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Prodromus to a Twin Study of Sensitivity to Intoxication and Alcohol Metabolism

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As Gibson and Oakeshott[1,2] indicated earlier in this volume, a wide range of biochemical and behavioural responses follow alcohol ingestion and some of these are correlated with such factors as age, sex, body build and drinking experience. However, there is little quantitative information on the relationships amongst the various responses, the extent of individual differences in these responses and the genetic and environmental causes of individual differences. In this paper we describe the design and some preliminary results of an investigation of twins intended to provide such information.

Our sample includes healthy twins of both sexes resident in Sydney and aged between 18 and 35. Each twin participating attends a testing session beginning about 9.00 am, having eaten a light, non-fatty breakfast about an hour earlier. Four sets of variables are measured in an eight hour session; personality and drinking history, parameters of the blood ethanol profile, physiological responses to ethanol and behavioural responses to the ethanol. Before testing begins a 20 ml blood sample and a urine sample are collected; one aliquot of blood is used for typing to establish zygosity and another aliquot of blood and the urine sample are used for quantitative haematological and biochemical assays, including plasma levels of gamma glutamyl transpeptidase, aspartate aminotransferase, alkaline phosphatase and triglyceride, all of which are putative indicators of previous drinking experience.

Subjects are trained on apparatus used to test psychomotor performance and then "pre-alcohol" measurements are taken of all the physiological and behavioural tests. Subjects are given an alcohol dose of 0·75 g ethanol/kg body weight diluted to 10% v/v in sugarless lemon squash (equivalent to about 2/3 to a full bottle of wine) and are asked to drink it in 20 minutes. After a further 20 minutes "post-alcohol" testing begins with repeated measurements of breath alcohol, blood alcohol, blood pressure, pulse, skin temperature, motor co-ordination, body sway, hand steadiness, simple and complex reaction times, cognitive impairment, mental alertness and mood state. Each subject is measured for each of these five times at hourly intervals, although additional readings of breath and blood alcohol are taken to increase information about the profile.

The data will be analysed by the classical twin method, which compares the variances between individuals within pairs of monozygotic (MZ) and dizygotic (DZ) twins. Variance within MZ twin pairs, who are genetically identical, must be due to either error in measurement or individual environmental influences not shared by the twin (E_1). Variance within DZ twin pairs will be due to both genetical and individual environmental differences ($G + E_1$). Environmental differences between families, such as cultural, class and parental treatment influences (E_2) will contribute to between pairs variance equally in both MZ and DZ twins. However, genetical differences between pairs will be relatively more important in MZ than DZ pairs. Use of these inequalities enables estimates of the genetical and environ-

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TABLE 1
Alcohol study—twins tested during 1979

	MZF	MZM	DZF	DZM	DZO	Total
Pairs tested on first occasion	23	18	15	10	13	79
Pairs tested on second occasion	9	11	5	2	2	29
Total	32	29	20	12	15	108 pair days

mental parameters to be obtained by the method of weighted least squares and also tests the adequacy of the model.

The sex, age and zygosity characteristics of the 79 pairs successfully tested during 1979 are given in Table 1. Twenty-nine of these pairs were tested twice to provide data on the repeatability of the traits being measured, allowing us to estimate the relative contributions of measurement error and environmental influences *sensu stricto* to E_1.

The total of 79 pairs tested so far is inadequate for a full genetic analysis. Power calculations by Martin *et al.*[3] show that the sample sizes used in most twin studies to date on traits of intermediate inheritance have been too small to give any confidence in the results obtained. The information gained from a twin study increases with sample size but investigations involving less than 100 pairs have a very low probability of providing a critical test of relevant hypotheses when used for traits which are incompletely inherited (see references in Gibson and Oakeshott[1]). Our study aims to collect data on at least 200 pairs of twins and we will not present any premature genetic analysis here. At this stage of the work we can give some preliminary analyses demonstrating two striking aspects of the data. First, there is considerable variation between individuals in measured biochemical, physiological and behavioural responses to alcohol and second, there is little relationship between the levels of body alcohol and responses to psychomotor tests in different individuals. We illustrate these two points with the data on the first fifty-two pairs tested successfully.

Table 2 shows the means and standard deviations of blood and breath alcohol readings for males and females separately. Blood readings are obtained on a Hewlett Packard 5700A gas liquid chromatograph. Breath readings are taken on two Alcolmeter (AE-D) breathalysers which operate on a breath:blood partition coefficient of 1:2100. It can be seen that blood readings are consistently higher than those for breath which may be due to the conservatism of the partition coefficient on which the breathalyser operates.[4] Female readings are consistently higher than those for males which may reflect the greater average adiposity of females. The main feature of the table, however, is the considerable variation

TABLE 2
Breath and blood alcohol readings—means and standard deviations (mg ETOH/100 ml blood)

Time (mins) since began drinking	Breath ♀	Breath ♂	Blood ♀	Blood ♂
40	·076 ± ·018	·073 ± ·013		
53	·081 ± ·015	·073 ± ·011	·092 ± ·023	·090 ± ·018
66	·087 ± ·016	·076 ± ·011	·096 ± ·020	·089 ± ·017
80	·085 ± ·016	·072 ± ·013	·098 ± ·015	·089 ± ·016
100	·083 ± ·015	·070 ± ·010		
120	·074 ± ·013	·062 ± ·011	·090 ± ·014	·080 ± ·015
160	·074 ± ·013	·058 ± ·010		
180	·062 ± ·012	·049 ± ·011	·076 ± ·012	·065 ± ·014
220	·057 ± ·012	·047 ± ·011		
240	·048 ± ·011	·038 ± ·011	·058 ± ·013	·048 ± ·013
280	·040 ± ·012	·030 ± ·011		
300	·030 ± ·011	·022 ± ·009	·039 ± ·013	·029 ± ·012
325	·027 ± ·011	·018 ± ·010		

TABLE 3
Means for alcohol measurement

	Breath		Blood	
	♀	♂	♀	♂
Peak B.A.C.	0·094 ± ·05	0·084 ± ·010	0·104 ± ·017	0·097 ± ·016
Time to peak (mins)	77 ± 26	72 ± 26	86 ± 30	72 ± 24
β (mg/100 ml/hr)	−0·0170 ± ·0028	−0·0144 ± ·0029	−0·0177 ± ·0033	−0·0172 ± ·0039

about the mean manifested at each sampling, suggesting large differences between individuals. There appears to be a positive relation between mean and standard deviation which might explain the somewhat larger standard deviations for females at each sampling time. The extent of variation between individuals is again seen in Table 3 with the standard deviations and means of the peak blood alcohol concentration, time to peak and rate of ethanol elimination (β).

In Table 4 we present the results of the effect of alcohol on a psychomotor test which measures the time taken to accumulate a fixed number of degrees of forward-backward sway on a body-sway platform; the steadier a subject the larger the reading. Subjects are tested with eyes open and again with eyes closed, and duplicate measurements are taken of each reading. At any given time subjects are about half as steady with eyes closed as with eyes open. From the initial state of steadiness subjects reach a maximum sway between 45 and 105 minutes after the start of alcohol drinking and then gradually return towards their pre-alcohol steadiness. Once again there are high variances about the means and the suggestion of a relationship between mean and variances. Females are significantly more steady than males in the pre-alcohol tests and also in tests with eyes closed, 225 minutes after the alcohol dose. There is also a suggestion that, at the time of the maximum decrement in performance, females are less steady than males. Since steadiness will be greater in subjects with a lower centre of gravity it is not surprising that shorter, lighter females are steadier when sober. The tendency for greater sway among females at 45 and 105 minutes may reflect their higher alcohol levels during this period and on the face of it, comparison of *mean* alcohol and body sway readings might suggest a relationship between blood alcohol levels and impairment of psychomotor performance.

TABLE 4
Body sway—seconds to accumulate a fixed amount of sway. Means and standard deviations

Time (mins)	Eyes open		Eyes closed	
	♀	♂	♀	♂
Pre-alcohol	128 ± 47	107 ± 33	62 ± 27	53 ± 20
45	77 ± 35	81 ± 27	34 ± 19	35 ± 16
105	76 ± 40	84 ± 27	35 ± 24	39 ± 16
165	97 ± 50	93 ± 28	45 ± 27	45 ± 17
225	107 ± 47	98 ± 29	58 ± 32	48 ± 17
285	116 ± 50	103 ± 30	62 ± 30	54 ± 17

If these correlations are calculated on an *individual* basis, however, it becomes clear that there must be considerable heterogeneity within these means because the correlations are smaller and much less consistent. Table 5 shows individual correlations between features of blood and breath ethanol profiles and body sway on the first two occasions after alcohol. Because body sway is affected by height and weight and blood alcohol readings are affected by adiposity, partial correlations are given in which these three covariates are controlled.

The most striking feature of these data is the lack of consistent correlation between any of the alcohol parameters and body sway. Only three of the twelve correlations with proximal blood or breath alcohol readings are significant and in the direction expected on the basis of a positive effect of blood alcohol levels on psychomotor performance. Similarly, only two of the correlations with peak alcohol readings are significant and in the expected direction. There seems to be no relationship between impairment of performance and rate of ethanol elimination but this may be because rate of ethanol decay is not relevant at the early stages of metabolism at which the decrements were observed. Most interesting perhaps, are the correlations between impairment and time to peak alcohol reading—

TABLE 5

Partial correlations between alcohol and body sway measurements controlling for height, weight and skinfold thickness

	Sway at 45 min.				Sway at 105 min.			
	Eyes open		Eyes closed		Eyes open		Eyes closed	
	♀	♂	♀	♂	♀	♂	♀	♂
Breath (40/100)†	−·33*	−·17	−·11	−·11	−·01	−·01	−·21	−·01
Breath (53/120)†	−·23	−·12	−·07	−·12	−·06	·00	−·19	−·19
Blood (53/120)†	−·32*	·02	−·29*	−·18	−·17	·34*	−·21	·02
Peak breath	−·16	−·11	−·07	−·18	−·07	−·20	−·10	−·24
Peak blood	−·36**	−·19	−·11	−·10	−·27*	·26*	−·05	−·01
Time peak breath	·47***	·05	·38**	·01	·37**	−·06	·17	−·02
Time peak blood	·21	·40**	·23	·46**	·08	·25	·01	·26
β breath	−·14	·04	−·18	·00	−·25*	·05	−·04	·01
β blood	·23	·05	−·12	·09	·05	−·20	·00	·00

†In the first three rows correlations with sway at 45 minutes are with breath readings at 40 and 53 minutes and blood at 53 minutes, while correlations with sway at 105 minutes are with breath readings at 100 and 120 minutes and with blood at 120 minutes.
*$0{\cdot}01 < P < 0{\cdot}05$ **$0{\cdot}001 < P < 0{\cdot}01$ ***$P < 0{\cdot}001$.

the quicker the rate of absorption the greater the impairment. However, even here the correlation is only significant with the breath parameter in females and with the blood parameter in males. These features of the differences between the sexes have not previously been found and it will be interesting to see whether they persist in larger samples.

Overall, these data suggest that an individual's performance on the sway test, although markedly impaired after ingestion of alcohol, is not adequately indicated by either breath or blood alcohol levels *per se*, nor their rates of elimination. It remains to be tested whether breath or blood acetaldehyde levels are better indicators, as work on other mammals suggests they might be.[1] Whatever the relationship between components of alcohol metabolism and behaviour, our data clearly show that there are considerable differences between individuals and it will be important to attempt to partition this variation into genetic and environmental components.

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References

1. Gibson JB, Oakeshott JG. Genetics of biochemical and behavioural aspects of alcohol metabolism. Aust NZ J Med 1981;11: 128–31.
2. Oakeshott JG, Gibson JB. The genetics of human alcoholism: a review. Aust NZ J Med 1981;11:123–8.
3. Martin NG, Eaves LJ, Kearsey MJ, Davies P. The power of the classical twin study. Heredity 1978;40:97.
4. Jones AW. Variability of the blood:breath alcohol ratio in vivo. J Stud Alcohol 1978;19:1931.