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Alcohol-related Biochemical Changes in Heavy Drinkers

J. B. Whitfield

From the Department of Biochemistry, Royal Prince Alfred Hospital, Sydney, NSW

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It is common-place clinical observation that some alcoholics progress fairly rapidly to cirrhosis of the liver or other alcohol-related diseases, while others drink equally heavily for many years but seem immune to such problems. This impression has been confirmed by more formal studies[1] and it seems to me an interesting question why this should be so. What factor causes the liver diseases in some people? Or alternatively and more generally what factors underlie differing degrees of response to the same stimulus? Obviously the difference could lie either in inherited or environmental factors. Some of the less common conditions associated with excessive intake have been shown to have enzyme abnormalities[2] or to be inherited within families. However, for the most important medical complication of heavy drinking, alcoholic cirrhosis, no such finding has been established. Nutrition has been suggested as an environmental factor; studies both emphasising its role[3] and dismissing it as an important factor[4] have been published. Genetic aspects have been explored through the association between cirrhosis and certain HLA antigen, but the correlation is much less than absolute and reports from different groups are contradictory.[5, 6]

TABLE 1
Questions relating to alcohol intake

In the past year, how often did you drink alcohol?
—Every day or most days
—A couple of times a week
—Once every week or two
—Very rarely
How many drinks (wine, whisky, beer, cocktails, etc.) did you usually have on each drinking day in the past year?
—Total of nine drinks a day or more
—Six to eight drinks a day
—Three to five drinks a day
—Two drinks or less a day

To mount a classical twin study on this topic would be very difficult, but it may be practical to look at some responses to heavy drinking which could represent the early stages of alcoholic liver disease. The benefit of this approach is that around 10% of the male population of Australia are heavy drinkers, and so it may be possible to collect a sufficient number of twin pairs.

Most of this paper will relate to the studies I have been involved with over the past four years on the relationship between heavy drinking within an Australian population, and the results found for certain biochemical and haematological tests. Towards the end I would like to speculate somewhat on how twin studies on the dose-response relationship might be of use.

The subjects of the original study, conducted with Dr. Gallagher of the Medicheck Centre, and Dr. Hensley of Royal Prince Alfred Hospital, were some 8000 adults (about 5000 men and 3000 women) who attended Medicheck, a multiphasic health screening centre in Sydney. Among many other questions and measurements they had blood taken for biochemical and haematological tests and answered, via a computer terminal, the questions shown in Table 1. We related their answers to the results of a number of tests and significant associations were found in a number of cases, shown in Table 2. The association with urea was slight and it differed in its direction between men and women. Little or no association was found with the conventional liver

TABLE 2
Association between test results and drinking

Significant association with drinking habits:
Gamma glutamyl transpeptidase
Mean corpuscular volume
Uric acid
Triglycerides
Aspartate aminotransferase
Urea
Little or no association:
Alkaline phosphatase
Bilirubin
Albumin

TABLE 3
Percentage of "abnormal" results for plasma gamma glutamyl transpeptidase

Frequency	Males	Females
Very rarely	6·9	6·4
Once every week or two	6·9	6·5
Couple of times a week	10·9	7·8
Every day or most days	25·5	13·5
	$P<0·001$	$P<0·001$
Amount		
1 or 2	9·1	6·4
3 to 5	16·4	14·8
6 to 8	29·2	26·5
9 or more	44·1	27·7
	$P<0·001$	$P<0·001$

function tests, alkaline phosphatase, bilirubin and albumin. Similar results have been reported on other populations.[7]

Our initial approach was to look at the answers to the the two questions separately and Table 3 shows what happened when we took a fairly arbitrary upper limit of normal, for gamma glutamyl transpeptidase and calculated what proportion of the group exceeded this limit for each possible answer to the question, both for the frequency of drinking and for the amount of drinks taken for men and for women. Figure 1 shows these results for gamma glutamyl transpeptidase in the form of histograms, and it will be seen both that the proportion of abnormalities increased with increasing frequency or number of drinks, and also the shape of the frequency distribution altered being increasingly skewed to the right as drinking increased. When a similar procedure was carried out for the results for erythrocyte mean corpuscular volume (Table 4) again the percentage of abnormalities increased with increasing frequency or number of drinks both for men and for women. However, in Figure 2 the histograms for mean corpuscular volume are shown and it can be seen that the change is different in nature, in that the frequency distributions are shifted increasingly to the right but without the increasing skewness found for gamma glutamyl transpeptidase. Tables 5, 6 and 7 show the percentage of abnormalities for triglyceride, uric acid and aspartate aminotransferase in plasma, which are sensitive to the amount or frequency of drinking in all cases in males and for triglyceride and aspartate aminotransferase but not uric acid in women.

We then derived an estimate of alcohol intake in drinks per month by multiplying the frequency

TABLE 4
Percentage of "abnormal" results for erythrocyte mean corpuscular volume

Frequency	Males	Females
Very rarely	0	3·9
Once every week or two	2·5	4·1
Couple of times a week	6·9	6·7
Every day or most days	21·1	14·3
	$P<0·001$	$P<0·001$
Amount		
1 or 2	5·8	5·8
3 to 5	12·8	15·6
6 to 8	22·7	18·7
9 or more	34·9	15·8
	$P<0·001$	$P<0·001$

TABLE 5
Percentage of "abnormal" results for plasma triglycerides

Frequency	Males	Females
Very rarely	4·5	4·3
Once every week or two	7·5	1·0
Couple of times a week	6·4	1·5
Every day or most days	12·6	2·6
	$P<0·001$	N.S.
Amount		
1 or 2	6·0	1·6
3 to 5	9·7	2·1
6 to 8	13·8	6·9
9 or more	19·9	10·5
	$P<0·001$	$P<0·001$

TABLE 6
Percentage of "abnormal" results for plasma urate

Frequency	Males	Females
Very rarely	4·7	3·2
Once every week or two	12·1	1·7
Couple of times a week	13·7	1·3
Every day or most days	25·5	3·0
	$P<0·001$	N.S.
Amount		
1 or 2	11·9	1·5
3 to 5	18·6	3·8
6 to 8	29·4	3·7
9 or more	37·9	0
	$P<0·001$	N.S.

by the number from the two original questions.[8] The results for men and for women are shown in Figures 3 and 4, and in each case it will be seen that there was an increase in the median value with increasing drinking but that the shapes of the distributions differed, as in the examples of gamma glutamyl transpeptidase and mean corpuscular volume. In the first type of test there is an increasing scatter of the results with increasing alcohol intake, indicating that some people would still have normal results at high alcohol intake, whereas others would have grossly abnormal results. Thus these individuals seemed to differ in their response to alcohol intake. This was not found for mean corpuscular volume.

TABLE 7
Percentage of "abnormal" results for plasma aspartate aminotransferase

Frequency	Males	Females
Very rarely	0	5·5
Once every week or two	1·8	2·9
Couple of times a week	3·8	2·5
Every day or most days	9·3	3·3
	$P < 0{\cdot}001$	$P < 0{\cdot}001$
Amount		
1 or 2	2·4	2·8
3 to 5	5·5	3·5
6 to 8	10·1	3·7
9 or more	22·7	11·1
	$P < 0{\cdot}001$	$P < 0{\cdot}001$

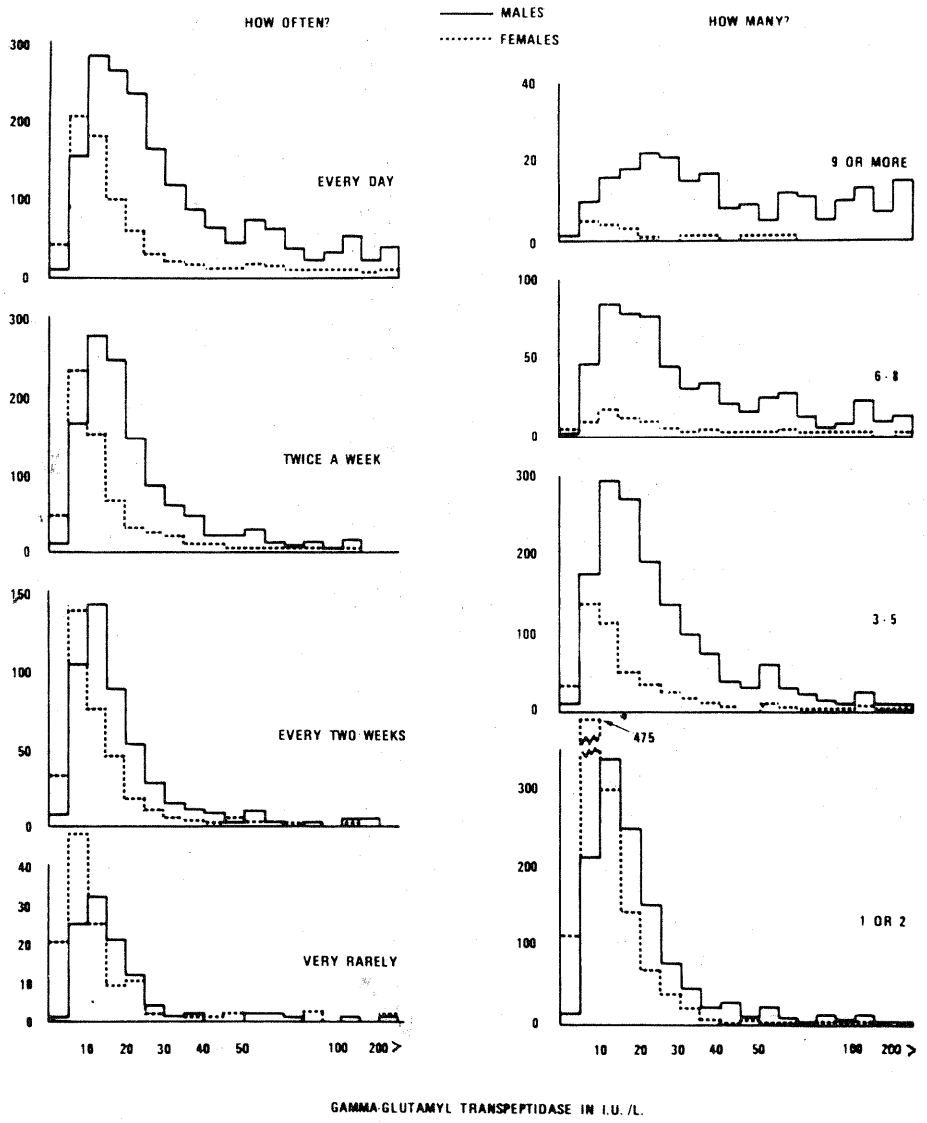

FIGURE 1. Histograms of plasma gamma-glutamyl transpeptidase, classified by responses to questions on alcohol intake.

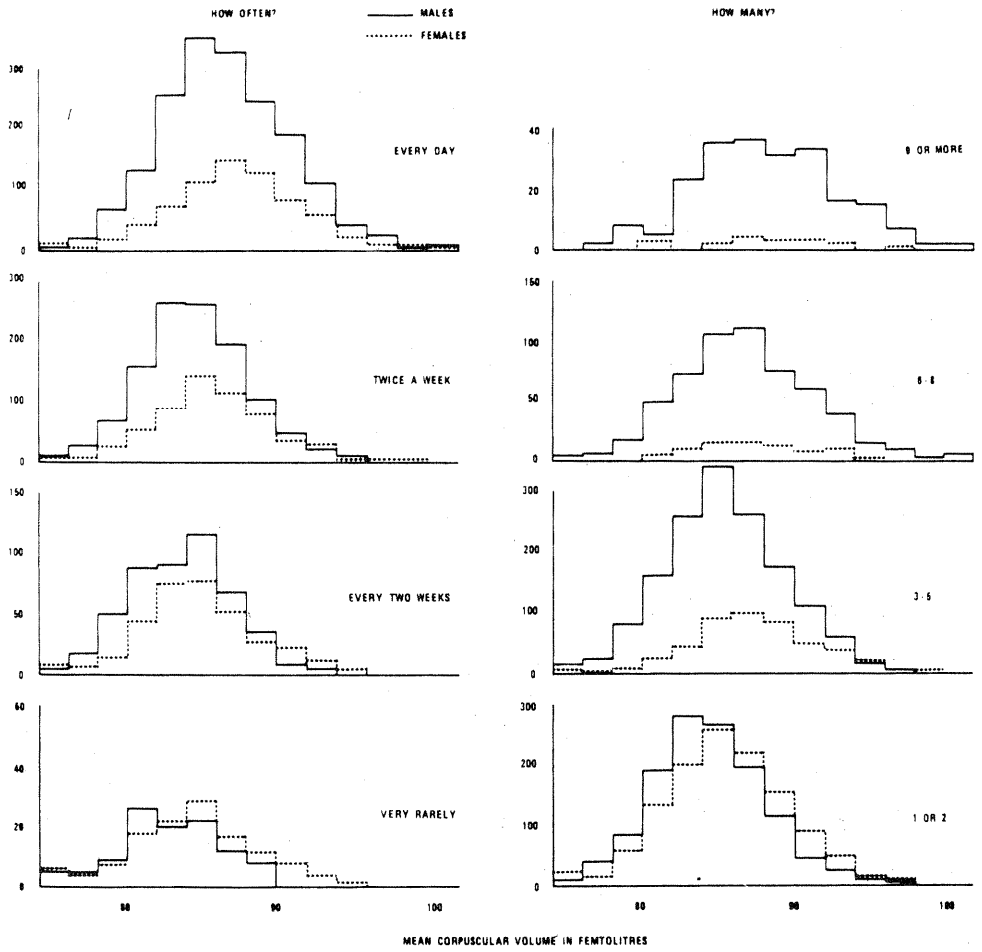

FIGURE 2. Histograms of erythrocyte mean corpuscular volume, classified by responses to questions on alcohol intake.

Since we had a number of tests it seemed possible that some combination of them would be better than any one alone, so by courtesy of the Department of Population Biology at the Australian National University, and with the use of their computer facilities, we derived multiple regression equations for men and women relating the individuals' test results to the declared alcohol intake. This technique produced an improvement which, although statistically significant, was not very large. For instance, in the men the correlation coefficient for the best single test, mean corpuscular volume, was 0·43, and for gamma glutamyl transpeptidase 0·30. Introduction of the values for all the tests produced a multivariate predictor with a correlation coefficient of 0·52 which represents an improvement in the proportion of variance explained of some 50% but is still a comparatively low correlation coefficient. Similar improvement was found for women. A curve could be generated plotting the declared alcohol consumption against alcohol consumption predicted by the multivariate equation; as for the single tests different people varied widely from it. Those below the regression line might be considered less affected and those above it more affected biologically by their alcohol intake.

Taking one group out of the whole population we look next at about 65 male heavy drinkers. It will be recalled that the heavy drinkers were very variable in their biochemical results. Figure 5 shows this for gamma glutamyl transpeptidase. These heavy drinkers can be divided, to some extent arbitrarily, into those with comparatively

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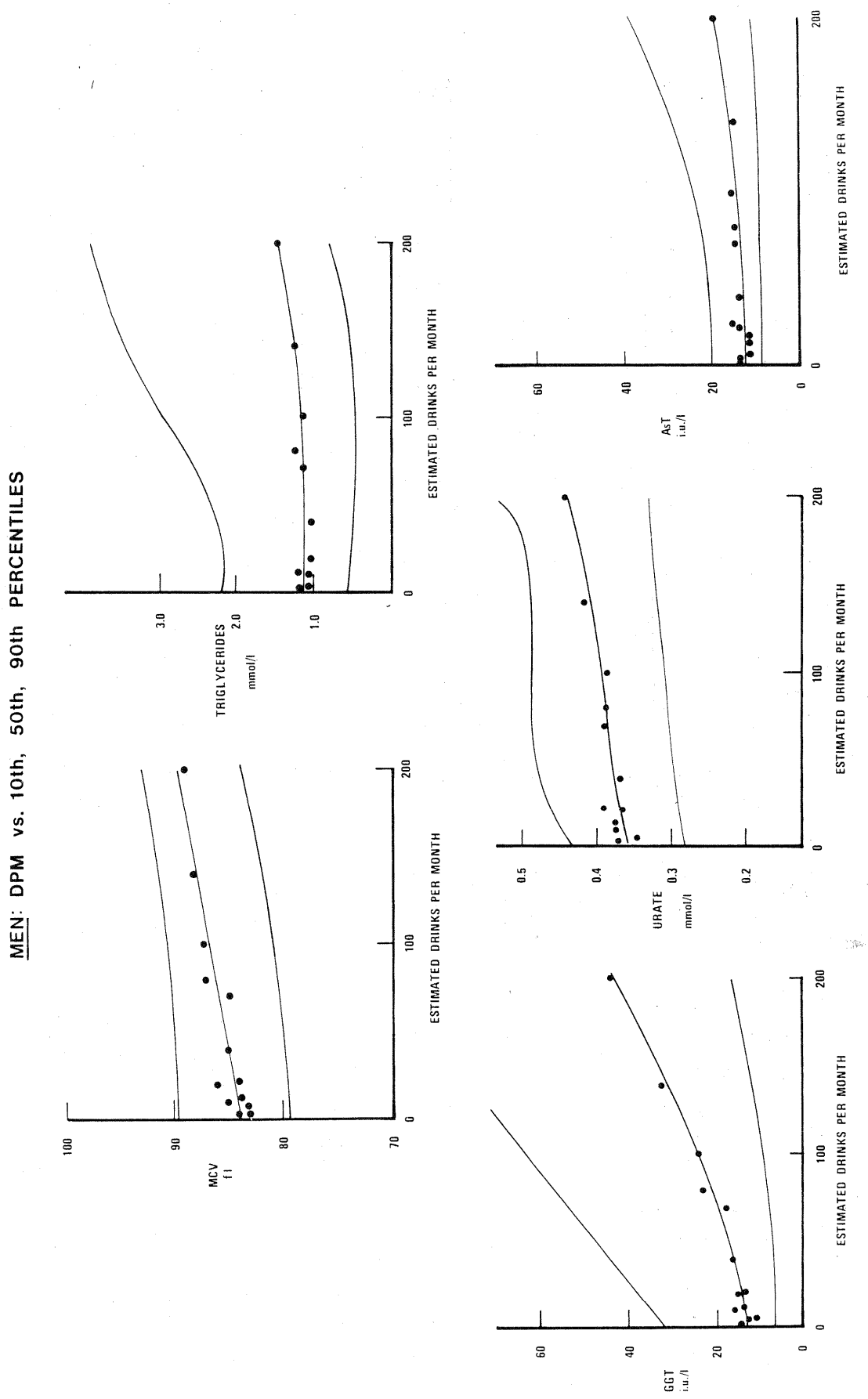

FIGURE 3. Median test results vs. monthly alcohol consumption, for men.

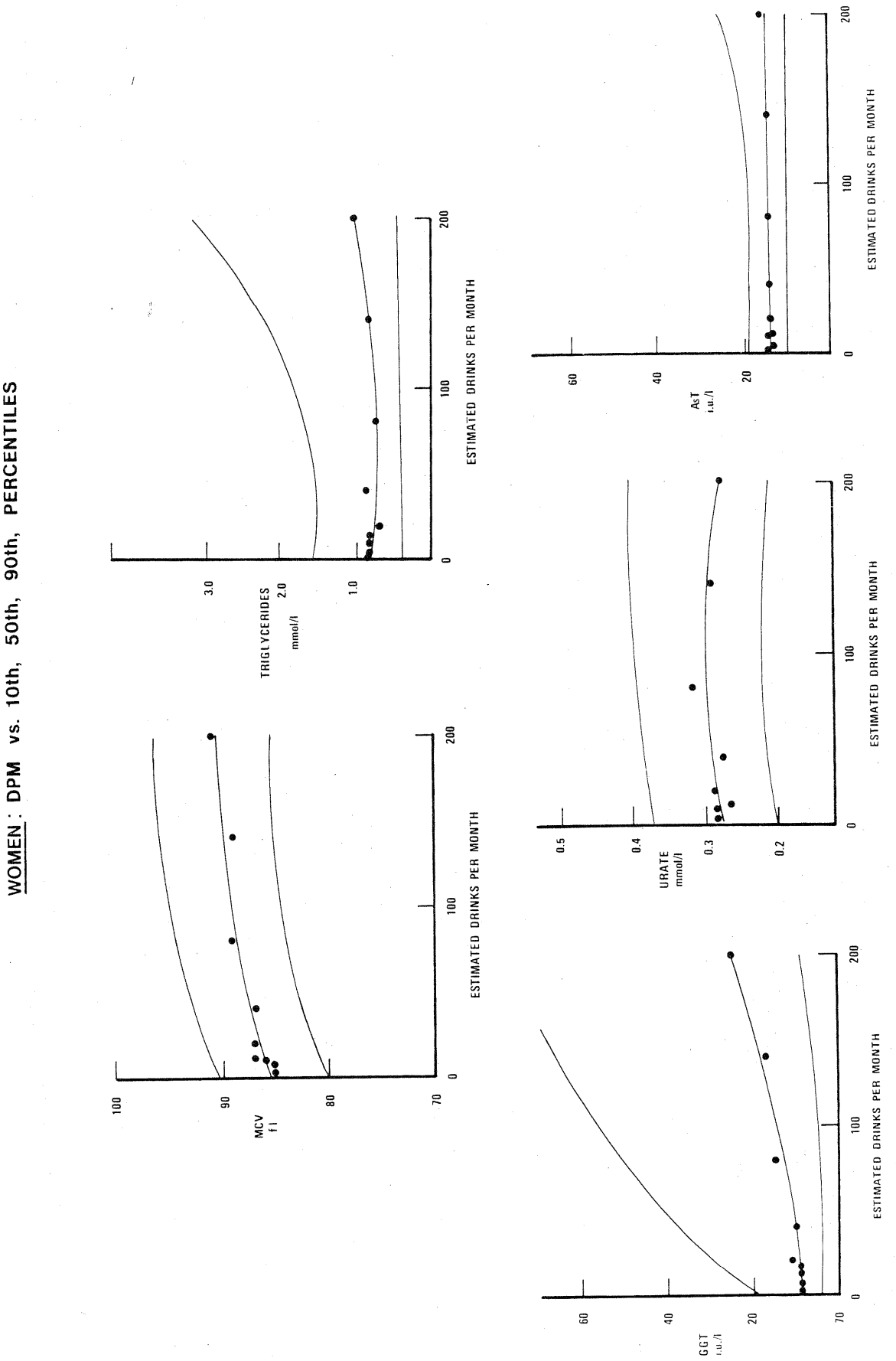

FIGURE 4. Median test results vs. monthly alcohol consumption, for women.

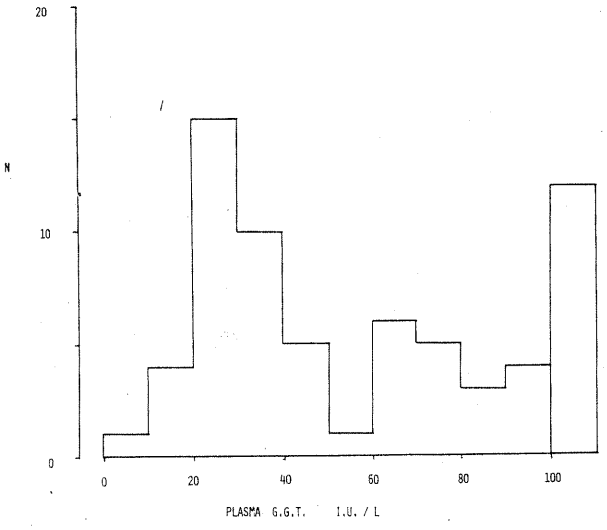

FIGURE 5. Frequency distribution of plasma gamma-glutamyl transpeptidase in male heavy drinkers.

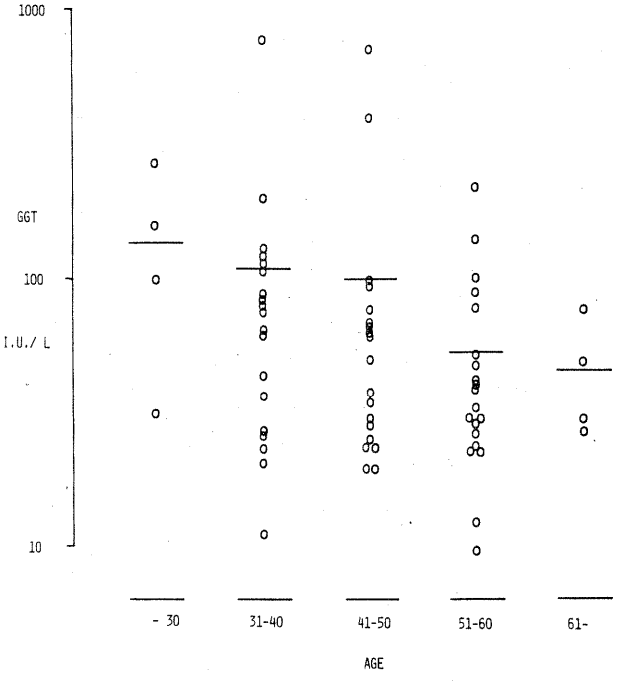

FIGURE 6. Age and gamma-glutamyl transpeptidase in heavy drinkers.

	MALE HEAVY DRINKERS		
	GGT < 60 (37)	GGT > 60 (29)	
MCV	89.7 ± 3.9	92.1 ± 3.9	P < 0.02
URIC ACID	6.53 ± 1.31	7.44 ± 1.53	P < 0.02
TRIGLYCERIDE	145 ± 84	201 ± 166	N.S.
AS.T.	16.8 ± 6.1	36.3 ± 29.0	P < 0.005

FIGURE 7. Differences in results of other tests between heavy drinkers with lower or higher gamma-glutamyl transpeptidase.

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normal and those with higher gamma glutamyl transpeptidase, perhaps above and below 60 international units per litre. We then asked what other differences there were between these two groups. Was there perhaps a difference in their alcohol intake? This does not seem to be so because they are all taken from the heaviest drinking group. Perhaps the duration of alcohol abuse could vary; this question cannot be directly studied but it would be expected to be reflected in the ages of the people in these two groups, and if one looks at Figure 6 it can be seen that this is not so. The prediction would be that the gamma glutamyl transpeptidase would be higher in those who are older and had therefore been drinking for longer, but it seems in fact that the gamma glutamyl transpeptidase decreased slightly with age within this group of heavy drinkers. We next asked whether these two groups differed in other test results, and Figure 7 shows that this was indeed so for mean corpuscular volume, for uric acid, and for aspartate aminotransferase, although not significantly for triglycerides. Figure 8 shows the correlations between results of these different tests, in this group of heavy drinkers, and it will be seen that gamma glutamyl transpeptidase was correlated with a number of other tests including alkaline phosphatase, bilirubin, mean corpuscular volume, aspartate amino transferase, triglyceride, and that correlations between other pairs of tests were also found to exist. Only those correlations which were significant at the 1% level are shown in this figure.

Therefore it can be concluded that there are

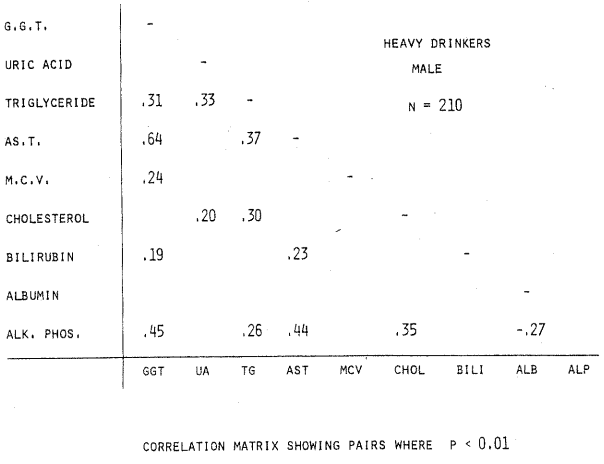

FIGURE 8. Cross-correlations between test results in heavy drinkers.

different responses to alcohol abuse, as expressed by these test results. This is shown in the most marked form in these heavy drinkers. The future studies which seem desirable are firstly to follow up asymptomatic heavy drinkers to see if biochemical differences predict their future clinical course, and secondly to seek out twins who are moderate to heavy drinkers to see if differing responses have a genetic or environmental cause.

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