innumerable questioners asked where that minister's parish was so that they might go and hear him again. They found it hard to believe that they had been listening to a man of 80 and that he had retired from his last post nine years previously. It was no exaggeration for one of his admirers to desribe him as "one of the greatest Scots of his time."

Mediator

One of the things that Archie Craig sought to do was to keep alive a real sense of what it meant to be part of a university. In Glasgow the faculties were becoming inclined to drift apart. So he formed in the 1950s a group which invited new professors to dine with them—handsomely—and then to spend an hour or more putting the case for their having a successor.

"You personally are welcome, most welcome," they said, "but, on academic grounds, can you justify the university's appointing a successor? In particular, are not the academic principles of your discipline adequately promoted by some other department?"

These were stimulating and enjoyable occasions, and a real challenge to the newcomer as well as a means of keeping interfaculty relationships alive. I recall the occasion when a new professor of divinity—"the queen of the sciences"—was challenged by the professor of moral philosophy.

"I do not see a need for your successor," said the challenger; "I am already dealing with the essentials of your subject."

The professor of divinity looked worried for a moment, but then triumphantly replied: "Not at all. *I* am fostering an uncommitted study of commitment; *you* are making a committed study of uncommitment."

"You're right," generously agreed the professor of moral philosophy; "I hadn't thought of it in that way."

"Revelatory," said Archie. It was one of his favourite words.

For Debate . . .

Role of macrophages in the pathogenesis of alcohol induced tissue damage

S N WICKRAMASINGHE

In some people the chronic consumption of excessive quantities of ethanol has harmful effects on one or more tissues. The affected organs and cell systems are the central and peripheral nervous systems, the liver, the pituitary and gonads, cardiac and skeletal muscle, the pancreas, the bone marrow, blood cells, and certain fetal tissues.[1-6] Alcoholism also impairs the body's defences against infections.[1,7] Some of the deleterious effects of alcoholism are a direct or indirect consequence of alcohol in the body and others are a consequence of impaired nutrition, which is often associated with alcoholism. Although much research has been carried out, it is not clear how alcohol causes tissue damage, particularly extrahepatic tissue damage. Recent evidence suggests that macrophages and related cells play an important part in the causation of ethanol induced extrahepatic tissue damage.

Acetaldehyde

Hypotheses of the pathogenesis of alcohol related liver disease are centred on the assumption that hepatocellular damage results from a consequence of the high rate of metabolism of ethanol by hepatocytes. Normally hepatocytes first convert ethanol to acetaldehyde, mainly through the action of the enzyme alcohol dehydrogenase and to a lesser extent through the cytochrome P450 dependent microsomal ethanol oxidising system[8] or by an oxygen radical dependent mechanism.[9] The acetaldehyde is then converted to acetate under the influence of the enzyme acetaldehyde dehydrogenase[8]; the acetate so generated is incorporated into acetyl coenzyme A and used in various biosynthetic and energy generating reactions. The metabolism of ethanol by hepatocytes causes an alteration in their redox state since the alcohol dehydrogenase dependent oxidation of ethanol is accompanied by the conversion of the coenzyme nicotinamide adenine dinucleotide to its reduced form (NADH). It has been proposed that hepatocellular damage may result from (*i*) a consequence of the alteration of the intracellular redox state,[10] (*ii*) toxic effects of acetaldehyde formed during the oxidation of ethanol,[11,12] or (*iii*) deleterious effects of oxygen derived free radicals such as the hydroxyl and superoxide radicals generated by a variety of oxyradical generating systems—for example, the coupled oxidation of hypoxanthine or xanthine through the enzyme xanthine oxidase—for the purpose of oxidising some of the ethanol.[9,13] Superoxide is known to damage cell membranes by peroxidation of lipids and has been implicated in the pathology of several diseases.[14,15] It is thought that the wide variation in the susceptibility of different people to alcohol induced damage may be partly based on genetic differences, but the nature of these differences has yet to be defined.

Acetaldehyde is highly reactive, and there is evidence that it may be the most important substance responsible for ethanol related tissue damage. Thus in vitro studies have shown that acetaldehyde binds covalently to bovine serum albumin,[16] haemoglobin,[17] and erythrocyte membrane proteins.[18] The formation of acetaldehyde-protein complexes seems to occur in two stages[17,19]: (*i*) an initial easily reversible reaction between the carbonyl group of acetaldehyde and free amino groups of the protein (particularly the amino groups of valine, lysine, and tyrosine) to form a Schiff's base and (*ii*) a subsequent reduction of the Schiff's base to form an irreversible acetaldehyde-protein complex. The formation of stable complexes between acetaldehyde and certain cellular enzymes may impair enzyme activity and hence cell function. Thus it is of interest that acetaldehyde impairs mitochondrial function,[2,20,21] inhibits cardiac microsomal protein synthesis,[22] inhibits protein synthesis and glycoprotein secretion by the liver,[23,24] and at a concentration of 45-360 μmol/l prolongs the doubling time and increases the modal volume of human cell lines.[25] The results of recent studies have shown that some of the ^{14}C acetaldehyde derived from the oxidation of ^{14}C ethanol by rat liver slices binds to preformed hepatocyte proteins[19]; thus functional disturbances of the type mentioned above may be caused by stable

St Mary's Hospital Medical School, London W2 1PG
S N WICKRAMASINGHE, SCD, FRCPATH, professor of haematology

complexes being formed between acetaldehyde and cellular proteins. The combination of acetaldehyde with cell surface proteins may perhaps also result in the formation of neoantigens and the consequent generation of immune responses that damage the altered cells.[2] Since aldehydes are known to bind to DNA as well as to protein the little discussed possibility that chronic alcoholism may be implicated in the pathogenesis of myelodysplastic syndromes or certain forms of malignant disease now merits some consideration.

Macrophages

When compared with hepatocytes cells from human and rat bone marrow and from mouse bone marrow, spleen, and testis show low rates of ethanol metabolism in vitro.[26-29] After the removal of the adherent cells from such cell suspensions the rates of ethanol metabolism by the residual non-adherent cells are considerably reduced,[27 29] indicating that much of the ethanol metabolism by the whole cell suspensions was probably dependent on the activity of macrophages. This is confirmed by the demonstration that macrophages that are derived from human blood monocytes, bone marrow, and spleen (unpublished data) and from mouse bone marrow, thymus, and spleen have a considerable capacity to metabolise ethanol to acetate in vitro.[27-29] The rate of ethanol metabolism by these cells, when expressed in nmol/10^7 cells/hour, is about five to 12 times lower than that by isolated human (unpublished data), rat, and mouse hepatocytes.[26 29] Since hepatocytes are considerably larger than macrophages, however, these two cells probably metabolise ethanol at more comparable rates if metabolic activity is expressed per gram wet weight per hour. Indeed, when the data are expressed in this way mouse macrophages are found to metabolise ethanol at about twice the rate shown by mouse hepatocytes.[29] Interestingly, although ethanol metabolism by hepatocytes is mainly mediated by alcohol dehydrogenase, ethanol metabolism by macrophages derived from blood monocytes and other tissues is largely independent of alcohol dehydrogenase and probably mediated by the cytochrome P450 dependent microsomal ethanol oxidising system.[28 29] These findings suggest that ethanol induced damage to extrahepatic tissues may result in part from deleterious effects of the metabolism of ethanol by tissue macrophages on surrounding parenchymal cells rather than from the effects of ethanol on the parenchymal cells themselves. This seems likely in tissues that contain large numbers of macrophages, such as bone marrow, lymphoid tissue, and the gut. Furthermore, since ultrastructural studies have shown that several thin cytoplasmic processes extend outwards from the periphery of each macrophage and that these processes are in intimate contact with many surrounding parenchymal cells a single ethanol metabolising macrophage may adversely affect a large number of parenchymal cells.

The metabolism of ethanol by tissue macrophages appears to be associated with the release of acetaldehyde from such cells and would therefore be expected to result in much higher concentrations of acetaldehyde immediately adjacent to macrophages than in circulating blood. Thus supernatants from ethanol-containing cultures of macrophages derived from human blood monocytes[30 31] and of murine macrophages derived from the liver, bone marrow, spleen, and thymus[29] show a non-dialysable cytotoxic activity. In human cultures there is strong circumstantial evidence that the cytotoxic activity is in albumin molecules (from the culture medium) that have complexed with acetaldehyde.[31] The use of improved methods for measuring blood acetaldehyde has shown that acetaldehyde is usually undetectable or barely detectable in the blood of healthy volunteers who are given ethanol[32]; therefore the production of acetaldehyde by tissue macrophages may be the most important mechanism by which cytotoxic concentrations of this aldehyde are achieved in tissues.

Macrophages and other cells of the mononuclear phagocyte system are distributed throughout most, if not all, tissues of the body, and it appears from studies in mice that over 80% of the macrophages in the body are in tissues other than the liver.[33] If extrahepatic tissue damage results from the release of acetaldehyde, and possibly other cytotoxic factors, from macrophages as a consequence of ethanol metabolism by these cells this may account for the variety of tissues that may be damaged by chronic alcoholism. The substantial capacity of macrophages to metabolise ethanol may also explain the pain that is sometimes felt in patients with some tumours, such as Hodgkin's disease and carcinoma of the cervix, after consuming ethanol.[34] Such alcohol intolerance may result from the cytotoxic effects of acetaldehyde generated by macrophages in the tumours.

The ratio of the number of hepatocytes to the number of macrophages (Kupffer's cells) in the adult rat liver can be calculated from published data as roughly 6·5[35 36] and the ratio of the number of hepatocytes to the number of littoral cells (Kupffer's cells plus sinusoidal lining cells) in the human liver is reported to be 1:5·5.[37] As macrophages are roughly one order of magnitude less active than hepatocytes in metabolising ethanol per cell, these ratios show that the hepatic macrophages may be responsible for a small percentage only of ethanol metabolism and acetaldehyde production by the liver. Thus in the liver, unlike other organs, resident macrophages may play only a minor part in the initial events leading to alcohol induced tissue damage.

Neuroglial cells, like macrophages, belong to the mononuclear phagocyte system. It has recently been reported that a human neuroglial cell line, U-251 MG, metabolises ethanol at a substantial rate, largely by a cytochrome P-450 dependent pathway, and thus closely resembles tissue macrophages.[38] Neuroglial cells may therefore have a similar role to other tissue macrophages in the pathogenesis of ethanol induced damage by generating acetaldehyde locally within neural tissues. Neuronal cells can also metabolise ethanol, but their capacity for oxidising ethanol may be considerably less than that of neuroglial cells.[38]

A pattern of malformation has been recognised in the offspring of mothers who are chronic alcoholics,[6] described as the fetal alcohol syndrome. The results of studies in rats have shown that chronic intake of ethanol before and during gestation decreases fetal viability and diminishes the weights of the fetal liver and brain, probably with a decrease in the total cellularity of the brain.[39] Cells that can form discrete colonies of granulocytes and macrophages (CFU-GM) are found in human fetal blood during the twelfth week of gestation,[40] and macrophages are found in the mesodermal layer of the human yolk sac as early as the fourth week of gestation.[41] Since acetaldehyde has been shown to impair cell proliferation in vitro[25] the fetal alcohol syndrome may result in part from impaired cell proliferation during embryogenesis and fetal development as a consequence of the effects of acetaldehyde generated during ethanol oxidation by fetal macrophages.

Macrophages (including Kupffer's cells) may be damaged by the acetaldehyde they produce, and such damage might account for some of the disturbances in macrophage function (reduced adherence, mobility, and phagocytic and bactericidal activity) that have been reported in alcohol treated animals.[7 42 43] The evidence suggests that macrophage dysfunction may be one mechanism underlying the increased prevalence of tuberculosis and other infections in the alcoholic. In addition, it has been proposed that bacterial endotoxins derived from the gut may contribute to hepatocellular damage in alcoholics because of a failure of the Kupffer's cells to detoxify endotoxins at a normal rate.[44]

Circulating cytotoxic protein

Some of the acetaldehyde formed from the oxidation of ethanol in vivo by hepatocytes, macrophages, and other cells seems to bind to plasma albumin and circulate as a cytotoxic acetaldehyde-albumin complex. After three volunteers drank 500-700 ml of wine over 20 to 35 minutes the cytotoxic activity in plasma was greatest six to 10 hours after the consumption of ethanol started (when blood alcohol concentrations were back to normal or near normal) and persisted for at least 24 hours.[31] The generation of a circulating cytotoxic protein molecule provides a mechanism by which tissues that do not metabolise ethanol at a great rate may be damaged. It also extends the period of potential cytotoxicity towards all types of tissue (whether they metabolise ethanol actively or not) beyond that during which blood ethanol concentrations are high. Thus in any tissue parenchymal cells may be damaged both by acetaldehyde molecules (and possibly other cytotoxic substances) that are generated and released by the macrophages and any ethanol metabolising parenchymal cells present in that tissue and by the action of a long acting circulating cytotoxic albumin-acetaldehyde complex which is formed from some of the acetaldehyde generated by all ethanol metabolising cells in the body.

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Letter from Amsterdam

Inner city care

ROBIN HULL

In a recent Independent Television documentary on the acquired immune deficiency syndrome (AIDS) two Edinburgh prostitutes were interviewed. Both knew that they were seropositive to the human immune virus (HIV) but made it clear that for them "it was business as usual." The Roman phrase caveat emptor might, had their classical education been better, have tripped from their lips. But how many buyers are wary, particularly when spending in the brothel?

On another occasion boys infected with the virus acquired from homosexual prostitution since childhood went further. They were so embittered by having caught the disease that they were determined to give it to as many people as possible before they died from it. This was their revenge against a society that had hardly treated them well.

No one can condone such attitudes but they are as understandable and pathetically futile as Jewish gestures of defiance at Auschwitz or Babi Yar. Rather than the pseudoreligious denunciation of human beings whose behaviour patterns are abhorrent to us that we hear from some quarters, we should try to understand and to help. We can do little about this new disease, which, like syphilis, plague, cholera, and typhus, may have as profound an effect on world history as the discovery of nuclear fission, but we may be able to control its spread. The most important vector is promiscuous sexual behaviour. The British government has invested enormous sums of money into education of consumers of commercial sex and is to be commended on its teaching campaign, since evidence from America suggests that alteration of sexual practice has coincided with a slight reduction in the rate of increase of the AIDS pandemic. But the consumer of commercial sex is only one of the pair; what about the provider—the male or female prostitute, whose business is promiscuity. If these providers take the attitude of the Edinburgh prostitutes of the television interview then the infection rate will increase. We need, therefore, not just to educate the occasional consumer but the habitual provider. That is not an easy task but at least one attempt is being made in the red light district of Amsterdam.

Institute of General Practice, Free University, 1007 MC Amsterdam
ROBIN HULL, MB, FRCGP, professor of general practice

Oldest profession in the oldest street

Some 20 years ago a mission was established in the Ouderzijds Achterburgwal—one of the oldest streets in Amsterdam. With its long history as a major port Amsterdam has always offered