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.

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Effects of cigarette smoke on metabolism of vasoactive hormones in rat isolated lungs

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Exposure of rats to an atmosphere containing tobacco smoke alters the activity of enzymes metabolizing polycyclic hydrocarbons like benzo[a]pyrene (Welch, Loh & Conney, 1971; Uotila, Pelkonen & Cohen, 1977). We have recently studied the effects of smoke exposure on pulmonary enzymes metabolizing the endogenous substrates, 5-hydroxytryptamine (5-HT), angiotensin I, bradykinin and prostaglandin E_2.

Male rats were exposed to cigarette smoke for 1 h per day for 1 day or for 10 consecutive days. 'Sham exposed' animals were treated identically except that no smoke was added to their environment (Uotilla & Marniemi, 1976). The day after the last exposure, the lungs were removed and perfused through the pulmonary circulation with oxygenated, warmed Krebs solution (Alabaster & Bakhle, 1970). The activation of angiotensin I (by hydrolysis to angiotensin II) and inactivation of bradykinin and prostaglandin E_2 were measured by bioassay on the rat colon, guinea-pig ileum and hamster stomach strip respectively, superfused with the lung effluent. Metabolism of 5-HT was measured by a radiochemical method using [^{14}C]-5-HT (Southgate & Collins, 1969).

The results summarized in the table show a significant increase in angiotensin I conversion and decrease in prostaglandin E_2 inactivation after 1 day's exposure when compared with control, i.e. untreated animals, and with 'sham exposed' animals. After 10 days' exposure, angiotensin I conversion returned to control levels whereas prostaglandin inactivation was still considerably less than normal. However, in the latter case the 'sham exposed' animals also showed decreased inactivation and the change cannot be reliably attributed to the smoke exposure. Bradykinin and 5-HT metabolism were unchanged throughout the experiment.

Our results show that it is possible to alter the metabolism of some endogenous vasoactive substances by exposure of animals to cigarette smoke. Such changes may be relevant to the cardiovascular changes shown by habitual smokers (U.S. Department of Health, Education and Welfare, 1975).

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Table 1 Metabolism of endogenous substrates on passage through the pulmonary circulation of isolated rat lung

Treatment	*Angiotensin I (100–200 ng)†* *(% conversion)*		*Bradykinin (1000–2000 ng)* *(% survival)*		*Prostaglandin E_2 (500–1500 ng)* *(% survival)*		*5-Hydroxytryptamine (3.75 μM)* *(% metabolite)*	
	1 day	10 day	1 day	10 day	1 day	10 day	1 day	10 day
Control	20 ± 4		1.6 ± 0.3		4.4 ± 0.6		79 ± 1	
Sham exposed	33 ± 6	26 ± 3	2.2 ± 0.1	0.9 ± 0.1	4.3 ± 0.7	12.3 ± 3.5	74 ± 6	74 ± 2
Smoke exposed	51 ± 4*	33 ± 4	1.6 ± 0.3	1.0 ± 0.2	8.8 ± 1.4*	17.9 ± 4.0	76 ± 6	77 ± 3

Values shown are the means (±s.e. mean) of 4–17 animals (usually 6).
* Significantly different from sham exposed rats; $P < 0.05$, t-test.
† Level of substrate used.