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Review article

Clinical pathology of alcohol

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SUMMARY There is good though not conclusive evidence that a small to modest average daily intake of alcohol—that is, 20-30 g/day is associated with increased longevity due mainly to a reduction in death from cardiovascular disease. Larger average daily alcohol intakes—especially those in excess of 60 g/day for men and 40 g/day for women—are associated with gradually increasing morbidity and mortality rates from a variety of diseases.

Alcohol may be unrecognised as the cause of somatic disease, which can occur without overt psychosocial evidence of alcohol abuse, unless the index of suspicion is high and a thorough drink history obtained. Laboratory tests for the detection and/or confirmation of alcohol abuse are useful but subject to serious limitations being neither as sensitive nor specific as sometimes believed. The value of random blood and/or breath alcohol measurements, in outpatients, as an aid to diagnosis of alcohol-induced organic disease is probably not sufficiently appreciated and, though relatively insensitive, is highly specific.

Ethanol, more commonly referred to as alcohol, shares with caffeine and nicotine the distinction of being amongst the three most widely used drugs in the world. Its ability to cause disease through a variety of mechanisms has been recognised since early times, but the full spectrum has only recently become apparent and is probably still incomplete. It has displaced syphilis as the great mimic and should be thought of as a potential aetiological factor in almost any differential diagnosis of somatic or psychopathology.[1] It has been estimated that in Britain, at the present time, alcohol is a major contributing factor in over a quarter of the illnesses leading to admission to acute medical units.[2] Despite the greater awareness of the role of alcohol in the pathogenesis of disease, almost nothing is known about the molecular mechanisms involved. Some of the systemic abnormalities that have been described are explicable on the basis of the known consequences of alcohol metabolism in the liver and others are a consequence[3–5] of associated nutritional deficiencies.[6] In the majority of cases, however, no such simple explanations are possible and their elucidation awaits further research.

It is important, in any discussion of the pathophysiology of alcohol to distinguish between the acute effects of modest, subinebriating amounts of alcohol and those of larger intoxicating doses. Similarly, it is important to differentiate between the acute effects of alcohol in previously healthy subjects and those which result only from long continued alcohol abuse. The latter may itself produce different effects depending on whether drinking is continuing (ie the drinking alcoholic), or whether it has been discontinued in the recent or remote past. The former type of subject is referred to as the "acutely withdrawn" and the latter as the "recovered" alcoholic. Though many diseases are largely or wholly attributable to chronic alcohol abuse the factors that determine why so relatively few of those at risk suffer from any particular adverse effect are largely unknown. Attempts to correlate susceptibility to alcohol liver disease with HLA types have been made,[7] without unanimity, and the possibility of genetic factors determining which organ, if any, will bear the brunt of alcohol assault, though attractive, must be considered unproven.[8]

During recent years many books devoted mainly or entirely to the metabolic and clinical aspects of alcohol[9–14] have appeared. In this review the major emphasis will be on the laboratory detection and measurement of organ damage due to chronic alcohol abuse but consideration will also be given to those functional abnormalities induced by alcohol that are themselves largely, if not wholly, dependent upon laboratory diagnosis.

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Alcohol in the community

The use of alcohol is ubiquitous but its pattern of usage is enormously varied; what constitutes abnormal or excessive alcohol use is, therefore, determined more by cultural than by clinical factors. Not only are there large differences in the average amount of alcohol consumed by individuals in different cultures, but also in the proportion of the population who are total abstainers. In Britain as a whole, for example, less than 10% of the adult population are abstainers (in 1982) but there are large regional differences which do not necessarily correspond with average alcohol intake.[15] These are held to account for divergences from the general rule that the greater the consumption of alcohol by a community, the higher its incidence of alcohol-induced disease.

There is epidemiological evidence from several sources that regular, modest alcohol consumption—that is, 20-30 g/day, is associated with optimum health and maximum longevity and that this is due mainly to a reduction in coronary artery occlusion[16] and the number of premature deaths from arteriovascular disease.[17–20] A causal relation with alcohol has not, however, been established nor has the association been universally observed[21] and there is currently insufficient confidence in the beneficial effects of small doses of alcohol to warrant advocating their use as a health measure.

An average daily intake of alcohol greater than 40 g/day is associated with gradually increasing morbidity and mortality rates. The Royal College of Psychiatrists' report[22] recommends that the average daily intake of alcohol must be kept below 60 g/day (eight drinks*) if the risks of suffering from its physical or social consequences are to be kept to an acceptable figure. Doubtless some people acquire alcohol-induced disease at lower average daily intakes than this whilst many who exceed it do not. Nevertheless, this admittedly arbitrary figure does provide a useful dividing line between moderate and excessive alcohol use except in pregnancy[23 24] where it is undoubtedly too high (see below), and probably in women as a whole since they appear to be more sensitive to the tissue damaging effects of alcohol than men.[25] This, however, may be related more to their smaller size than their biology and certainly warrants further investigation.

Absorption, disposition

Though generally taken by mouth, alcohol can be absorbed through any mucosal surface, including the skin;[26] indeed the lungs provide one of the best routes for getting large quantities of alcohol (as vapour) into the blood of experimental animals over prolonged periods.[27] It is absorbed with great facility along the whole length of the gastrointestinal tract, but more rapidly from the small intestine than from the stomach. More than twice as much alcohol can be consumed with a meal as without one, yet produce a smaller rise in blood alcohol concentration.[28] This is probably mainly as a result of delayed gastric emptying but also to changes in the pharmacokinetics of alcohol[29] which are still poorly understood despite more than 80 years of research.

Orthodox teaching, based upon the work of Mellanby,[30] is that "the rate of oxidation (of alcohol) is constant throughout the whole period (ie from the beginning of absorption to the end of oxidation and elimination) and this is the case in spite of the fact that the amount of alcohol in the body is getting progressively less. The interpretation of the fact is, therefore, that whatever the amount of alcohol in the body the rate of oxidation is independent of the amount drunk". This view of alcohol disposal, espoused and developed by others—notably Widmark[32] who coined the term beta (β) to describe the rate of fall in blood alcohol concentration with time—has not gone unchallenged[29 32] and must now be considered too simplistic to warrant uncritical acceptance. It presupposed that alcohol is removed from the body pool by a single metabolic pathway. This is now known to be incorrect and at least two mechanisms capable of converting alcohol to carbon dioxide and water, in addition to that employing alcohol dehydrogenase, have been described; one utilises catalase the other an NADP-dependent microsomal oxidising system (MEOS). The quantitative importance of these two metabolic pathways in alcohol metabolism is still controversial both in relation to each other and to overall body metabolism and current opinion inclines to the view that the alcohol dehydrogenase pathway is responsible for disposal of 70% or more of alcohol ingested, at least for as long as blood alcohol concentrations remain below 20 mmol/l (92 mg/100 ml). At higher blood alcohol concentrations the MEOS, and possibly also the catalase system, assumes greater relative and absolute importance. This ability to involve additional metabolic pathways probably explains why alcoholic subjects can often dispose of up to 500 g alcohol a day for weeks on end. This is roughly three times as much as would be expected on the basis of metabolic studies performed on countless subjects which indicate that, at more socially acceptable

*By an interesting quirk almost all drinks provide 7-9 g alcohol when consumed in the conventional "public house measure," ie 280 ml beer; 120 ml wine; 60 ml sherry, 24 ml whisky, gin, or vodka.

blood alcohol concentrations—for example, 2-22 mmol/l, the normal rate of alcohol oxidation is roughly 100 mg/kg/h, ie 7 g/h or 168 g/day for a 70 kg person.[5]

Time of day is one of the important factors determining the rate of alcohol metabolism[33] as it is of other drugs, although it has received relatively scant attention from most investigators. What evidence there is currently suggests that alcohol disappears from the blood faster in the morning than in the evening.[33] If this is confirmed it could explain some of the discrepancies that dog the alcohol-metabolism literature.

The limiting factor determining the rate of alcohol metabolism at any time of the day is not known with certainty. It is not, as was once thought, the amount and availability of alcohol dehydrogenase in the liver, but probably is something to do with the rate of reoxidation of the NADH which is formed whenever alcohol is oxidised to CO_2 and water.

Alcohol dehydrogenase exhibits marked polymorphism. Three autosomal gene loci (ADH_1 ADH_2 ADH_3) are thought to be concerned with determining the structure of alcohol dehydrogenase in man—the first two manifesting themselves almost exclusively during fetal life and the last during infancy and adulthood.[34] An "atypical" alcohol dehydrogenase (ADH_2^2) has been distinguished from the typical enzyme (ADH_2^1) by its optimum pH and greater activity at physiological hydrogen ion concentrations. It is said to occur in 5-20% of Europeans and in 90% of Oriental populations and could be responsible for the high incidence of alcohol-induced flushing observed in the latter.[35] This seems less likely than formerly, however, and currently comparatively little importance is attached by most investigators to genetic variance of alcohol dehydrogenase in the pathogenesis of alcohol-induced symptoms, organ damage, or of alcoholism itself.[36]

Acetaldehyde

Acetaldehyde is the first metabolic product of alcohol metabolism regardless of whether oxidation is effected by alcohol dehydrogenase, catalase, or MEOS. It has attracted considerable interest in the past few years and has been held responsible for many, if not most, of the tissue-damaging effects of chronic alcohol abuse as well as for the unpleasant reaction experienced by people taking certain drugs or belonging to particular racial groups.[37 38]

Acetaldehyde is an extremely reactive compound capable, at very low concentrations, of interfering in vitro with a number of vital processes including protein synthesis and secretion by cells, mitochondrial ATP production and the inactivation of diverse thiol-containing compounds.[39] In vivo it is normally rapidly deactivated by acetaldehyde dehydrogenase, an enzyme which, like ADH, exhibits polymorphism.[40 41] It, too, utilises NAD as cofactor with the production of NADH whose rate of reoxidation is one of the main determinants of alcohol metabolism in vivo. The role of acetaldehyde dehydrogenase itself in determining the rate of alcohol metabolism is unknown. It might reasonably be expected to play a central role since it is responsible for oxidation, to acetate, of the acetaldehyde formed by all three alcohol oxidative pathways. This supposition is, however, difficult to square with the observation that hepatic acetaldehyde dehydrogenase activity is reduced in alcoholics[42] and as an inherited anomaly in Japanese[38] despite their normal or enhanced capacity to metabolise alcohol.

MEASUREMENT

The assay of acetaldehyde in biological fluids has presented many difficulties in the past[43] and only very recently have methods capable of accurately measuring it in blood become available.[44 45] Special attention must be paid to the method of collecting the sample if reliable results are to be obtained. Data collected using such methods suggest that studies performed before 1980 grossly overestimated the concentration of acetaldehyde in blood after the ingestion of alcohol by normal and alcoholic subjects, and that many of the conclusions based upon them may be wrong. It appears, moreover, that much of the acetaldehyde present in blood is protein-bound[46] and might not, therefore, be available for measurement by widely used gas chromatographic methods[47–50] that depend upon analysis of head-space vapour. Older colorimetric,[51] spectrophotometric[52] and enzymatic[53] techniques, though capable of measuring protein-bound acetaldehyde are so unreliable on other counts as to be worthless for clinical investigation.

SIGNIFICANCE

Several studies, using gas chromatographic methods, have revealed marked differences in blood acetaldehyde concentrations after alcohol ingestion between normal and alcoholic subjects, being much higher in the latter.[54] This differential acetaldehyde response to alcohol is said[55] also to extend to the healthy sons and other blood relatives of alcoholics (who are at risk of becoming alcoholics themselves) and might be supposed to result from the inheritance of an abnormal (or atypical) acetaldehyde dehydrogenase. It could also serve as a marker predicting alcoholism in later life and would therefore be immensely useful clinically. Confirmatory or

negatory studies using reliable methodology are, therefore, essential and are awaited with interest.

Certain drugs sensitise patients to alcohol. Two of them, disulfiram and citrated calcium carbimide are used therapeutically for the treatment of alcoholism because of the predictability of their effect whilst for most others—for example chlorpropamide, tolbutamide, metronidazole, pargyline, furazolidone, griseofulvin and chloramphenicol, sensitisation is only a troublesome side effect that occurs in a variable number of subjects. It has long been suspected that accumulation of acetaldehyde in the blood is responsible for some of the unpleasant symptoms that follow ingestion of alcohol. This has been confirmed in the case of disulfiram and citrated calcium carbimide by direct measurements of acetaldehyde in the blood. Accumulation of acetaldehyde in these circumstances is due to inactivation of aldehyde dehydrogenase which, in the case of disulfiram, develops slowly over 12 hours;[56] restoration of aldehyde dehydrogenase activity depends upon de novo synthesis which occurs over six days or more.[57] Much less predictable than disulfiram induced alcohol sensitivity is that produced by chlorpropamide[58] which occurs in a variable proportion of diabetic patients receiving treatment with the drug or who are given it experimentally. The propensity to develop chlorpropamide-alcohol flushing [CPAF] is said to be inherited as a dominant trait[59] and to have a higher prevalance in patients with non-insulin dependent diabetes (type II) than in those with insulin-dependent diabetes (type I) and control subjects, though others have not confirmed this.[60 61] Patients with chlorpropamide-alcohol flushing are said also to have a reduced risk of developing "diabetic complications" but this too requires confirmation.

The cause of the flushing is unknown but several hypotheses have been put forward,[62–64] one of the most favoured being that it is due to the accumulation of acetaldehyde in the blood.[58 65] A certain resemblance to disulfiram-induced alcohol sensitivity—which is, however, generally much more severe[66] and often accompanied by symptoms of intensive palpitations, dyspnoea, nausea, vomiting and headache which are never observed in the chlorpropamide-induced variety—and to racial alcohol flushing supports this suggestion. In both of these latter conditions plasma acetaldehyde concentrations rise higher after alcohol ingestion than in non-affected controls,[38 64] though seldom to the concentrations encountered during severe disulfiram reactions.

The possibility that acetaldehyde formed from alcohol might condense chemically with dopamine and other catecholamines to produce morphine-like compounds was first raised on theoretical grounds by Davis and coworkers[67] and developed by Sandler[68] who demonstrated the presence, after alcohol, of significant amounts of salsolinol—a vaguely morphine-like compound—in the urine of Parkinsonian patients receiving L-dopa.

Although there are many differences between morphine and alcohol physical dependence, the tetrahydroisoquinoline hypothesis—as it is now called—cannot be dismissed completely.[69] There is evidence that salsolinol is present at 20 times greater concentrations in the urine of "drinking alcoholics" than of control subjects and that it falls to baseline concentrations within four days of alcohol withdrawal.[70] Though it has not yet been established whether salsolinol itself is addictive—that is, responsible for withdrawal symptoms, it is perhaps not without interest that the chlorpropamide-alcohol flush can be blocked by the specific opiate antagonist, naloxone, and reproduced by an enkephalin analogue with opiate-like activity.[63]

Acute metabolic effects of alcohol

In addition to its well known direct actions upon the nervous system, alcohol has certain profound, acute metabolic effects upon the body, the nature and extent of which depend upon a variety of factors. These include the quantity of alcohol consumed, previous dietary history, the presence or absence of pre-existing organic and/or metabolic disease and the genetic make-up of the individual. Many, though by no means all, of the effects on metabolic processes are mediated through changes in the intrahepatic redox potential consequent upon the formation of NADH, and the resultant depletion of intracellular NAD, during oxidation of alcohol and acetaldehyde. Others are an indirect consequence of intoxication and its activation of sympathetic nervous activity and other neurohumoral mechanisms. In some cases the effects are the result of alcohol-drug interactions,[71 72] a small number of which have been used therapeutically as in the case of disulfiram and citrated calcium carbimide.[73]

Metabolic consequences of the changes in intracellular redox potential include the accumulation of lactate in the blood, a rise in hydrogen ion concentration—that is, fall in pH, and an increase in the plasma lactate:pyruvate ratio. A rise in plasma urate, due to impaired excretion of urate by the kidneys, and inhibition of gluconeogenesis, which manifests itself as hypoglycaemia and ketonaemia if alternative sources of glucose—for example, food and/or liver glycogen, are not available, also occur. Plasma fatty acid concentrations may rise or fall depending upon dosage.

Probably the most dramatic example of alcohol precipitating a metabolic emergency in genetically predisposed individuals is acute intermittent porphyria[74 75] and in Glasgow it was the third commonest precipitating factor accounting for 13% of all the acute attacks observed during a three-year period. Alcohol is also one of the main aetiological agents in the development of cutaneous hepatic porphyria[76] through its effect upon haem synthesis, though in this instance the disturbance is subacute rather than acute in onset.

Alcohol-induced (fasting) hypoglycaemia is equally dramatic[77] as acute porphyria but can occur in anyone—providing the circumstances are right—as well as in the genetically or otherwise predisposed. It is, however, especially common in children, the malnourished, and alcoholics. The blood glucose concentration is invariably low and plasma lactate and β-hydroxybutyrate high. Blood alcohol is more often below than above 25 mmol/l by the time the hypoglycaemia develops.

Large doses of alcohol can, though seemingly only very rarely, precipitate acute hyperglycaemic (diabetic) ketoacidosis in diabetic subjects previously stabilised on dietary treatment alone.[78] More commonly[79–82] it produces a type of ketoacidosis which resembles diabetic ketoacidosis clinically but in which hyperglycaemia plays no part. It is accompanied by marked increases in plasma and urinary lactate and ketone concentrations but, because of the shift in the ratio of β-hydroxybutyrate to acetoacetate produced by the change in redox potential the ketosis can easily be overlooked since conventional tests for urinary (and the semi-quantitative tests for plasma) ketones are insensitive to β-hydroxybutyrate.

Alcohol is one of the most important causes of hyperlipidaemia[83] and its possible aetiological role should be suspected whenever this condition is encountered. Gross hypertriglyceridaemia sometimes observed after comparatively mild alcohol use is partly due to increased triglyceride formation in the liver and partly to impaired removal of chylomicrons and VLDL from the circulation. This may occur whenever alcohol and fatty food are ingested together and persist for up to 14 hours after the meal.

Differentiation of alcohol-induced from genetically determined hypertriglyceridaemia may be difficult without a detailed history since increases in plasma gamma glutamyl transferase and urate are common in both.

Whether such well known somatic manifestations of alcohol ingestion as acute pancreatitis, alcoholic hepatitis, gastritis, myocarditis, and muscle disease are "metabolic" in origin is unknown. If so, the mechanism involved is still uncertain though hypotheses abound.

Endocrine function

The profound effects of alcohol upon endocrine function, which can arise as a result of both acute and long-term ingestion, have only been fully appreciated within the past 10 years or so.[84–89] Almost no part of the endocrine system is exempt though some glands and systems are more susceptible than others. Though interest has centred mainly upon the hypothalamic-pituitary-adrenal axis and latterly the gonads, disturbances of other endocrine functions have attracted attention, notably those of the pancreas,[90] adenohypophysis[99] and thyroid.[92] The ability of alcohol to stimulate calcitonin release in patients with medullary carcinoma of the thyroid,[93 94] flushing in patients with carcinoidosis[95] and adrenaline release in patients with pheochromocytoma[96] is sometimes used diagnostically.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

It has long been known that large intoxicating doses of alcohol given to animals activate adrenocortical as well as adrenomedullary activity. More recently it has been reported[97–99], that the administration of modest but intoxicating doses of alcohol stimulate cortisol secretion in healthy volunteers although it now seems likely that the intoxication rather than alcohol itself is the operative agent.[100] More clinically relevant is the recognition that occasional chronic alcohol users develop physical and biochemical stigmata resembling those of Cushing's syndrome from which they can often be distinguished only with great difficulty.[101–106] The most telling point is that both the clinical and biochemical features of adrenocortical hyperactivity abate within 2–3 weeks of withdrawal from alcohol. Chronic alcoholics without either clinical or biochemical evidence of Cushing's syndrome often show impaired suppression of adrenocortical activity in response to dexamethasone,[107] the most likely cause of which is defective hypothalamic function though accelerated metabolism of dexamethasone by alcohol-induced enzymes and its consequent failure to reach and maintain suppressive plasma concentrations, has not been excluded.

More common than alcohol-induced Cushing's syndrome, but less clinically evident, is a reversible form of ACTH deficiency which can often only be demonstrated by the failure of plasma ACTH and cortisol concentrations to rise in response to insulin-induced hypoglycaemia.[85 101 108 109] This abnormality occurs in up to 25% of alcoholics and is

often accompanied by an impairment of growth-hormone secretion which can also occur as an isolated, but reversible, abnormality.[110] In a small proportion of cases the abnormality in ACTH and/or growth hormone secretion is accompanied by a propensity to develop symptomatic fasting hypoglycaemia especially in response to alcohol ingestion.

There is no evidence that either primary or secondary adrenocortical insufficiency predisposes to alcoholism. There is, however, a cult—which originated, and is especially influential in the United States, where it has many adherents both amongst registered medical practitioners and the laity—which maintains that it does. Warnings have been issued in the medical press by the American Diabetes Association, American Medical Association and Endocrine Society[111 112] on two occasions in the past 10 years against practitioners who, amongst other things, attribute many of the vague symptoms experienced by alcoholic and other patients to "hypoglycaemia" for which there is invariably no diagnostic laboratory evidence apart from an abnormal glucose tolerance test, the general worthlessness of which in the diagnosis of genuine hypoglycaemia is now well established.[77]

Chronic alcoholism is often associated with reduced urinary excretion of 17-oxosteroids (formerly thought to be a useful index of adrenocortical function), due to alcohol-induced alterations in steroid metabolism in the liver, as well as with an increased propensity to the development of both fasting and (experimental) reactive hypoglycaemia. These facts have been used by adherents of the cult to support their "scientific arguments" that hypoglycaemia predisposes to alcoholism and their habit of prescribing inactive adrenocortical extracts for its treatment.

HYPOTHALAMIC-PITUITARY-GONADAL FUNCTION

The well known effects of alcohol upon sexual function in both men and women have long been attributed mainly to liver damage.[113 114] Although this is still recognised to play a contributory role when it is present, there is good evidence for a more direct effect of alcohol upon the hypothalamic-pituitary-gonadal axis[115 117] and gonads themselves.

Ethanol administration to immature male rats prevents the normal rise in plasma LH concentration that occurs with the onset of puberty[118] and produces a fall in plasma testosterone concentrations. In normal human subjects its administration leads to an acute fall in plasma testosterone[119–121] which may, paradoxically, lead to an acute rise in plasma LH but usually does not, indicating a hypothalamic-pituitary involvement as well as a gonadal effect.

Chronic alcohol ingestion may produce gonadal atrophy, severe germ cell injury and a marked reduction in plasma steroid concentrations in experimental animals reminiscent of those seen in chronic alcoholic men in whom spuriously high plasma levels of 17β-hydroxy androgens are sometimes[85 108] seen, possibly due to an increase in sex hormone binding globulin (SHBG) concentration.[122] Evidence from a number of quarters suggests that the effects of alcohol on sexual function are exerted through multiple mechanisms including indirectly through the hypothalamus, by direct inhibition of testosterone synthesis in the testes and its increased metabolism in peripheral tissue.[87 122] Much less is known about the effect of alcohol on gonadal function in women, though impaired fertility is a recognised complication of chronic alcohol abuse.[123] As mentioned elsewhere the regular ingestion of even small amounts of alcohol—for example, 30 g alcohol per day, during pregnancy increases the incidence of fetal abnormalities.[23 24]

SYMPATHETICO-ADRENOMEDULLARY FUNCTION

Experiments on animals, and experimental and clinical observations in man, have shown that intoxicating doses of alcohol activate sympathetico-adrenomedullary activity.[84 99] Whether smaller non-inebriating doses, or chronic alcohol abuse, have similar effects is unknown. Conclusions relating to sympatheticoadrenomedullary function in alcoholics based on urine analysis are complicated by the fact that alcohol alters the metabolism of catecholamines through changes in redox potential in the liver. As a result, urinary excretion of 3-methoxy-4-hydroxy mandelic acid (HMMA; VMA) the normal major product of adrenaline and noradrenaline catabolism—is decreased and there is a corresponding increase in 3-methoxy-4-hydroxy phenyl glycol (MHPG) excretion.[124 125]

Few studies have been made of the effects of modest amounts of alcohol on catecholamine release using modern analytical techniques with sufficient sensitivity and specificity to detect small but significant changes in plasma adrenaline and noradrenaline. An unpublished study in my own laboratory, using an isotope derivatisation technique with chromatographic separation for the measurement of adrenaline and noradrenaline, showed that alcohol given on an empty stomach to healthy volunteers in doses sufficient to raise blood alcohol concentrations to 10—21 mmol/l (50–100 mg/100 ml) had no effect upon plasma adrenaline and only a small, clinically unimportant stimulatory effect on

plasma noradrenaline concentrations unless symptoms of alcohol intoxication intervened when plasma concentrations of both catecholamines rose dramatically. What role, if any, sympathetic nervous activation plays in the aetiology of reversible hypertension observed in some heavy alcohol users is unknown but would probably repay investigation.

Though catecholamine production is markedly increased during alcoholic inebriation, as well as by alcohol withdrawal, a certain number of chronic alcoholics—two out of 12 in the series reported by Wright[91]—for example—show no sympathetico-adrenomedullary response to insulin-induced hypoglycaemia, suggesting that the hypothalamic depression noted in respect of growth hormone and ACTH secretion extends to the autonomic nervous system. Suppression of sympatheticoadrenomedullary activation by alcohol is not confined to chronic alcohol users. Modest amounts of alcohol prevent the normal homeostatic restoration of blood glucose to normal following its experimental depression by exogenous insulin, and a combination of alcohol and exercise in the cold can lead to severe and potentially dangerous hypoglycaemia in healthy volunteers, presumably due to impaired hypothalamic function[126] and impaired gluconeogenesis.

ENTEROINSULAR AXIS

The effect of alcohol upon the enteroinsular axis, like that of other endocrine systems, is profoundly affected by dose and duration.[90] In modest doses it enhances the insulinotropic effects of various secretagogues—for example, glucose and glucagon, through an unknown mechanism which involves increased cAMP production in the pancreatic B cells. One effect of enhancement is that ingestion of an appropriate mixture of alcohol and sugar—for example, gin and tonic, may, if taken on an empty stomach, predispose to development of (symptomatic) reactive hypoglycaemia one and a half to three hours later.[127 128] Small carbohydrate-yielding snacks may exacerbate rather than diminish the tendency which can have important implications for those who drink and drive.[129]

Larger doses of alcohol—that is, those leading to blood alcohol concentrations greater than 25 mmol/l do not enhance and may even inhibit glucose-induced insulin secretion. This, together with the activation of sympathetic nervous activity that follows heavy drinking, may explain the well known ability of alcohol abuse to depress rather than to improve glucose tolerance.[90]

Alcohol consumed whilst the subject is fasting or on a low carbohydrate intake may cause fasting hypoglycaemia by inhibition of gluconeogenesis.[77] In this condition, which is extremely dangerous, plasma insulin secretion is inhibited and plasma concentrations are low. Glucagon secretion, on the other hand, is stimulated but in the absence of hepatic glycogen stores is ineffective in raising the blood glucose concentration.

Diagnostic considerations

The ingestion of alcohol is associated with numerous changes in blood chemistry and morphology, the nature, magnitude and number of which are determined by the amount and duration of alcohol consumption and the interval since any was last consumed. Hopes have long been expressed that it might be possible, by measuring one or more of the constituents of the blood, to determine the average daily dose of alcohol ingested and whether alcohol-induced tissue damage was present. None of these hopes has been more than partially fulfilled and current evidence suggests that even a battery of laboratory tests is less sensitive or specific than a properly conducted interview.[130–133] There is no doubt, however, that laboratory tests are occasionally helpful in detecting alcohol-induced disease before it becomes clinically apparent, and for assessing the response to treatment.[134–138] They have recently been reviewed.[139 140]

ALCOHOL IN THE BLOOD

Alcohol is not normally present in blood in more than trace amounts unless it has been imbibed recently; even then it seldom exceeds a concentration of 15 mmol/l except in the presence of clear evidence of intoxication. The presence of such high concentrations without cerebral dysfunction is evidence of habituation and consequently, indirectly, of chronic alcohol abuse. The signs of cerebral dysfunction need not necessarily be distressing to the subject himself, and may only be apparent if actively sought. They consist mainly of mild euphoria, increased self-confidence, decreased inhibitions, reduced attention and loss of efficiency in fine performance tests. Amongst the criteria proposed by the American National Council on Alcoholism[141] for the diagnosis of alcoholism, is the presence of a blood alcohol concentration greater than 65 mmol/l (300 mg/100 ml) at any time, or of over 33 mmol/l (150 mg/100 ml) without symptoms. The finding of a blood alcohol concentration of 22 mmol/l (100 mg/100 ml) during a routine clinical examination provides strong presumptive evidence of the diagnosis. Blood alcohol concentrations seldom rise above 35 mmol/l even after quite heavy social drinking though it is still possible, in the latter circumstances, for blood alcohol concentrations to exceed 10 mmol/l the following morning.[142]

In view of the ease[143] with which blood alcohol measurements can now be carried out—on breath as well as on blood itself—it is suprising how rarely they are included in routine health screening programmes or, despite their proven usefulness,[144 145] employed by clinicians confronted with alcohol abuse as a differential diagnosis. In a study of 1476 patients, carried out in Switzerland, 2% of patients attending the medical outpatient clinic, 9% of all new admissions to the medical emergency ward and no less than 12% of those admitted to the surgical emergency ward had blood alcohol concentrations on arrival at the hospital in excess of 22 mmol/l.[146] In another study from America, blood alcohol measurements were made on 76 patients attending the emergency room of a large hospital in Pennsylvania over a period of two years, who admitted drinking alcohol within the past six hours but were deemed sober or "non-intoxicated" by the examining physician.[147] Patients who were drunk or otherwise considered incapable of being released from the emergency room on their own recognisance, were excluded from the study. No alcohol was detected in the blood of 11 of the subjects but in the remaining 65, its average concentration was a staggering 58·2 ± 2·2 mmol/l (range 26–117 mmol/l; 120–540 mg/100 ml). Concentrations such as these are generally associated with stupor or coma from acute alcoholic poisoning and serve to illustrate how unreliable clinical impressions can be in assessing the extent of alcohol use by habitual users.

Blood alcohol measurements, though already very simple to carry out in a clinical laboratory setting, would undoubtedly be used more frequently if, as is now technically possible, simple quantitative stick tests—analogous to those used for glucose and other blood and urine constituents—were readily available for use in clinics and outpatient departments. Laboratory reagent manufacturers may have been inhibited from making them from fear of litigation arising from their (mis)use for forensic rather than for clinical purposes. Hopefully, this and other obstacles to the introduction of these potentially useful diagnostic aids will soon be overcome.

PLASMA ENZYMES

Chronic excessive alcohol ingestion is associated with increased activity of many of the enzymes normally found in the plasma. Most of those that have been studied extensively derive mainly, if not exclusively, from the liver,[148] and their presence in increased amounts in the plasma has been construed as evidence of potential or real liver damage though this interpretation is not necessarily correct. Enzymes that have attracted most attention include gamma glutamyl transferase (GT), aspartate animotransferase (AST), alanine aminotransferase (ALT) glutamate dehydrogenase (GDH), and alkaline phosphatase (ALP), of which the first is by far the most important.[149 150]

Gamma glutamyl transferase (GT)

The measurement of plasma GT activity as a biochemical index of alcohol consumption was introduced and popularised by Rosalki.[149] It has subsequently come to enjoy a unique place in the detection of alcohol abuse in patients with a variety of somatic and psychosocial diseases. Early reports indicated that between 75% and 85% of chronic alcoholics had moderately to markedly raised plasma GT activities[150–153] but subsequently lower figures of between 30–50% were reported.[133 154] The latter figure corresponds well with the sensitivity—that is, the percentage correctly identified, of plasma GT measurements in detecting excessive alcohol use (an average intake of more than 65 g alcohol per day) amongst 8000 attendees at a Medicheck Centre in Sydney,[135] and in healthy manual workers and company directors[155] who volunteered to participate in an extensive investigation of drinking habits in Edinburgh. In the latter study plasma GT measurements yielded false-positive results in 11% of the manual workers and 22% of the company directors if their accounts of their own alcohol intakes are to be believed. Thus, GT is not only a relatively insensitive test (despite being the best there is) but also a non-specific one for the detection of alcohol abuse even in a high risk population.

Aspartate aminotransferase (AST)

Of the other plasma enzymes perturbed by chronic alcohol abuse, aspartate aminotransferase is the most sensitive, being pathologically raised in 25–30% of chronic alcoholics[150 154] and in 10–15% of those who drink more than 65–80 g of alcohol a day without overt evidence of liver damage.[133 135 138]

Glutamate dehydrogenase (GDH)

Plasma GDH, like the two enzymes already mentioned, correlate positively with alcohol consumption but is an even less sensitive index of alcohol abuse than either[156] being abnormally raised in only 15–25% of all heavy alcohol users.[133] It is, however, remarkably specific (98%) for alcohol abuse when used in an apparently healthy population and being a mitochondrial enzyme probably identifies latent or occult hepatocellular damage.[156 157]

Other enzymes

Various other serum enzyme activities—for example, isocitrate dehydrogenase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase,

ornithine carbamoyltransferase, are raised in alcoholics and heavy alcohol users but none has sufficient sensitivity and/or specificity to make it useful either for screening or diagnosis.[154] One of the most promising of the enzymes to have been investigated for the diagnosis of alcohol abuse is red-cell Δ-amino-laevulinic dehydrase[158–160] which is said to be depressed in 90% of heavy alcohol users.[158] It is, however, an unstable enzyme whose measurement is difficult and it has not been introduced into the clinical laboratory repertoire.

MEAN RED CELL VOLUME (MCV)

In unselected populations, mean red cell volume (MCV) correlates positively with average daily alcohol intake.[133 134] The average difference in red cell size between abstainers and heavy users is, however, less than 4·5 fl (approximately 5%) and although abnormally large red cells are said to be comparatively common in alcoholics and chronic alcohol abusers, the exact proportion depends heavily upon the upper reference limit (of normality) set by the investigator. Clearly, with such small percentage differences in MCV between abstainers and heavy alcohol users (whether considered in absolute terms or in relation to the variation between healthy individuals) there is a premium on both accuracy and precision of measurement. Wu *et al*,[161] for example, reported that 89% of 63 patients consuming more than 80 g ethanol daily had a macrocytosis compared with healthy controls with an upper reference limit of 92 fl. In a subsequent larger study[162] no less than 94% of women and 71% of men who were drinking excessively (over 80 g alcohol per day) had a macrocytosis by these criteria. Whitfield *et al*,[135] using a similar upper reference limit of 90 fl for men and 92 fl for women, reported an incidence of macrocytosis in 35% of subjects drinking more than 65 g alcohol per day against 6% in abstainers or infrequent alcohol users. Using the more realistic figure of 96 fl as the upper reference limit for MCV Bernadt *et al*[133] found no macrocytosis amongst 42 excessive drinkers (over 120 g alcohol per day) and only one case amongst 49 alcoholics attending a psychiatric clinic for the first time. Between these two extremes are the results reported by Chick *et al*[155] who, having set the upper reference limit for MCV at 98 fl, observed macrocytosis in 10 out of 47 manual workers (a sensitivity of 23%) and in 10 out of 30 company directors admitting to a daily alcohol intake of more than 65 g. Employing identical criteria, macrocytosis was observed by Stockdill and Allan[163] in 386 out of 9474 consecutive blood specimens (4·1%) submitted for analysis by General Practitioners in Edinburgh, of which 20% could be accounted for by vitamin B_{12} and/or folate deficiency. The authors warned against too ready acceptance of macrocytosis as evidence of alcohol abuse without further investigation.[163 164]

URIC ACID

Serum uric acid concentrations correlate positively with alcohol intake[133–135 165] even though the average value in heavy users is only 15% higher than in abstainers. It is not surprising, therefore, that serum urate is both non-specific[135] and insensitive as an indicator of alcoholism (a sensitivity of 20%) or excessive drinking (a sensitivity of 18%) in an unselected population[133] though higher percentage figures for sensitivity have been quoted,[165] especially in men. Nevertheless, serum urate may occasionally provide a clue to an unsuspected alcoholic aetiology of a patient's disease[165] or add weight to a presumptive diagnosis of alcoholism.

PLASMA LIPIDS

Triglycerides

Although plasma triglyceride concentrations[134 135] correlate positively with average daily alcohol intake in fasting subjects, unlike those of total plasma cholesterol[133] which show neither positive nor negative correlation, neither its sensitivity (20%) nor specificity (6%) makes it suitable as a diagnostic test of alcohol abuse. Nevertheless, because of its high prevalence, chronic alcohol abuse is one of the commonest causes of (fasting) hypertriglyceridaemia. It should, therefore, always be suspected as an aetiological factor in the pathogenesis of fasting, or indeed random, lipaemia since alcohol not only increases triglyceride synthesis in the liver, but also prolongs the hypertriglyceridaemia produced by ingestion of fatty meal. The mechanism of this hypertriglyceridaemia is incompletely understood but is probably due more to the delayed clearance of chylomicrons from the plasma than to accelerated absorption from the gut.

Cholesterol

Contrary to earlier suggestions[166 167] there is no correlation between average daily alcohol intake and plasma total cholesterol concentration[133] in the general population. It has, however, been established that in healthy volunteers addition of moderate amounts of alcohol to the diet produces a temporary rise in plasma α-lipoprotein cholesterol (HDL), which returns to baseline values when drinking ceases[168 169] and that actively drinking alcoholics (but not dried-out ones) have higher plasma HDL concentrations than abstainers and modest alcohol drinkers.[140] It has been suggested[170] that this could provide the basis of a test for chronic alcohol abuse,

but its low sensitivity, especially in patients with alcohol-liver disease, makes it more suitable as an adjunct to diagnosis—especially in hyperlipidaemic patients with raised plasma GT and urate concentrations[171] who deny excessive or indeed any alcohol consumption—than as a screening procedure.

It is still unsettled as to whether the changes in plasma HDL produced by alcohol contributes to the reduction in deaths from myocardial infarction observed in moderate social drinkers compared with abstainers, a reduction incidentally which does not carry over into immoderate drinking which is itself a risk factor for acute, fatal myocardial infarction.[172]

TRANSFERRIN

An unusual transferrin band can be found, by isoelectric focusing followed by immunofixation, in the serum of 80% of chronic alcoholics admitting to an average daily consumption of 60g alcohol during the week prior to testing, compared with only 8% of those who claim to have been abstinent.[173,174] The same anomalous transferrin can be found in the serum of only 1% of control subjects. The protein, therefore, appears to provide a specific and a moderately sensitive test for the detection of excessive alcohol use which is independent of hepatocellular disease since it is absent from the serum of patients with non-alcohol induced liver disease. Confirmatory reports of its value for diagnostic purposes are awaited with interest for although the methodology of its detection and measurement are at present too complicated for regular clinical use, they could undoubtedly be simplified if the need existed.

OTHER PLASMA CONSTITUENTS

Over the years many other constituents of the plasma have been reported to be qualitatively or quantitatively altered by chronic alcohol abuse; some, such as the ratio of α-amino-n-butyric acid to leucine, were thought originally to be more or less specific[175] but turned out not to be so,[176] whilst others were considered inconsequential because of their non-specificity from the very beginning. References to these substances can be found in the literature.[12]

Urine

Chronic alcohol abuse is accompanied in approximately 50% of cases by an increased excretion of glucaric acid.[152] Generally looked upon as a non-invasive marker of microsomal enzyme induction, glucaric acid excretion is increased by the long-term use of many drugs and is consequently not specific for alcohol. It can, however, provide valuable confirmatory evidence of heavy alcohol use in subjects who are not regularly taking known enzyme-inducing drugs. Lack of specificity reduces its clinical usefulness as a screening procedure. The same constraints probably also apply to urinary 6-β-hydroxycortisol measurements which have been used in other contexts as an indicator of enzyme induction.

Conclusions

Alcohol is an important cause of illness in man when consumed in excess and sometimes even in socially acceptable amounts over prolonged periods. The psychosocial features of chronic alcohol abuse are often inconspicuous and the alcoholic aetiology of a patient's illness may be unsuspected unless specifically sought since patients often underestimate their average daily alcohol intake. Laboratory tests—notably measurements of blood alcohol, plasma GT, aspartate transferase, alkaline phosphatase activities, urate and triglycerides, and the MCV—often provide the first clue to an alcoholic aetiology in a patient with symptoms, or point to the possibility of alcohol abuse in an otherwise seemingly fit person undergoing a "routine" medical check-up. Although none of the tests yet devised is as reliable, alone or in combination, as a well conducted interview, discriminant function analysis of only three of them—namely, GT, ALP and MCV—is said[177] to identify correctly 80% of subjects whose alcohol intake is "excessive".

There is little doubt that alcohol is no exception to the rule that pharmacodynamic and toxicological responses to drugs are highly individualist and often bear little or no relation to dose or duration of use, except in a statistical or epidemiological sense. My own practice is, therefore, to use laboratory abnormalities as an aid to convincing patients in whom they are demonstrably due to alcohol that, regardless of how little alcohol they are drinking, or admit to, it is clearly too much for them as an individual.

It must, however, be admitted here, though not necessarily in the clinic, that clear proof is still lacking that the presence of biochemical (and haematological) abnormalities demonstrable only in the laboratory portends the appearance of clinical disease at a later date. Likewise, it would be misguided to believe that a diagnosis of alcoholism made on psychosocial or clinical grounds is rendered untenable by failure to detect evidence of it in the laboratory, though prudent re-examination of the evidence upon which the diagnosis was originally made may be indicated.

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