of oxygen consumption in the presence of a NADPH regenerating system. Intraperitoneal injection of 3-amino-1,2,4-triazole which decreases the catalase content in the liver (Heim, Appleman & Pyfrom, 1956) as well as the content of cytochrome P450 (Baron & Tephly, 1969) increased the rate of oxygen consumption as did the addition of azide *in vitro*. Therefore, H_2O_2 seems to be the direct reduction product of oxygen. This is in accordance with the increased oxidation of methanol to formaldehyde in the microsomal system in the presence of PQ which also has been observed by others (Ilett *et al.*, 1974). This agrees with the observed NADPH/O_2 ratios.

The effect of PQ on microsomal electron transport is directly comparable to that of menadione which increases NADPH oxidation (Gillette, Brodie & La Du, 1957), O_2 uptake (Sato, Nishibayashi & Omura, 1962) and methanol oxidation with the same NADPH/O_2 ratio as PQ does. Menadione, however, is not NADPH-specific. Both substances divert the electrons from the flavoproteins to oxygen, keeping the flavoproteins in the oxidized state. Thereby they inhibit the mixed function oxidations. The inhibition of MDA formation by PQ in this system with a high rate of oxygen reduction does not support the intermediate formation of superoxide anions.

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The production of periportal necrosis by allyl alcohol in the rat

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Daily dosing of rats with allyl alcohol or its esters produces a characteristic liver lesion, periportal necrosis, which has been found to regress by d.28 in spite of continued administration. Butterworth, Carpanini, Gaunt, Grasso & Lloyd (1975) have found a correlation between the hepatotoxicity of such esters and the rate of their hydrolysis *in vitro* to allyl alcohol. The periportal necrosis produced is believed to depend on the metabolism of the alcohol to acrolein (Reid, 1972; Serafini-Cessi, 1972). The abilities of allyl alcohol and acrolein to induce hepatic lesions have been compared when given by intraportal infusion to minimize the effects of differences in the absorption of allyl alcohol and acrolein. Preliminary experiments to investigate the development of tolerance to the administration of allyl alcohol have also been performed.

Groups of 3 male Wistar-derived weanling rats were anaesthetized with pentobarbitone sodium (120 mg/kg i.p.). Either allyl alcohol or acrolein was injected as a solution in saline (0.9% w/v NaCl soln.) through heparin-primed polyethylene tubing tied into a mesenteric vein. An infusion of 0.1 ml was made over a 10 s period, the vein ligated and the animal allowed to recover. After 24 h the rats were killed by cervical dislocation, the incidence of macroscopic liver lesions determined and the tissues examined histologically.

Allyl alcohol (8.5, 17.0 or 25.5 mg/kg) produced no liver lesions, but acrolein (0.425, 0.85 or 1.70 mg/kg) produced periportal necrosis in 0, 2 and 3 rats respectively. No hepatotoxicity was produced in the control rats given saline intraportally. These results show that acrolein is effective in producing liver lesions when administered by intraportal infusion, in contrast to the allyl alcohol. These lesions were histopathologically similar to those observed after repeated oral administration of allyl alcohol or its esters.

In a second series of experiments, groups of 10 rats were given corn oil (5 ml/kg) with or without allyl alcohol (25 mg/kg), daily by intubation for 28 days. The absence of macroscopic liver lesions in any of the alcohol-treated animals at d.28 was taken as evidence that tolerance to the alcohol had developed.

Then acrolein (1.7 mg/kg) was infused as previously into all these rats and the livers examined 24 h later. Pretreatment with allyl alcohol made no difference to the severity or incidence of macroscopic liver lesions after intraportal acrolein infusion. A repeat experiment gave the same result.

The experiments were unable to confirm that the acquired tolerance to allyl alcohol was mediated by increased detoxification of acrolein, but do not preclude this possibility since the affects of acute intraportal infusion may have overridden any mildly induced mechanism for acrolein disposal. Alternatively, the increased tolerance may be due to a decreased production of acrolein from allyl alcohol, possibly due to a reduction in the activity of alcohol dehydrogenase (Serafini-Cessi, 1972).

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Ototoxic effects of gentamicin and kanamycin in the guinea-pig

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Histological methods have probably contributed more than other techniques to our knowledge of the ototoxic effect of some drugs, notably the aminoglycoside antibiotics. In a series of studies, light microscopy, scanning electronmicroscopy (SEM) and transmission electronmicroscopy (TEM) have been used to examine the normal and drug-damaged guinea-pig cochlea. It has been reported previously (Bridges & Harpur, 1976) that light microscopy provides inadequate detail for evaluation of minor changes in the neuro-epithelium of the organ of Corti. This information is best obtained by a combination of SEM and TEM.

Healthy guinea-pigs were injected either intramuscularly or subcutaneously, daily for 14 days, with gentamicin (50, 100 and 140 mg/kg) or subcutaneously, daily for 10 days, with kanamycin (500 mg/kg). The gentamicin-injected guinea-pigs were killed 1, 7 or 35 days following the last injection whereas the kanamycin-injected guinea-pigs were killed 1, 10, 17 or 30 days after the last injection.

The cochleas were removed immediately after death and fixed through openings in the round window and the apex. The fixatives used and further preparation of the specimens varied depending on the intended method of histological examination.

The information gained from light microscopic studies is limited to gross structural alteration, such as loss of sensory (hair) cells and supporting cells. This type of damage was seen in the organ of Corti of guinea-pigs after administration of gentamicin (140 mg/kg) and kanamycin (500 mg/kg).

Using SEM the most marked changes after both kanamycin and gentamicin were seen in the basal turn of the cochlea. In kanamycin-injected animals, killed after 30 days, there was complete loss of sensory and supporting cells in part of this region. With both drugs, isolated cell loss, hair fusion and cuticular plate degeneration were observed throughout the organ of Corti. The distribution and frequency of these changes depended both on the dose administered and the time before death. At the lower dose levels of gentamicin there was no evidence with SEM of cochlear hair cell degeneration and the observed minor surface changes could not be attributed unequivocably to the effect of drug administration or to tissue preparation.

TEM was used to further elucidate the findings of SEM and light microscopy, but was confined to the gentamicin-injected animals. TEM revealed that even after gentamicin (140 mg/kg) the surface morphology could be essentially normal, while the underlying cells showed signs of extensive damage. These included changes in, or loss of, mitochondria, cytoplasmic vacuolation with shrinkage and nuclear swelling.

After gentamicin (100 mg/kg), TEM showed extensive damage to the mitochondria of the hair cells and this was only occasionally accompanied by cuticular plate abnormalities. These included vacuolation of, and protrusions of the cuticular plate into the cochlear duct. With SEM these had been observed as spherical elevations of the cell surface. These irregularities of the cuticular plate were still occasionally seen with TEM after the lowest dose of gentamicin, although mitochondrial disruption was rare.

It is apparent from these findings that both TEM and SEM can make essential contributions to the histopathological studies of ototoxic damage.