Blood cells and alcohol consumption with special reference to smoking habits

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SUMMARY In the course of the Paris study on risk factors of cardiovascular disease in a large professional group, 7710 active and apparently healthy men aged between 48 and 54 were examined. This study measured the relationship between clinical abnormalities suggesting alcoholic liver disease (ALD) and the following blood parameters: white (WBC) and red (RBC) blood cell counts, haematocrit (H), and mean corpuscular volume (MCV), the former computed as H/RBC ratio. A subsequent analysis was performed on a random sample of 485 subjects without ALD who were questioned on their daily average alcohol consumption. Each subject was classified as 'smoker' or 'non-smoker' according to his daily tobacco consumption for the last five years. Analysis of the data confirmed that smoking and alcohol were related to the blood parameters; but, according to smoking habit, different relationships between alcohol consumption (or ALD) and MCV, RBC, or WBC counts were found: for smokers, RBC count significantly decreased and MCV increased with alcohol consumption (or ALD); for non-smokers, WBC count significantly increased with alcohol consumption (or ALD). So, it would be of interest to consider the relation between alcohol and tobacco in interpreting possible changes in blood parameters and in formulating hypotheses on the mechanisms of their specific action.

Recent papers have shown a relationship between alcohol consumption and mean corpuscular volume (MCV) in patients free of chronic liver disease or liver cirrhosis (Buffet *et al.*, 1975; Wu *et al.*, 1974; Wu *et al.*, 1975; Morin and Porte, 1976). Also epidemiological studies have shown that the white blood cell count (Howell, 1970; Corre *et al.*, 1971; Friedman *et al.*, 1973; Okuno, 1973), haematocrit, and MCV increased with smoking (Lambert and Morris, 1971; Okuno, 1973). Because of the well-known strong association between alcohol and smoking, it was of interest to consider tobacco consumption in order to study the influence of alcohol on blood cells, especially in healthy subjects.

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Material and methods

The present enquiry was made within the framework of the prospective study on cardiovascular risk factors carried out in Paris by the Groupe d'Etude sur l'Epidémiologie de l'Athérosclérose (GREA) (Ducimetière *et al.*, 1973) concerning 7710 actively employed and apparently healthy men aged between 48 and 54 from a large professional group.

The routine examination included: (1) Screening for clinical abnormalities: volume and consistency of the liver suggestive or not of alcoholic liver disease (ALD); (2) A fasting venous blood sample taken from the antecubital vein into an EDTA tube. From this sample white and red cell (WBC and RBC) counts were measured by Fisher's autocytometer. Haematocrit (H) was measured and the MCV was calculated as the ratio H/RBC. (3) A questionnaire on smoking habits: the subjects were divided into 'non-smokers' and 'smokers', depending on whether their mean daily consumption of tobacco in the last five years had been less or more than 1 g[1].

[1]1 cigarette = 1 g, 1 pipe = 2 g, 1 cigar = 4 g

Table 1 *Blood parameter means ($\pm$ SEM) according to clinical signs of alcoholic liver disease in 7710 subjects*

ALD	Total population 1	Non-smokers 2	Smokers 3	d (3-2)	Comparison smokers/non-smokers
WBC/mm³					
No	6403 ± 23	5720 ± 33 (1952)*	6654 ± 28 (5317)	934	P < 10⁻⁹
Yes	6750 ± 97	6332 ± 224 (71)	6830 ± 107 (370)	498	P < 0·05
Difference	341	612	176		
P	P < 10⁻³	P < 10⁻²	NS		I†:P < 0·05
RBC/mm³					
No	4672 ± 4	4695 ± 8 (1950)	4663 ± 5 (5316)	− 32	P < 10⁻³
Yes	4532 ± 21	4691 ± 48 (71)	4502 ± 23 (369)	− 189	P < 10⁻³
Difference	− 140	− 4	− 161		
P	P < 10⁻⁹	NS	P < 10⁻⁹		I:P < 0·05
Haematocrit					
No	45·0 ± 0·03	44·7 ± 0·06 (1945)	45·2 ± 0·04 (5306)	0·5	P < 10⁻⁹
Yes	45·0 ± 0·16	45·2 ± 0·35 (71)	45·0 ± 0·18 (367)	− 0·2	NS
Difference	0	0·5	0·2		
P	NS	NS	NS		I:NS
MCV/μ³					
No	96·6 ± 0·06	95·3 ± 0·10 (1943)	97·1 ± 0·07 (5304)	1·8	P < 10⁻⁸
Yes,	99·7 ± 0·31	96·6 ± 0·60 (71)	100·3 ± 0·35 (366)	3·7	P < 10⁻⁷
Difference	3·1	1·3	3·2		
P	P < 10⁻⁹	P < 0·05	P < 10⁻⁹		I:P < 0·05

*Number of subjects in parentheses
†I = interaction

In addition, of these 7710 subjects a random sample of 485 men without ALD attending between October 1969 and December 1970 were questioned on their dietary habits (Papoz *et al.*, 1974). The techniques used provided, in particular, the mean daily alcohol consumption expressed in grams of pure alcohol[1] assessed from the quantities of the various drinks taken in the course of the week and their respective alcohol content.

Results

BLOOD CELLS, ALCOHOLIC LIVER DISEASE, AND SMOKING HABIT (Table 1)

Signs of definite or possible alcoholic liver disease were found in 6% of the 7710 subjects in the study. It can be seen (first column of Table 1) that the RBC count was significantly lower and the WBC count and MCV higher for subjects with ALD than for those without.

When smoking habits were taken into account in a two-way analysis of variance, a significant interaction between ALD and smoking was seen.

On the one hand, the differences between subjects with and without ALD varied according to smoking habit:

[1] 1 litre of 10° wine contains 80 g of pure alcohol.

Among smokers, there was no significant difference in the WBC count, but the RBC count was significantly lower in subjects with ALD than in subjects without ALD.

Among non-smokers, there was no significant difference in the RBC count, but the WBC count was significantly higher when subjects showed signs of ALD.

MCV was significantly higher in men with ALD whatever their smoking habits, but the difference was much greater in smokers than in non-smokers (3·2 v 1·3 μ^3, Table 1).

On the other hand, the comparison between smokers and non-smokers shows that the influence of tobacco differed according to the presence or absence of clinical signs of ALD: thus, the difference in WBC counts barely reached the 5% level of significance (P = 0·03) and the haematocrits did not differ significantly between smokers and non-smokers who had clinical signs of ALD, but the values were significantly higher in the group of smokers without signs of ALD. The RBC counts were significantly lower in smokers than in non-smokers, independent of the presence or absence of clinical signs of ALD but the difference was more evident in subjects with ALD (32/mm³ × 10³ without ALD and 189/mm³ × 10³ with ALD); for the MCV there was a similar observation: the

mean differences in MCV between smokers and non-smokers respectively were 3·7 and 1·8 μ^3, depending on whether they did or did not have clinical signs of ALD.

BLOOD CELLS, SMOKING HABITS, AND ALCOHOL CONSUMPTION (Table 2)

This second analysis was undertaken on the random sample of 485 subjects to confirm, by estimating their alcohol consumption, the results obtained from the clinical observation of ALD on the whole population.

For this sample a one-way analysis of variance of the blood parameter means in groups of men with increasing amounts of ingested alcohol and a comparison of correlation coefficients showed a significant decrease in the RBC count and a significant increase in the MCV. Haematocrit did not vary significantly, and the WBC count increased

but barely reached the 5% level of significance for the correlation coefficient (first column of Table 2).

The specific role of alcohol was studied by once again separating smokers from non-smokers and adjusting for the amount smoked. Significant relationships between the quantity of alcohol ingested and either the WBC or the RBC counts or the MCV appeared in non-smokers only for WBC, and in smokers for RBC and MCV also. The interaction computed from a two-way analysis of variance did not reach the 5% level of significance except for the RBC count. A comparison of the correlation coefficients showed no significant differences although for WBC and RBC counts the actual significance levels were respectively $p = 0.07$, $p = 0.06$, and $p = 0.14$ for MCV. The specific role of smoking could not be studied in the same way, since too few subjects were total abstainers.

It could, however, be noted that the association

Table 2 *Changes in blood parameters according to amount of alcohol ingested and smoking habit in random sample of 485 subjects (mean ± SEM)*

Alcohol (g/day)	Total population 1	Non-smokers 2	Smokers 3	d (3-2)	Comparison smokers/non-smokers
WBC/mm³					
<40	6382 ± 107	5823 ± 153 (75)*	6705 ± 136 (128)	882	$p < 10^{-4}$
40-59	6641 ± 155	5841 ± 189 (32)	6900 ± 189 (99)	1059	$p < 10^{-4}$
60-79	6724 ± 190	6473 ± 357 (11)	6766 ± 214 (67)	293	—
≥80	6834 ± 213	6617 ± 414 (18)	6938 ± 251 (55)	321	—
Significance (analysis of variance)	—	—	—		Interaction NS
'r' correlation coefficient	0·09 $p < 0.05$	0·20 $p < 0.05$	0·03 —		NS $p < 0.07$
10³RBC/mm³					
<40	4717 ± 24	4618 ± 35	4725 ± 31	107	$p < 0.02$
40-59	4656 ± 28	4716 ± 54	4637 ± 33	−79	—
60-79	4635 ± 34	4882 ± 108	4594 ± 33	−288	$p < 0.01$
≥80	4568 ± 42	4678 ± 88	4535 ± 48	−143	—
Significance (analysis of variance)	$p < 0.01$	—	$p < 0.01$		Interaction $p < 0.05$
'r' correlation coefficient	−0·18 $p < 10^{-4}$	0·03 —	−0·22 $p < 10^{-4}$		NS $p < 0.06$
Haematocrit					
<40	45·0 ± 0·2	44·5 ± 0·3	45·2 ± 0·2	0·7	NS
40-59	45·0 ± 0·2	44·5 ± 0·4	45·2 ± 0·2	0·7	NS
60-79	45·1 ± 0·3	46·4 ± 0·9	44·9 ± 0·9	−1·5	NS
≥80	44·9 ± 0·3	44·9 ± 0·6	45·0 ± 0·4	0·1	NS
Significance (analysis of variance)	—	—	—		Interaction NS
'r' correlation coefficient	−0·02	0·04	0·05		NS
MCV/μ^3					
<40	95·5 ± 0·3	94·8 ± 0·5	95·9 ± 0·4	1·1	NS
40-59	97·0 ± 0·4	94·6 ± 0·6	97·8 ± 0·6	3·2	$p < 0.001$
60-79	97·5 ± 0·5	95·1 ± 1·0	97·9 ± 0·5	2·8	$p < 0.02$
≥80	98·7 ± 0·7	96·2 ± 0·9	99·5 ± 0·9	3·3	$p < 0.02$
Significance (analysis of variance)	$p < 10^{-4}$	—	$p < 10^{-3}$		Interaction NS
'r' correlation coefficient	0·23 $p < 10^{-6}$	0·10	0·35 $p < 10^{-5}$		NS $p < 0.14$

*Number of subjects in parentheses

between smoking habit and blood parameters was not always the same according to the amount of alcohol ingested, especially for the WBC count. Significant differences between smokers and non-smokers were observed only for alcohol consumption below 60 g/day, and smokers had higher RBC counts for an alcohol consumption below 40 g/day and lower RBC counts for an alcohol consumption over 60 g/day.

Discussion

The results obtained in the present study support some findings already described by other authors, especially the relationship between MCV and chronic alcoholism or alcohol ingestion.

With regard to the relationship between chronic alcoholism and blood cells, many studies have been carried out on patients suffering from cirrhosis or chronic liver disease. They have revealed the presence of erythrocytic macrocytosis with or without anaemia and no change in haematocrit (Bianco and Joliffe, 1938; Herbert *et al.*, 1963; Kumar *et al.*, 1966; Boivin, 1968; Boivin and Fauvert, 1969; Buffet *et. al.* 1975; Morin and Porte, 1976).

With regard to the relationship between alcohol consumption and changes in blood parameters, there seem so far to be only two studies on healthy subjects (Unger and Johnson, 1974; Wu *et al.*, 1974) that have dealt with this. One, by Wu *et al.* (1974), compares 63 subjects with no detected liver disease, drinking more than 80 g of alcohol daily, with 61 healthy subjects, members of the medical staff. It shows, in the first group, an increased MCV without anaemia and no change in haematocrit. The other, by Unger and Johnson (1974), shows that among 77 subjects, employees of an insurance company systematically selected for their increased MCV, 27 were heavy or very heavy drinkers.

Our study gives additional information on the relationship between alcohol consumption and counts of both white and red blood cells, and especially on the separate roles of smoking and alcohol that no other study seems to have investigated simultaneously so far. Associated with an increased MCV was a fall in the RBC count, though not to the extent of anaemia, the product of these two variables—haematocrit—being constant. However, the correlation of alcohol consumption with the RBC count and MCV was more marked in smokers; on the other hand, its correlation with the WBC count was more marked in non-smokers.

From the pathological point of view, the mechanism by which chronic alcoholism acts on the blood parameters is not known. Without excluding that concomitant parameters related to drinking

and smoking (ie, dietary habits) are major factors, it seems reasonable to assume that alcohol has a direct toxic effect independent of hepatic disease (Wu *et al.*, 1974; Buffet *et al.*, 1975). As to the interactions mentioned above, it is difficult to find an explanation: for the WBC changes it is possible only to suggest that the effect of tobacco is so strong (Corre *et al.*, 1971; Friedman *et al.*, 1973) that, among smokers, the relation to alcohol cannot be determined.

In conclusion, this study, carried out on 7710 active and healthy subjects who submitted to systematic clinical examination and questioning as to their smoking habits and, for nearly 500 of them, their alcohol consumption, confirms that smoking and alcohol may affect the blood parameters. It emphasises the need to consider the relation between two products currently consumed, alcohol and tobacco, when (1) formulating hypotheses on the mechanism of their specific action and their possible interaction; and (2) interpreting possible changes in blood parameters, whether as a criterion for the early diagnosis of alcoholism or as a reference for alcohol withdrawal (Buffet *et al.*, 1975; Morin and Porte, 1976).

References

Bianco, A., and Joliffe, N. (1938). The anemia of alcoholics addicts. Observations as to the role of liver disease, achlorhydria, nutritional factors and alcohol on its production. *American Journal of Medical Sciences*, **196**, 414-420.

Boivin, P. (1968). Quelques aspects de la biologie du foie alcoolique en dehors de la cirrhose. *Revue Internationale d'Hépatologie*, **18**, 243-264.

Boivin, P., and Fauvert, R. (1969). Les anémies des cirrhoses. Revue critique. *Pathologie et Biologie*, **17**, 645-655.

Buffet, C., Chaput, J. C., Albuisson, F., Subtil, E., and Etienne, J. P. (1975). La macrocytose dans l'hepatite alcoolique chronique histologiquement prouvée. *Archives Françaises des Maladies de l'Appareil Digestif*, **64**, 309-315.

Corre, F., Lellouch, J., and Schwartz, D. (1971). Smoking and leucocyte-counts. Results of an epidemiological survey. *Lancet*, **2**, 632-634.

Ducimetière, P., Bonnaud, G., Claude, J. R., Corre, F., Elgrishi, I., Eschwege, E., Gélin, J., Lellouch, J., Richard, J. L., Schwartz, D., and Warnet, J. M. (1973). Facteurs de risque des cardiopathies ischémiques. Premiers résultats de l'étude prospective parisienne. *Colloques de l'INSERM*, **21**, 115-138.

Friedman, G. D., Siegelaub, A. B., Seltzer, C. C., Feldman, R., and Collen, M. F. (1973). Smoking habits and the leukocyte count. *Archives of Environmental Health*, **26**, 137-143.

Helman, N. (1974). Leukocyte count in smokers (Letter). *New England Journal of Medicine*, **291**, 630.

Herbert, V., Zalusky, R., and Davidson, C. S. (1963). Correlation of folate deficiency with alcoholism and associated macrocytosis, anemia, and liver disease. *Annals of Internal Medicine*, **58**, 977-988.

Howell, R. W. (1970). Smoking habits and laboratory tests (Letter). *Lancet*, **2**, 152.

Kumar, S., Dube, B., and Mehrotra, P. N. (1966). The macrocytosis in cirrhosis of the liver. A clinical and experimental study. *Acta Haematologica*, **35**, 30-45.

Lambert, R. J. W., and Morris, J. E. W. (1971). Red cell size and air composition (Letter). *British Medical Journal*, **3**, 706.

Morin, J., and Porte, P. (1976). Macrocytose érythrocytaire chez les éthyliques. *La nouvelle Presse Médicale*, **5**, 273.

Okuno, T. (1973). Smoking and blood changes. (Letter). *Journal of the American Medical Association*, **225**, 1387-1388.

Papoz, L., Cubeau, J., Eschwege, E., and Pequignot, G. (1974). Exploitation par ordinateur des enquêtes alimentaires quantitatives. Programme général d'analyse nutritionnelle. *Annals de la Nutrition et de l'Alimentation*, **28**, 465-485.

Unger, K. W., and Johnson, D. Jr. (1974). Red blood cell mean corpuscular volume: a potential indicator of alcohol usage in a working population. *American Journal of Medical Sciences*, **267**, 281-289.

Wu, A., Chanarin, I., and Levi, A. J. (1974). Macrocytosis of chronic alcoholism. *Lancet*, **1**, 829-831.

Wu, A., Chanarin, I., Slavin, G., and Levi, A. J. (1975). Folate deficiency in the alcoholic—its relationship to clinical and haematological abnormalities, liver disease and folate stores. *British Journal of Haematology*, **29**, 469-478.