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ENVIRONMENTAL FACTORS AFFECTING ANTIPYRINE METABOLISM IN LONDON FACTORY AND OFFICE WORKERS

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1 Measurements of antipyrine clearance in saliva have been made in 128 London factory and office workers.

2 Mean antipyrine clearance in 56 Asian immigrants was 40% slower than in 72 White subjects.

3 Although dietary differences existed between the two groups, analysis of their effect independently of race was impossible since all but one of the vegetarians were Asian and the non-vegetarians were nearly all White.

4 In the White subjects, use of the oral contraceptive reduced clearance by 38% in women, while cigarette smoking increase clearance by 38% in men.

Introduction

The drug metabolizing activity of the microsomal membrane mono-oxygenases varies widely in different humans and both within and between species of animals. The basal amount of enzyme is under genetic control but the amount and activity of the enzyme can change in response to environmental stimuli. In animals there is evidence that change in expression of the gene determining the amount of the microsomal mono-oxygenase in response to inducing agents is also under genetic control.

The rate of oxidation in man shows wide inter-individual differences (Alvares, Anderson, Conney & Kappas, 1976; Loeser, 1961; Vesell, 1972; Vesell & Page, 1968a, b & c). The influence of genetic factors has been studied in identical and fraternal twins in the United States and in Sweden. One of these studies (Vesell & Page, 1968c) showed a very high correlation of the half-lives of antipyrine in identical twins who were not being treated with any other drugs. The correlation was less good in the fraternal twins and calculations suggested that 76% of the variance of half-life was explicable by genetic factors (Vesell & Page, 1968a). There are two important qualifications to this conclusion. The first is that it probably overstates the genetic component due directly to microsomal mono-oxygenases since identical twins tend to resemble one another in their habits and environment as well as their body composition. The second is that it applies to a particular set of environmental conditions obtaining among the twinships studied. More extreme and varied environmental conditions might have altered the conclusion.

There have been reports that administration of other drugs, both medical and social, and environmental factors can alter the rate of drug oxidation in man. Drugs that will induce drug oxidation are numerous (Conney, 1967), phenobarbitone being the most powerful. Drugs that inhibit oxidation include isoniazid (Kutt, Winters & McDowell, 1966), some sulphonamides (Christensen, Hansen & Kristensen, 1962), and chloramphenicol (Christensen & Skovsted, 1969). Environmental factors that increase the rate of drug oxidation include occupational exposure to chlorinated hydrocarbon insecticides (Kolmodin, Azarnoff & Sjoqvist, 1969), anaesthetic gases (O'Malley, Stevenson & Wood, 1973) and cigarette smoke (Hart, Farrell, Cooksley & Powell, 1976; Vestal, Norris, Tobin, Cohen, Shock & Adres, 1975). The steroidal oral contraceptive pill inhibits drug oxidation (O'Malley, Stevenson & Crooks, 1973).

Most previous studies of drug oxidation in man have either examined a particular occupational group, e.g. exterminators exposed to insecticides or operating theatre personnel exposed to anaesthetic gases or they

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Table 1 Distribution by age and sex of 128 London subjects

Age group (years)	*Males* (n)	*Females* (n)	*Totals*
18–30	21	31	52
31–40	9	28	37
41–50	9	16	25
51–60	5	9	14
Totals	44	84	128
Mean age	34.6	33.9	34.2

have utilized readily accessible groups of normal volunteers such as students and laboratory personnel. The aim in this study was to use individuals drawn from the community and to include a range of race and environment. We have already reported a study of this kind carried out in a village community in Gambia in West Africa (Fraser, Bulpitt, Kahn, Mould, Mucklow & Dollery, 1976). The present study was carried out in London.

Methods

Subjects and procedure

Letters were written to the personnel managers of twenty-five large London firms requesting co-operation in the study. Four firms agreed to allow an approach to be made to their employees, who were then circulated with an explanation of the nature and purpose of the study. For a number of reasons a random sample could not be made and volunteers were invited to indicate their willingness to take part by giving signed, informed consent. Liver, heart or thyroid disease, any chronic illness, a history of jaundice, use of sedatives and other regular medication were contraindications to inclusion in the study.

In order to obtain a uniformly distributed sample, volunteers were stratified for sex and age (18–30, 31–40, 41–50 and 51–60 years). As there was an excess of women aged 18–30 and 31–40, subjects were randomly selected from the volunteers in those two categories. The distribution by sex and age is shown in Table 1. There was a 2:1 ratio of females to males, with a predominance of younger people, reflecting the distribution of the employees of the four factories.

A total of 128 subjects were studied, covering all social classes from manager to messenger, and divided equally between office and factory workers. There were 72 Whites and 56 Asians, and 38 of the latter were factory workers from a single firm.

Weights and heights of all subjects were recorded. A history was taken of all socially used drugs, i.e. cigarettes, alcohol, coffee, tea and the contraceptive pill. Subjects were classified as smokers or non-smokers and the number of cigarettes per day was recorded. Alcohol consumption was estimated as drinks per week, one half-pint of beer being equated with a standard measure of spirit, sherry or glass of wine (approximately 12 g of alcohol) (Laurence, 1973). A coffee/tea score of 'cups of coffee per day + 0.6 × cups of tea per day' was obtained (Nagy, 1974), and use of contraceptive pill was recorded.

Diet was classified as vegetarian or non-vegetarian. Only 7 of 56 Asians were non-vegetarian, and one White subject was a vegetarian. Some Asians ate meat only occasionally and were classified as vegetarians. The quantity of dairy products and eggs eaten varied considerably among vegetarians but no attempt was made to assess this further.

On arrival at work after an overnight fast each subject received 600 mg antipyrine and 1.5 g paracetamol orally, accompanied by 150 ml drinking water. No food or drink was permitted until after the first saliva sample was obtained. Samples were collected at 2, 3, 5, 8, 24 and 32 h, salivary flow being stimulated by a piece of Parafilm (Gallenkamp). After the particulate matter in the sample had settled, the supernatant was decanted, and the 3, 5 and 8 h samples divided into two portions. The 2, 3, 5 and 8 h samples were analysed for paracetamol (the results of which will be the subject of a separate report) and the 3, 5, 8, 24 and 32 h samples for antipyrine. Blood samples were taken by venepuncture on the second day of the study for total protein, albumin, bilirubin, alkaline phosphatase and aspartate transaminase estimations. Nine subjects declined blood sampling and their values were set to the mean for males or females in the subsequent analysis. Subjects were requested not to drink alcohol or take analgesics for 24 h before, or during the study.

Antipyrine analysis

Antipyrine estimations were performed by a gas chromatographic method as described previously (Fraser, Mucklow, Murray & Davies, 1976), and half-lives ($T_{\frac{1}{2}}$) estimated using the method of least squares.

The saliva antipyrine concentration at zero time (Co) was obtained by back extrapolation of the terminal regression line. Metabolic clearance was calculated using the formula:

$$\text{Clearance} = \frac{0.693 . \text{Dose}}{T_{\frac{1}{2}} . \text{Co} . \text{body wt}} \text{ ml min}^{-1} \text{ kg}^{-1}$$

Serum samples were analysed on a Technicon SMA plus. Multiple regression analysis were carried out using the stepwise regression programme (Biomedical Computer Programme BMD 02R). Differences

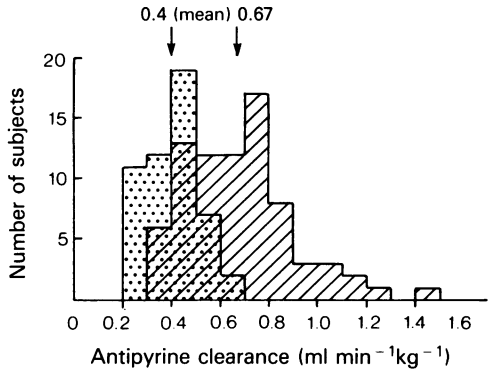

Figure 1 Frequency distribution of antipyrine clearance in vegetarians ($n=50$, ▨) and non-vegetarians ($n=78$, ▨).

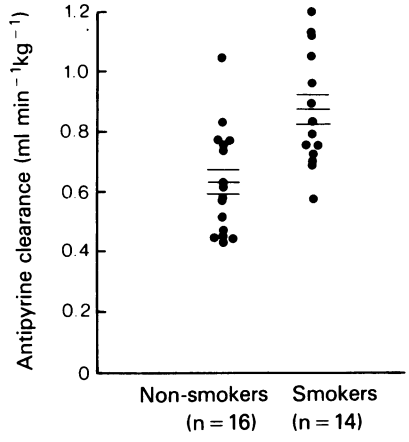

Figure 2 Antipyrine clearance in White male cigarette smokers and non-smokers. (Horizontal lines indicate mean ± s.e. mean.)

between groups were tested for significance using Student's t-test.

Results

The anthropometric and biochemical indices of nutritional status are shown in Table 2, according to sex and ethnic origin. Whites were taller and heavier than Asians but ponderal indices showed no difference. Women had a lower haemoglobin than men ($P<0.001$) and Asian women had significantly lower values than White women ($P<0.001$). Serum albumin was also significantly lower in Asians than in Whites ($P<0.01$) while globulin was higher in Asians than in Whites ($P<0.001$). There were no significant differences in bilirubin, alkaline phosphatase or aspartate transaminase.

The use of social drugs differed considerably in the two ethnic groups (Table 3). Asians used all these

Table 2 Nutritional indices of 128 Londoners, by sex and ethnic origin

	Males		*Females*	
	Whites (n=30)	*Asians (n=14)*	*Whites (n=42)*	*Asians (n=42)*
Weight (kg)	73.5	65.5	61.7	60.4
Height (cm)	174	168	162	158
Ponderal index (wt/ht²: g/cm²)	2.43	2.32	2.36	2.42
Albumin (g l⁻¹)	46.9	46.5	45.2	43.9
Globulin (g l⁻¹)	27.7	30.7	28.3	30.5
Haemoglobin (g 100 ml⁻¹)	15.0	14.7	13.3	11.8

Table 3 Social drug use among 128 London subjects, by sex and ethnic origin

	Males		*Females*	
	Whites (n=30)	*Asians (n=14)*	*Whites (n=42)*	*Asians (n=42)*
Smokers	14	7	19	0
Number of cigarettes per day (mean)	9.8	5.9	9.9	0
Coffee/tea index per day (mean)	5.5	2.6	5.1	2.3
Users of contraceptive pill	—	—	12	2

Table 4 Antipyrine clearance, half-life and volume of distribution for 72 Whites, 56 Asians, and all 128 London subjects

	Whites	*Asians*	*All subjects*
Clearance (ml min^{-1} kg^{-1})			
Mean	0.69	0.42**	0.57
s.d.	0.22	0.12	0.23
Half-life (h)			
Mean	10.6	15.2**	12.6
s.d.	3.2	4.4	4.4
Volume of distribution (l kg^{-1})			
Mean	0.58	0.53*	0.56
s.d.	0.09	0.08	0.08

Significance of difference between Asians and Whites: $^{**}P < 0.001$; $^{*}P < 0.005$.

drugs to a lesser extent than Whites. No Asian women smoked, only two drank alcohol and only two used the contraceptive pill.

Antipyrine clearances, half-lives and volumes of distribution are shown in Table 4. The mean antipyrine clearance in Asians was 40% less than in Whites and the mean half-life 43% longer. The range of half-life for the whole sample was 5 to 27 h. There was no difference in clearance or half-life between men and women. Volume of distribution of antipyrine was greater in men (0.61 ± 0.07 l kg^{-1}) than in women (0.53 ± 0.08 l kg^{-1}) ($P < 0.001$) and was greater in Whites than in Asians.

Because of the marked differences between Asians and Whites, both with respect to social habits and antipyrine elimination, the data were further analysed according to diet, cigarette smoking and use of the contraceptive pill (Figure 1, 2 and 3). Figure 1 shows frequency distribution curves for antipyrine clearances of vegetarians and non-vegetarians. Both are unimodal curves, with means of 0.4 and 0.67 ml min^{-1} kg^{-1} respectively. The clearances of the seven non-vegetarian Asians were evenly distributed between 0.32 and 0.73 ml min^{-1} kg^{-1}.

Figure 2 shows the distribution of antipyrine clearance in White males according to smoking status, factors of race, diet and sex being thus eliminated. Mean clearance was 38% greater in smokers than in

Table 5 First order correlation coefficients for

	Sex	*Height*	*Ponderal index*	*Haemoglobin*	*Albumin*	*Globulin*
Sex	1.000	−0.679***	−0.002	−0.607***	−0.383***	−0.090
Height		1.000	−0.087	0.489***	0.393***	−0.199*
Ponderal index			1.000	0.002	−0.044	0.217*
Haemoglobin				1.000	0.326***	−0.267**
Albumin					1.000	−0.030
Globulin						1.000
Race						
Diet						
Smoking status						
Number of cigarettes						
Alcohol						
Coffee/tea						
Oral contraceptive						
Antipyrine clearance						

Levels of significance: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

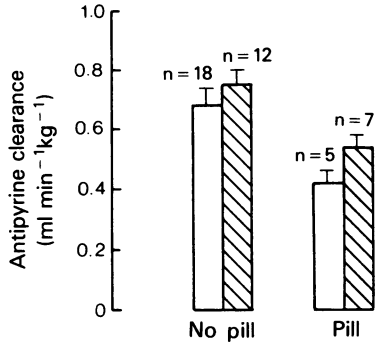

Figure 3 Antipyrine clearance in White women in relation to smoking habits and use of the contraceptive pill. □ non-smokers; ▨ smokers.

non-smokers ($P < 0.005$). In females the situation was complicated by use of the contraceptive pill. In Figure 3, mean clearance in White women is shown according to both smoking status and use of the pill. Smoking increased antipyrine clearance by 29% in women who used the pill ($P < 0.02$) but in those who did not use the pill, the trend did not achieve significance. The effect of the pill was similar in both smokers and non-smokers reducing the antipyrine clearance by 28% and 38% respectively ($P < 0.01$ in both cases). As a result antipyrine clearance in smokers who did not take the pill was almost twice that in pill-taking non-smokers (0.75 and 0.42 ml min^{-1} kg^{-1} respectively).

Multiple regression analysis

First-order correlation coefficients for antipyrine clearance and eleven observed variables reached a significant level ($P < 0.05$) as shown in the correlation matrix (Table 5). These variables were sex, height, ponderal index, haemoglobin, globulin, race, diet, smoking status, number of cigarettes per day, alcohol intake and coffee/tea index. The coefficients for race and diet were virtually identical. However, many of these variables correlated significantly with each other and stepwise multiple regression analysis was therefore performed to identify the independent correlates.

Only five variables were found to correlate independently with antipyrine clearance ($P < 0.05$). These were, in order, race, contraceptive pill usage, smoking status, ponderal index and albumin. The multiple regression equation was:

$$\text{Antipyrine clearance} = 1.65 - 0.13 \times \text{race} - 0.23 \times \text{pill status} + 0.15 \times \text{smoking status} - 0.12 \times \text{Ponderal index} - 0.01 \times \text{Albumin}.$$

Where race = 1 for Whites, 2 for Asians

pill status = 1 for non-users, 2 for users

smoking status = 1 for non-smokers, 2 for smokers

ponderal index = weight/height^2 (g/cm^2)

albumin = serum albumin in g l^{-1}

Multiple $R = 0.75$, $R^2 = 0.56$; all partial regression coefficients highly significant ($P < 0.01$) except for

antipyrine clearance and eleven observed variables

Race	*Diet*	*Smoking status*	*Number of cigarettes*	*Alcohol*	*Coffee/tea*	*Pill*	*Antipyrine clearance*
0.174*	0.209**	−0.217*	−0.149	−0.209*	−0.165	−0.254**	−0.252**
−0.386***	−0.344***	−0.251**	0.222*	0.326***	0.277**	−0.049	0.302***
0.027	0.058	−0.097	0.020	−0.019	0.075	−0.119	−0.188*
−0.363***	−0.386***	0.315***	0.268**	0.273**	0.291***	−0.076	0.313***
−0.217*	−0.200*	0.175*	0.096	0.194*	0.100	0.137	0.011
0.355***	0.387***	−0.268**	−0.217*	−0.332***	−0.145	0.083	−0.395***
1.000	0.876***	−0.394***	−0.408***	−0.424***	−0.597***	−0.208*	−0.585***
	1.000	−0.400***	−0.387***	−0.378***	−0.566***	−0.127	−0.584***
		1.000	0.847***	0.386***	0.418***	0.122	0.482***
			1.000	0.355***	0.528***	0.142	0.416***
				1.000	0.199*	0.121	0.302***
					1.000	0.062	0.471***
						1.000	−0.163
							1.000

albumin ($P < 0.05$). Thus clearance was slower in Asians and in pill-users, faster in smokers and fell as ponderal index or serum albumin increased.

Multiple regression analysis of the White sample separately identified oral contraceptive usage, smoking and ponderal index as highly significant ($P < 0.01$) independent correlates with antipyrine clearance, together accounting for 35% of the variance.

The analyses demonstrate that the effects of the contraceptive pill and of smoking were quite independent of either race or diet. Smoking status alone was important and not the number of cigarettes smoked, despite the fact that consumption varied from 2 to 40 cigarettes each day (overall mean 9.6).

Discussion

This study was an approximation to a community based sample of healthy adults, aged 18–60 years, in an industrial city. Within the sample there were two distinct sub-groups whose different cultures resulted in differences in a number of the environmental factors being investigated. The majority of subjects of Asian origin had retained traditional social customs which resembled more closely those of the Gambian villagers first studied (Fraser, Bulpitt *et al.*, 1976). Thus alcohol was taken by a minority (males only) and cigarettes and the contraceptive pill were rarely used. The majority ate a vegetarian diet, only seven eating meat regularly. By contrast, in the White sub-group there was a 50% use of cigarettes, 29% use of the contraceptive pill among women, moderate consumption of alcohol and double the intake of coffee and tea compared to the Asians.

While the diet of the Asians differed considerably from that of the Gambians studied previously both Asians and Gambians had significantly lower haemoglobin (12.5 ± 2.1 (s.d.) g 100 ml^{-1}, $P < 0.001$, and 13.2 ± 2.2 g 100 μl^{-1}, $P < 0.05$) than the Whites (13.9 ± 1.3 g 100 ml^{-1}) and significantly lower serum albumin (44.5 ± 2.2 g l^{-1}, $P < 0.01$ and 37.9 ± 4.1, $P < 0.001$) than the Whites (45.9 ± 2.8). These indices would suggest that neither the London Asians nor the Gambian villagers consumed a diet with as large a protein or iron content as the London Whites. Retrospective dietary histories in 14 female subjects (7 Asian, 7 White) supported this impression. Alvares *et al.* (1976) have shown that clearance of both antipyrine and theophylline is altered by simultaneous manipulation of protein and carbohydrate intake in volunteers, clearance being slower on a low protein diet. However, despite the obvious differences in diet within our population sample, it proved impossible to analyse their effect independently of race. Evaluation of the true contribution of diet to population variance would require an investigation of a single racial group of subjects with differing dietary habits.

The effect of the contraceptive pill bears out the finding, in small groups of women acting as their own controls, that the pill reduces antipyrine clearance and prolongs half-life (O'Malley *et al.*, 1973).

The effect of cigarette smoking confirms the findings of Vestal *et al.* (1975) in a series of 307 adult males, and of Hart and her colleagues (1976) using a small group acting as their own controls. Cigarette smoking has a greater effect on theophylline half-life (Jenne, Nagasawa, McHugh, MacDonald & Coyse, 1975) than on antipyrine half-life and the reason may be that theophylline is a substrate for both cytochromes P-448 and P-450 while antipyrine is a substrate only for P-450.

The effects of the pill and cigarette smoking partially negate each other (Figure 3), emphasizing that the observed antipyrine clearance represents the combined effect of multiple variables acting in concert. The effect of any one individual environmental factor may be relatively small in a group of subjects, but two or more factors can produce a two-fold difference or more in the clearance of the group and an order of variation in drug metabolism which would be clinically important. The most obvious example is the almost two-fold difference in clearance between women who smoke but do not use the pill and those who use the pill but do not smoke.

The amount of interindividual variation of drug oxidation in any sample of subjects which is explained by environmental factors will depend both on the sample and on the *identification* of the important environmental factors. The proportion of the variance not explained by environmental factors may be due both to hereditary determinants and to other unrecognized environmental factors.

The finding that environment plays a significant role in determining the clearance of antipyrine has implications both for therapeutic use of drugs and for toxicology. In long term therapy with lipid soluble drugs the metabolic clearance is one of the most important factors controlling the steady-state plasma concentrations. Changes within an individual and differences between individuals may be influenced to an important degree by environmental factors that are not normally taken into account by physicians when choosing dosage regimens. In countries and among people where very different diets and habits to those of Europe and North America are the rule, recommendations of drug dosage may also require modification. Finally, environmental factors which result in increased production of toxic intermediary metabolites due to accelerated oxidation of certain drugs and environmental pollutants may increase the likelihood of toxicity, mutagenicity or carcinogenicity.

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