

or signs have passed beyond the physiological boundaries and become pathological.

Dyspnoea in a young woman who is not pregnant immediately suggests some underlying disease, so that understandably many women (and their doctors) find it difficult to accept some breathlessness as a normal event. But in practice many healthy pregnant women with no history of cardiorespiratory disease do complain of dyspnoea. Milne *et al*³ studied the incidence, severity, and time course of dyspnoea in 62 such women. Nine were aware of dyspnoea during the first trimester, 31 by the 19th week, and 46 by the 31st week.

These results point to a physiological rather than a mechanical cause. The newborn infant (and presumably the fetus) is more sensitive to carbon dioxide than the adult,⁴ and Hytten⁵ has suggested that the fetus "resets" the mother's respiratory centres so that she overbreathes from early pregnancy, reducing her PCO_2 from about 40 mm Hg to 30 mm Hg or even less. This offers the fetus a favourable carbon dioxide transport system—but for the mother, accustomed to breathing with an alveolar PCO_2 of over 40 mm Hg, the ventilatory response to the lower PCO_2 level may appear "inappropriate," and according to Campbell and Howell⁶ it is this that gives rise to the sensation of dyspnoea.

The lowering of the PCO_2 by overbreathing leads to other changes in maternal homeostasis. The accompanying drop in plasma osmolality would normally be followed by a check in the secretion of vasopressin and a substantial diuresis. That early pregnancy is not associated with a continuous diuresis suggests that the osmoreceptors have been reset to maintain the new low level of osmolality in the same way as the respiratory centres are reset to accept the new low level of PCO_2 .⁵

This example of adaptation to pregnancy illustrates the dominant position of the fetus and its ability to reach out to alter the balance of the mother's central control mechanisms. A little dyspnoea is a small price to pay for helping to secure a favourable environment for the fetus, and the wonder is that such fundamental changes in the milieu intérieur cause relatively small upset to the mother's wellbeing. In practical terms it is important that the doctor should exclude any underlying disease before he reassures the patient and offers a simple, physiological explanation for her changed breathing pattern.

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² Leitch, I, *Proceedings of the Nutrition Society*, 1957, **16**, 38.

³ Milne, J A, Howie, A D, and Pack, A I, *British Journal of Obstetrics and Gynaecology*, 1978, **85**, 260.

⁴ Cross, K W, Hooper, J D M, and Oppé, T E, *Journal of Physiology*, 1953, **119**, 11.

⁵ Hytten, F E, *Acta Paediatrica Academiae Scientiarum Hungaricae*, 1976, **17**, 1.

⁶ Campbell, E J M, and Howell, J B L, *British Medical Bulletin*, 1963, **19**, 36.

Chronic effects of alcohol

Even in persons eating a nutritionally adequate diet a high intake of alcohol causes fatty infiltration of the liver, whose degree is proportional to the amount consumed.^{1 2} Baboons fed alcohol also develop fatty liver and, if alcohol feeding is continued for several months, they progress to alcoholic hepatitis and cirrhosis morphologically similar to that seen in man.³ A wealth of further epidemiological evidence links diseases of the liver, pancreas, and heart to excessive alcohol consumption.^{4 5}

In clinical practice it is far more difficult to relate the severity of these lesions to the amount of alcohol consumed. Because of the social stigma attached to alcoholism, especially in women, patients often minimise their true intake or attempt to conceal their problem completely. Furthermore, an individual's consumption of alcohol will vary according to its availability and cost and his income. Demotion or unemployment may reduce

his intake—or make him switch to less expensive forms of alcohol, possibly supplemented by methylated spirits. Not surprisingly, most research which has attempted to measure alcohol intake and relate it to human disease has come from wine-producing countries, where alcohol is cheap and a high intake more socially acceptable than in Britain.

Liver disease is of paramount importance in chronic alcoholism, and because of the wide range of possible damage and the relative ease of diagnosis attempts to measure the toxic dose of alcohol have mainly referred to its effect on the liver. Lelbach⁶ studied 319 men admitted to an alcohol detoxication unit from 1960 to 1963 in whom the history of alcohol intake was regarded as reliable. All had undergone liver biopsy. The mean daily alcohol intake of those with normal livers was 139.5 g (equivalent to eight pints of beer, a bottle of sherry, or two-thirds of a bottle of spirits), whereas patients with fatty liver, chronic hepatitis, and cirrhosis had mean intakes of 172 g, 203.5 g, and 245.5 g respectively. No patient with cirrhosis had an average daily intake of less than 190 g.

Such a positive association between amount consumed and degree of liver damage is strong evidence in support of a direct hepatotoxic effect of alcohol. Nevertheless, more recent work indicates that some patients, especially women, may develop advanced liver disease after consuming much less than these amounts, raising the possibility that genetic or immunological factors may lower the threshold dose of alcohol required to initiate damage or, once damage has occurred, favour its progression. Thus Pequignot,⁷ comparing the alcohol intake of patients with cirrhosis with that of a random sample of the population, concluded that there is an increased prevalence of cirrhosis when daily alcohol consumption exceeds 60 g for men and 20 g for women. As the group with cirrhosis included some with non-alcoholic disease, these levels will be underestimates.

A recent English study⁸ has confirmed that women seem more susceptible to alcoholic liver disease: despite there being a lower proportion of women consuming more than 150 g alcohol per day, their liver disease was more severe and they showed a definite increase in the incidence of smooth muscle and anti-nuclear antibodies and higher mean IgG and IgM concentrations. Another finding of interest was the higher prevalence of the histocompatibility antigen HLA-B8 in alcoholics with cirrhosis than in those with fatty change only.⁹ Patients with cirrhosis tended to be regular drinkers, while in those with less severe histological abnormalities an intermittent pattern of heavy drinking was more common.¹⁰

Both acute and chronic pancreatitis are associated with heavy alcohol consumption, and the proportion of patients who are alcoholic seems to be increasing.^{11 12} Unfortunately, we have comparatively few data on intake. Sarles *et al*¹³ found that the mean daily alcohol intake in 55 patients with chronic calcific pancreatitis was 175 g; only one patient abstained from alcohol. In an international survey of chronic pancreatitis¹⁴ the mean daily alcohol intake was about 150 g. By contrast, acute alcoholic pancreatitis tends to be a disease of "spree" drinkers, most commonly young men, rather than of chronic alcoholics.¹¹

The effects of alcohol on the heart present an interesting paradox. On the one hand, alcoholic cardiomyopathy is a well-established though uncommon sequel to chronic alcoholism; on the other, the incidence of ischaemic heart disease seems to be less in people who drink than in total abstainers. Alcoholic cardiomyopathy is seen most often in patients who have drunk heavily (over one-third of a bottle of spirits—80 g alcohol—per day) for at least five years,¹⁵ but nutritional deficiency may also be relevant—though frank deficiency of thiamine is uncommon in Western countries.

In both the Kaiser-Permanente¹⁶ and Framingham studies,¹⁷ the incidence of ischaemic heart disease was lower in people with a moderate intake of alcohol, and a study from Hawaii of middle-aged Japanese men showed an even stronger negative correlation.¹⁸ The cumulative incidence of ischaemic heart disease over six years showed a significant trend to lower levels

in those drinking up to 50 g alcohol per day. The number of persons in the survey who consumed over 50 g per day was not enough to show whether this trend continued or whether it was reversed at high intake levels. The Kaiser-Permanente group also studied the relation of alcohol consumption and blood pressure and found that a raised blood pressure (both systolic and diastolic) was more common among those consuming 40 g alcohol per day than in non-drinkers.¹⁹ Two other studies, however, have failed to show any link between blood pressure and alcohol intake.^{20 21}

Many questions about the toxic effects of alcohol remain unanswered. The average intake of alcohol necessary to cause damage is becoming established, but the nature of individual susceptibility is still imperfectly understood.

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- ²⁰ Schnall, C, and Wiener, J S, *Quarterly Journal of Studies on Alcohol*, 1958, **19**, 432.
- ²¹ Barboriak, J J, et al, *British Heart Journal*, 1977, **39**, 289.

Postmortem tissue problems

Increased public awareness of personal rights is not confined to those of the living. As an extension of the doctrine of informed consent problems have arisen over the use of cadaver tissue. Major techniques such as kidney transplants are well regulated, since organ donation is normally arranged and agreed before death, but for many years the removal and use of other tissues have been controlled by custom and tacit approval by the authorities rather than the Human Tissues Act. Some unfortunate episodes in a few mortuaries have now focused press attention on these traditional practices, causing consternation and in some cases a virtual standstill in the use of cadaver tissues.

The foremost need is for human pituitaries for the preparation of growth hormone—virtually the sole treatment for some types of growth retardation in children. For years now mortuary technicians have collected pituitaries and sent them to the Medical

Research Council for extraction of the hormone. Other organs or tissues have been used for research, for student teaching, and for trial of new surgical techniques; and at one time freeze-dried arterial grafts were in demand for transplantation.

All these innocent activities are illegal unless brought strictly within the terms of the Human Tissues Act. After some long period of confused discussion and numerous memoranda from bodies including the Department of Health, the Home Office, and the Medical Research Council, the conclusion as regards non-coroners' necropsies seems clear. When permission for post-mortem examination is sought from the relatives, a clause should be added to the form requesting the use of tissues for unspecified purposes connected with treatment, teaching, and research. The relative can agree or can strike the clause out, leaving only the permission for the necropsy itself. Once this signature is obtained then tissues may be removed legally, though there is still some doubt as to the degree of "informed consent" which such a brief blanket permission provides. For instance, does such a brief request equally cover the removal of both eyes as well as merely the pituitary unless a full explanation is given? Against the case for informed consent must be set the distress caused by the adding of gruesome details to the discussion with the bereaved relatives.

Greater difficulty surrounds coroners' cases, which now account for at least one-third of all necropsies, with the proportion rising as the number of "clinical" postmortem examinations has declined. With a coroner's necropsy, there is no question of asking the relative's permission for the examination, so that there is no opportunity to obtain signed consent for removal of organs. Coroners' cases are a major source of pituitary glands and other tissues retained for medical purposes; yet paradoxically the coroner himself cannot give permission for their removal. He can refuse removal of tissues, but this is entirely a prohibitory function, and his absence of refusal in no way fulfils the requirements of the Human Tissues Act. This point seems to have eluded some administrative bodies: several directives have appeared stating that the Home Office and even the police have looked into the difficulties and that pathologists can take such tissues with an easy mind. In fact, the matter is controlled solely by the Human Tissues Act, and only another Act of Parliament can amend its provisions.

At least one city has begun to use a brief permission form for the removal of tissues in coroners' cases, and with the co-operation of the coroner has now put the medicolegal necropsy on the same footing as the clinical postmortem examination, so that tissues are removed only in those cases in which the relative gives permission. The proportion will naturally be less, because many coroners' necropsies are done not only without the permission of the relatives but in the face of their active antagonism. Nevertheless, even a partial success rate is better than nothing.

Even though the DHSS has stipulated that the new two-part permission forms should be used for all hospital postmortem examinations, their use seems by no means universal. In many areas the practice of taking tissues in coroners' cases without any permission is continuing, with those concerned presumably relying on the ethical justification that the good that accrues from the use of such tissues will see them through any adverse comment. The climate of public opinion and the keen eye of the press make it imperative, however, that correct procedures be followed if we are to ensure no child need be short of growth hormone and that material for teaching and research is still available.