972;**13**:420-5.
- ⁴ Lawson DH, Henry DA, Lowe J, Reavey P, Rennie JAN, Solomon A. Acetylator phenotype in spontaneous SLE and rheumatoid arthritis. *Ann Rheum Dis* 1979;**38**:171-3.
- ⁵ Evans DAP. An improved and simplified method of detecting the acetylator phenotype. *J Med Genet* 1969;**6**:405-7.
- ⁶ Godeau P, Aubert M, Imbert JC, Herreman G. Lupus erythemateux disseminé et taux d'isoniazide actif. *Ann Med Interne (Paris)* 1973;**124**:181-6.
- ⁷ Fine A, Sumner DJ. Determination of acetylator status in uraemia. *Br J Clin Pharmacol* 1975;**2**:475-6.
- ⁸ Hall S. Evaluation of the sulphadimidine acetylator phenotyping test in patients with reduced renal function. *Act Med Scand* 1981;**209**:505-7.
- ⁹ Levi AJ, Sherlock S, Walker D. Phenylbutazone and isoniazid metabolism in patients with liver disease in relation to previous drug therapy. *Lancet* 1968;**i**:1275-9.
- ¹⁰ Lester D. The acetylation of isoniazid in alcoholics. *Q J Stud Alc* 1965;**25**:541-3.
- ¹¹ Olsen H, Morland J. Ethanol-induced increase in drug acetylation in man and isolated rat cells. *Br Med J* 1978;**ii**:1260-2.
- ¹² Olsen H, Morland J. Ethanol-induced increase in procainamide acetylation in man. *Br J Clin Pharmacol* 1982;**13**:203-8.
- ¹³ Shastri RA, Krishnaswamy K. Metabolism of sulphadiazine in malnutrition. *Br J Clin Pharmacol* 1979;**7**:69-73.
- ¹⁴ Shastri RA. Undernourished adults and acetylation phenotype. *Int J Clin Pharmacol Ther Toxicol* 1982;**20**:194-6.
- ¹⁵ Viznerova A, Sladikova Z, Ellard GA. The determination of the acetylator phenotype of tuberculosis patients in Czechoslovakia using sulphadimidine. *Tubercle* 1973;**54**:67-71.
- ¹⁶ du Souichi P, Courteau H. Induction of acetylating capacity with complete Freund's adjuvant and hydrocortisone in the rabbit. *Drug Metab Dispos* 1981;**9**:279-83.
- ¹⁷ Bulovskaya LN, Krupkin RG, Bochina TA, Shipkova AA, Pavlova MV. Acetylator phenotype in patients with breast cancer. *Oncology* 1978;**35**:185-8.
- ¹⁸ Lavigne JG, Barry A, d'Auteuil C, Delage JM. p-aminosalicylate metabolism in cancer patients sensitive and resistant to chemotherapy. *Br J Cancer* 1977;**35**:580-6.
- ¹⁹ Clarke CA, Edwards JW, Haddock DRW, Howel-Evans AW, McConnell RB. ABO blood groups and secretor character in duodenal ulcer—population and sibship studies. *Br Med J* 1956;**ii**:725-31.
- ²⁰ Evans DAP, Donohoe WTA, Hewitt S, Linaker BD. Le^a blood group substance degradation in the human alimentary tract and urinary Le^a in coeliac disease. *Vox Sang* 1982;**43**:177-87.
- ²¹ Evans DAP, Eze LC, Whibley EJ. The association of the slow acetylator phenotype with bladder cancer. *J Med Genet* 1983;**20**:330-3.
- ²² Haldane JBS. The estimation and significance of the logarithm of a ratio of frequency. *Ann Hum Genet* 1955;**20**:309-11.
- ²³ Woolf B. On estimating the relation between blood group and disease. *Ann Hum Genet* 1954;**19**:251-3.
- ²⁴ Lower GM Jr, Nilsson T, Neson CE, Wolf H, Gamsky TE, Bryan GT. N-acetyltransferase phenotype and risk in urinary bladder cancer: approaches in molecular epidemiology. Preliminary results in Sweden and Denmark. *Environ Health Perspect* 1979;**29**:71-9.
- ²⁵ Cartwright RA, Rogers HJ, Barham-Hall D, et al. Role of N-acetyltransferase phenotypes in bladder carcinogenesis: a pharmacogenetic epidemiological approach to bladder cancer. *Lancet* 1982;**ii**:842-6.
- ²⁶ Woodhouse KW, Adams PC, Clothier A, Mucklow JC, Rawlins MD. N-acetylation phenotype in bladder cancer. *Hum Toxicol* 1982;**1**:443-5.
- ²⁷ Weber WW, Brenner W. A filter paper method for determining isoniazid acetylator phenotype. *Am J Hum Genet* 1974;**26**:467-73.
- ²⁸ Platzer R, Kupfer A, Bircher J, Preisig R. Polymorphic acetylation and aminopyrine demethylation in Gilbert's syndrome. *Eur J Clin Invest* 1978;**8**:219-23.
- ²⁹ Ladero JM, Cano F. Fenotipo acetilador en la enfermedad de Basedow. *N Arch Fac Med* 1983;**41**:79-81.
- ³⁰ Mattila MJ, Tiitinen H. The rate of isoniazid inactivation in Finnish diabetic and non-diabetic patients. *Ann Med Exp Biol Fenn* 1967;**45**:423-7.
- ³¹ Burrows AW, Hockaday TDR, Mann JI, Taylor JG. Diabetic dimorphism according to acetylator status. *Br Med J* 1978;**i**:208-10.
- ³² McLaren EH, Burden AC, Moorhead PJ. Acetylator phenotype in diabetic neuropathy. *Br Med J* 1977;**ii**:291-3.
- ³³ Bodansky HJ, Drury PL, Cudworth AG, Evans DAP. Acetylator phenotypes and type I (insulin-dependent) diabetics with microvascular disease. *Diabetes* 1981;**30**:907-10.
- ³⁴ Shenfield GM, McCann VJ, Tjokresetio R. Acetylator status and diabetic neuropathy. *Diabetologia* 1982;**22**:441-4.
- ³⁵ Ladero JM, Arrojo A, de Salamanca RE, Gomez M, Cano F, Alfonso M. Hepatic acetylator phenotype in diabetes mellitus. *Ann Clin Res* 1982;**14**:187-9.
- ³⁶ Schröder H. Simplified method for determining acetylator phenotype. *Br Med J* 1972;**3**:506-7.
- ³⁷ Evans DAP, White TA. Human acetylation polymorphism. *J Lab Clin Med* 1964;**63**:394-403.
- ³⁸ Gow JG, Evans DAP. A study of the influence of the isoniazid inactivator phenotype on reversion in genitourinary tuberculosis. *Tubercle* 1964;**45**:136-43.
- ³⁹ White TA, Evans DAP. The acetylation of sulfamethazine and sulfamethoxypyridazine by human subjects. *Clin Pharmacol Ther* 1968;**9**:80-8.
- ⁴⁰ Price J. *Demethylation, methylation and schizophrenia. A pharmacogenetic study.* MD thesis, University of London, 1971.
- ⁴¹ Evans DAP, Bullen MG, Houston J, Hopkins CA, Vettors JM. Antinuclear factor in rapid and slow acetylator patients treated with isoniazid. *J Med Genet* 1972;**9**:53-6.
- ⁴² Eze LC, Evans DAP. The use of the Autoanalyser to determine the acetylator phenotype. *J Med Genet* 1972;**9**:57-9.
- ⁴³ Schröder H, Evans DAP. The polymorphic acetylation of sulphapyridine in man. *J Med Genet* 1972;**9**:168-71.
- ⁴⁴ Schröder H, Evans DAP. Acetylator phenotype and adverse effects of sulphasalazine in healthy subjects. *Gut* 1972;**13**:278-84.
- ⁴⁵ Schröder H, Lewkonja RM, Evans DAP. Metabolism of salicylazosulphapyridine in healthy subjects and in patients with ulcerative colitis. *Clin Pharmacol Ther* 1973;**14**:802-9.
- ⁴⁶ Ellard GA, Gammon PT, Tiitinen H. Determination of the acetylator phenotype using matrix isoniazid. *Tubercle* 1975;**56**:203-9.

- 47 Karim AKMB, Evans DAP. Polymorphic acetylation of nitrazepam. *J Med Genet* 1976;13:17-9.
- 48 Thom S, Farrow PR, Santos B, Alberti KGMM, Rawlins MD. Effects of oral glucose on isoniazid kinetics. *Br J Clin Pharmacol* 1981;11:423P.
- 49 Mattila MJ, Takki S. Half-lives of isoniazid and salicylic acid in serum and their modification by different drugs in psychiatric patients. *Ann Med Exp Biol Fenn* 1969;47:124-8.
- 50 Evans DAP, Davison K, Pratt RTC. The influence of acetylator phenotype on the effects of treating depression with phenelzine. *Clin Pharmacol Ther* 1965;6:430-5.
- 51 Marshall EF, Mountjoy CQ, Campbell IC, Garside RF, Leitch IM, Roth M. The influence of acetylator phenotype on the outcome of treatment with phenelzine in a clinical trial. *Br J Clin Pharmacol* 1978;6:247-54.
- 52 Caddy B, Tilstone WJ, Johnston EC. Phenelzine in urine: assay and relation to acetylator status. *Br J Clin Pharmacol* 1976;3:633-7.
- 53 Johnstone ED, Marsh W. Acetylator status and response to phenelzine in depressed patients. *Lancet* 1973;i:567-70.
- 54 Airaksinen E, Mattila MJ, Ollila O. Inactivation of isoniazid and sulphadimidine in Mongoloid subjects. *Ann Med Exp Biol Fenn* 1969;47:303-7.
- 55 Evans DAP. The acetylator phenotypes of duodenal ulcer patients. *Scand J Gastroenterol* 1967;2:289-92.
- 56 Mattila MJ, Frimen A, Larri TKI, Koskinen R. Absorption of ethionamide, isoniazid and aminosalicic acid from the post-resection gastrointestinal tract. *Ann Med Exp Biol Fenn* 1969;7:209-12.
- 57 Das KM, Eastwood MA. Acetylation polymorphism of sulfapyridine in patients with ulcerative colitis and Crohn's disease. *Clin Pharmacol Ther* 1975;18:514-20.
- 58 Sharp ME, Wallace SM, Hindmarsh KW, Brown MA. Acetylator phenotype and serum levels of sulfapyridine in patients with inflammatory bowel disease. *Eur J Clin Pharmacol* 1981;21:243-50.
- 59 Clarke DF, George D, Milsap RL, et al. Sulfasalazine metabolite pharmacokinetics in pediatric patients with inflammatory bowel disease. *Pediatr Pharmacol* 1982;2:323-33.
- 60 Khan AKA, Nurazzaman M, Truelove SC. The effect of the acetylator phenotype on the metabolism of sulphasalazine in man. *J Med Genet* 1983;20:30-6.
- 61 Reidenberg MM, Levy M, Drayer DR, Zylber-Katz E, Robbins WC. Acetylator phenotype in idiopathic systemic lupus erythematosus. *Arthritis Rheum* 1980;23:569-73.
- 62 Fisher C, Klotz U. High performance liquid chromatographic determination of aminosalicylate, sulfapyridine and their metabolites. Its application for pharmacokinetic studies with salicylazosulfapyridine in Man. *J Chromatogr* 1979;162:237-43.
- 63 Ellard GA, Gammon PT, Harris JM. The application of urine tests to monitor the regularity of dapsone self-administration. *Lepr Rev* 1974;45:224-34.
- 64 Ellard GA, Gammon PT, Helmy HS, Rees RJW. Dapsone acetylation and the treatment of leprosy. *Nature* 1972;239:159-60.
- 65 Gelber RH, Rees RJW. Dapsone metabolism in patients with dapsone-resistant leprosy. *Am J Trop Med Hyg* 1975;24:963-7.
- 66 Ellard GA, Gammon PT, Savin JA, Tan RSH. Dapsone acetylation in dermatitis herpetiformis. *Br J Dermatol* 1974;90:441-4.
- 67 Forstrom L, Mattila MJ, Mustakallio KK. Acetylator phenotype, minimal maintenance dose and haemolytic effect of dapsone in dermatitis herpetiformis. *Ann Clin Res* 1974;6:308-10.
- 68 Swain AF, Ahmad RA, Rogers HJ, Leonard JN, Fry L. Pharmacokinetic observations on dapsone in dermatitis herpetiformis. *Br J Dermatol* 1983;108:91-8.
- 69 Perry HM, Tan EM, Carmody S, Sakamoto A. Relationship of acetyl transferase activity to antinuclear antibodies and toxic symptoms in hypertensive patients treated with hydralazine. *J Lab Clin Med* 1970;76:114-25.
- 70 Jounela AJ, Pasanen M, Mattila MJ. Acetylator phenotype and the anti-hypertensive response to hydralazine. *Acta Med Scand* 1975;197:303-6.
- 71 Iisalo E, Laine T, Lehtonen A, Sellman R. Dihydralazine therapy and acetylator phenotype. *Int J Clin Pharmacol Biopharm* 1979;17:119-24.
- 72 Mansilla Tinoco R, Harland SJ, Ryan PJ, et al. Hydralazine, antinuclear antibodies and the lupus syndrome. *Br Med J* 1982;284:936-9.
- 73 Schröder P, Klitgaard NA, Simonsen E. Significance of the acetylator phenotype and the therapeutic effect of procainamide. *Eur J Clin Pharmacol* 1979;15:63-8.
- 74 Molin L, Larsson R, Karlsson E. Evaluation of the sulphapyridine acetylator phenotyping test in healthy subjects and in patients with cardiac and renal disease. *Acta Med Scand* 1977;201:217-22.
- 75 Campbell W, Tilstone WJ, Lawson DH, Hutton I, Lawrie TDV. Acetylator phenotype and the clinical pharmacology of slow-release procainamide. *Br J Clin Pharmacol* 1976;3:1023-6.
- 76 Williams DM, Wimpenny J, Asscher AW. Renal clearance of sodium sulphadimidine in normal and uraemic subjects. *Lancet* 1968;ii:1058-60.
- 77 Oka M, Seppala O. Acetylation phenotype in rheumatoid arthritis. *Scand J Rheumatol* 1978;7:29-30.
- 78 Ehrlich GE, Freeman-Narrod M, Wineburgh GS. Predominance of slow acetylators among patients with rheumatoid arthritis. *Eur J Rheumatol Inflamm* 1979;2:196-8.
- 79 Ehrenfeld M, Levy M, Zylber-Katz E. Acetylator phenotype in rheumatoid arthritis. *Isr J Med Sci* 1983;19:368-70.
- 80 Ladero JM, de Salamanca RE, Chinarro S. Hepatic acetylator phenotype in porphyria cutanea tarda. *Arch Dermatol Res* 1981;270:171-3.
- 81 Peters JH, Gordon GR, Karat AB. Polymorphic acetylation of the antibacterials sulfamethazine and dapsone in South Indian subjects. *Am J Trop Med Hyg* 1975;24:641-8.
- 82 Karim AKMB, Elfellah MS, Evans DAP. Human acetylator polymorphism: estimate of allele frequency in Libya and details of global distribution. *J Med Genet* 1981;18:325-30.
- 83 Hodgkin MM, Eidus L, Bailey WC. Isoniazid phenotyping of black as well as white patients. *Can J Physiol Pharmacol* 1979;57:760-3.
- 84 Glatthaar E, Gartig D, Stander MF, Kleeberg HH. Isoniazid levels in black patients dosed with a matrix preparation (Tebesium). *Prax Pneumol* 1977;31:885-9.
- 85 Eidus L, Glatthaar E, Hodgkin MM, Nel EE, Kleeberg HH. Comparison of isoniazid phenotyping of black and white patients with emphasis on South African blacks. *Int J Clin Pharmacol Biopharm* 1979;17:311-6.
- 86 Sunahara S, Urano M, Ogawa M, Yoshida S, Mukoyama H, Kawai K. Genetic aspect of isoniazid metabolism. *Jpn J Hum Genet* 1963;8:93-111.
- 87 Ellard GA, Gammon PT. Acetylator phenotyping of tuberculosis patients using matrix isoniazid or sulphadimidine and its prognostic significance for treatment with several intermittent isoniazid-containing regimens. *Br J Clin Pharmacol* 1977;4:5-14.
- 88 Evans DAP. Pharmacogenetics. *Am J Med* 1963;34:639-63.
- 89 Strandberg I, Boman G, Hassler L, Sjöqvist F. Acetylator phenotype in patients with hydralazine-induced lupoid syndrome. *Acta Med Scand* 1976;200:367-71.

- ⁹⁰ Batchelor JR, Welsh KI, Mansilla-Tinoco R, *et al.* Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet* 1980;**i**:1107-9.
- ⁹¹ Reidenberg MM, Martin JH. The acetylator phenotype of patients with systemic lupus erythematosus. *Drug Metab Dispos* 1974;**2**:71-3.
- ⁹² Larsson R, Karlsson E, Molin L. Spontaneous systemic lupus erythematosus and acetylator phenotype. *Acta Med Scand* 1977;**201**:223-6.
- ⁹³ Fishbein E, Alarcon-Segovia D. Slow acetylation phenotype in systemic lupus erythematosus. *Arthritis Rheum* 1979;**22**:95-6.
- ⁹⁴ Foad B, Litwin A, Zimmer H, Hess EV. Acetylator phenotype in systemic lupus erythematosus. *Arthritis Rheum* 1977;**20**:815-8.
- ⁹⁵ Vansant J, Woosley RL, John JT, Sergent JS. Normal distribution of acetylator phenotypes in systemic lupus erythematosus. *Arthritis Rheum* 1978;**21**:192-5.
- ⁹⁶ Morris RJ, Freed CR, Kohler PF. Drug acetylation phenotype unrelated to development of spontaneous systemic lupus erythematosus. *Arthritis Rheum* 1979;**22**:777-80.
- ⁹⁷ Johansson EA, Mustakallio KK, Mattila MM, Tiilikainen A. Cutaneous reactions to drugs, acetylation phenotype and HLA antigens in patients with and without systemic lupus erythematosus (SLE). *Ann Clin Res* 1976;**8**:126-8.
- ⁹⁸ Horai Y, Ishizaki T, Sasaki T, Koya G, Matsuyama K, Iguchi S. Isoniazid disposition, comparison of isoniazid phenotyping methods in, and acetylator distribution of Japanese patients with idiopathic systemic lupus erythematosus and control subjects. *Br J Clin Pharmacol* 1982;**13**:361-74.
- ⁹⁹ Glowinski IB, Radtke HE, Weber WW. Genetic variation in N-acetylation of carcinogenic arylamines by human and rabbit liver. *Mol Pharmacol* 1978;**14**:940-9.
- ¹⁰⁰ Mattila MJ, Tiitinen H, Alhava E. Acetylation pattern of different sulphonamides in rapid and slow isoniazid inactivators. *Ann Med Exp Biol Fenn* 1969;**47**:308-15.

Correspondence and requests for reprints to Dr D A Price Evans, Director of Medicine, Riyadh Armed Forces Hospital, PO Box 7897, Riyadh 11159, Saudi Arabia.