ipsilateral rotation; baclofen induced a significantly more intense ipsilateral circling response ($p < 0.05$) (figure 2). Histological examination revealed that injection sites were within SNR.

Discussion. In untreated and amphetamine-pretreated rats unilateral injections of baclofen into SNR produce contralateral and ipsilateral rotation respectively. These rotational responses are very similar to those seen after unilateral elevation of nigral GABA levels in both untreated[10] and amphetamine-pretreated[9] animals. While the nature of the interaction between striatonigral GABA neurones and nigrostriatal dopamine neurones within the substantia nigra is contentious[11], these effects following injections into SNR suggest that baclofen may have some GABA agonist activity following direct intracerebral injection. Though original reports that baclofen may be an antagonist of substance P[13] have failed to be confirmed subsequently[14,15], the recent demonstration of striatonigral pathways to SNR containing substance P[16] as well as GABA suggests that mechanisms for these present baclofen effects in terms of interactions with neurotransmitter systems other than those involving GABA cannot, however, be excluded.

Baclofen has been widely used as a putative GABA-mimetic substance both in animal studies[17] and in the clinic[18], without convincing evidence for GABA agonist activity. Its use in such experiments has, however, provided circumstantial evidence for GABA-ergic properties in that baclofen has been shown to mimic the effects of elevation of brain GABA levels on both animal[19] and clinical[20] models of nigrostriatonigral mechanisms. The wide range of pharmacological properties of baclofen[21,22] necessitates further study aimed at clarifying its status as a hypothetical GABA-mimetic agent.

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The relative sensitivity of pulmonary parenchymal cells to ^{239}plutonium dioxide[1]

A. G. Heppleston and A. E. Young

University Department of Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP (England),
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Summary. Alpha particles inhaled by mice affect primarily type II epithelial cells, whereas interstitial mononuclears, alveolar macrophages and type I epithelium are much more resistant and apparently react secondarily. The cellular responses, qualitative and quantitative, exhibit a time-dose relationship.

Materials and methods. A2G mice were exposed for 10 min to inhalation of a $^{239}PuO_2$ aerosol generated by an exploding wire technique in a specially constructed chamber[2]. In separate experiments the animals, in groups of 12, received estimated lung doses of approximately 22 nCi or 150 nCi, respectively referred to as the low and high dose series. Control mice were given a mock exposure in the same apparatus. Animals survived for 3–26 weeks after inhalation. Mice from control and both test groups were killed in pairs by i.p. pentobarbital and lung tissue embedded in araldite for electron microscopy. In addition to analyzing qualitative changes, differential counts of alveolar wall cells were made from electron micrographs, whose number and range of magnification were standardized for all groups. Throughout the period of observation radioactivity, as detected by X-ray measurements and autoradiographs of 1 μm sections, persisted in the lungs.

Results. The type II alveolar epithelial cell is essentially secretory in function[3], a main product being surfactant, which is associated with the osmiophilic lamellar bodies[4]. In normal mice these bodies were commonly vacuolated but their rounded outlines betrayed the former content of secretory material (figure 1,a). The number of type II cells in both test groups rose by 50% and vacuolated bodies became fewer though larger. In high-dose animals the subcellular changes were more severe and from 15 weeks pronounced alterations affected about half the population. The cytoplasm was then distended by large smooth spaces containing a little lamellar material and deforming the nuclei. Over some vacuoles the remaining cytoplasm was extremely thin (figure 1,b) and had ruptured onto the alveolar surface. As a late feature of high-dose mice, some cells developed changes suggesting regeneration, as evidenced by flattening, small and scanty but denser lamellar bodies and by intact mitochondria and endoplasmic reticulum.

Alveolar macrophages normally possess phagosomes (figure 2,a). Low-dose mice showed no quantitative change but the phagosomes tended to be larger. In high-dose mice, especially from the 10-week-interval, the number of macrophages rose and their cytoplasm was crowded with phagosomes or inclusions (figure 2,b), some of which strongly suggested lamellar bodies discharged by type II cells. Degenerative changes were not apparent. Interstitial cells (figure 1,a), distinct from fibroblasts, may be regarded as emigrated monocytes residing temporarily in the pulmonary interstitium before emerging onto the alveolar surface as mature macrophages. No qualitative changes were detected but,

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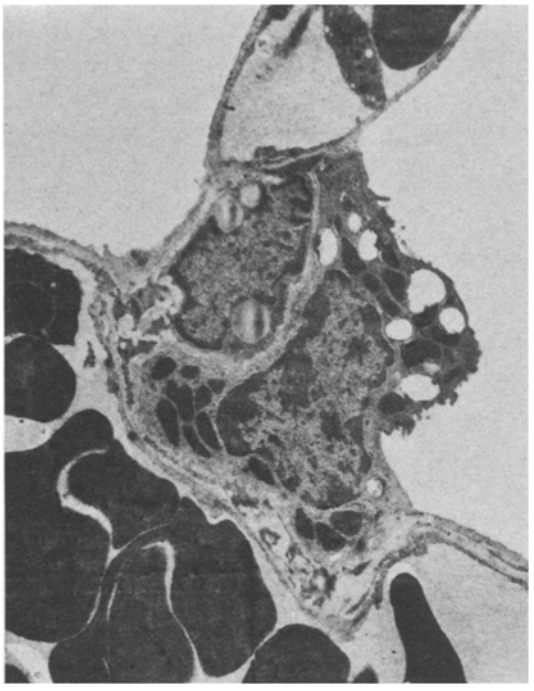

Fig. 1, a. Type II epithelial cell (below), showing prominent mitochondria but relatively few small vacuoles containing a little lamellar material. An interstitial cell, probably monocytic, lies above. Control mouse. EMG, ×5000.

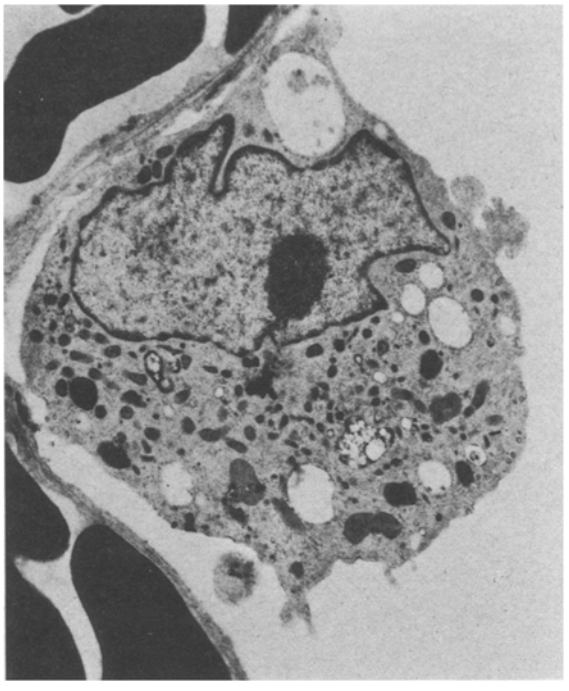

Fig. 2, a. Alveolar macrophage from an unexposed mouse. Mitochondria are numerous though small and there is a modest number of phagosomes that vary in morphology. EMG, ×5000.

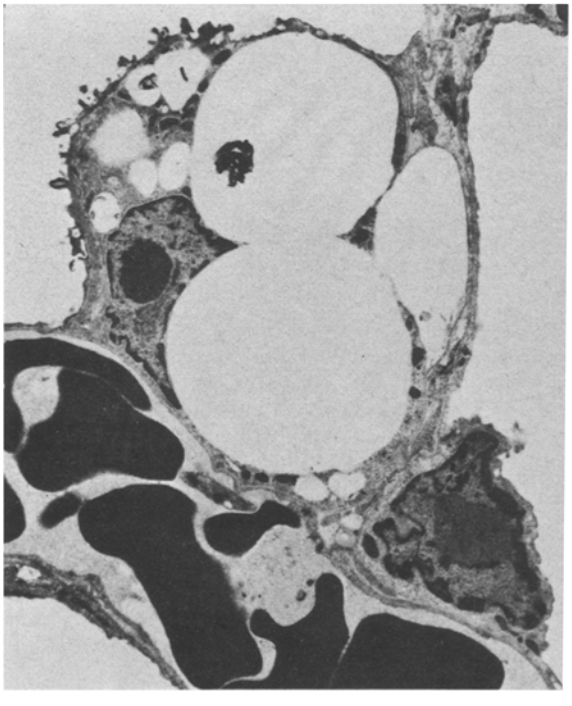

Fig. 1, b. Type II epithelial cell 26 weeks after the high dose. Huge vacuoles have coalesced and almost breached the alveolar surface; remnants of lamellar bodies remain whilst the nucleus is displaced and distorted by the vacuoles; mitochondria are inconspicuous. The type I epithelial cell (below right) appears normal, as does the capillary endothelium, despite the proximity of a severely affected type II cell. EMG, ×5000.

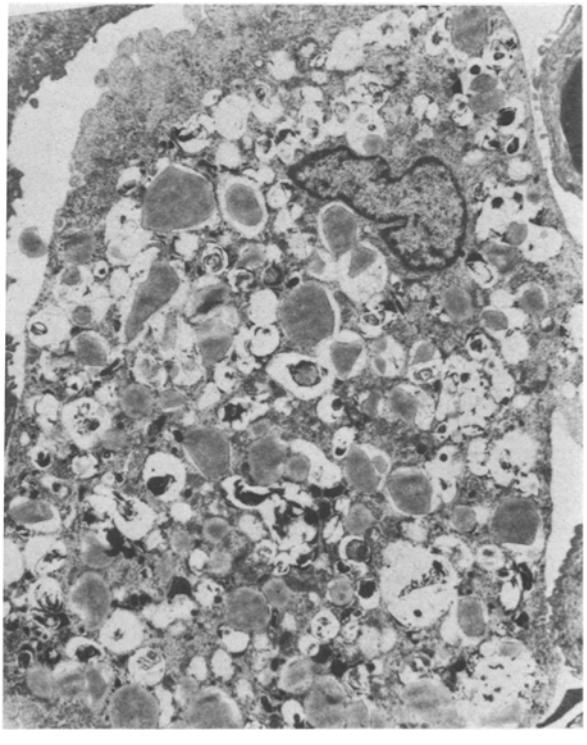

Fig. 2, b. A much enlarged alveolar macrophage whose cytoplasm is crowded with a variety of inclusions, including lamellar forms indicating an origin from type II cells. The cytoplasmic processes are stunted and club-shaped. Mouse survived the high dose for 10 weeks. EMG, ×4000.

whilst the low dose had no numerical effect, these cells were almost doubled by the high dose especially from 15 weeks.

Type I epithelium (figure 1, b) underwent no qualitative changes but cells became more numerous in longer-surviving, high-dose mice. If type I cells are derived from type II[5], augmentation of the former may merely reflect the situation with respect to the latter. Endothelial cells of irradiated mice in either group showed no quantitative or apparent qualitative abnormality.

Discussion. The observations point to type II epithelium as the prime sufferer from prolonged contact with plutonium emissions. Vacuolation of osmiophilic lamellar bodies has been noted after external application of X-rays[6] or ^{60}Co irradiation[7], but not to the same degree as in the present plutonium study. Such changes were not recorded in a study of the effects of $^{239}PuO_2$ inhalation[8]. Our ultrastructural evidence suggests a sequence of events, type II cells reacting by proliferation and probably by augmented secretory activity. Whether the surface properties of these lungs and their capacity for particle elimination are affected and whether the late phase of type II regeneration may progress to neoplasia remain to be determined.

The number and contents of alveolar macrophages rose notably in mice surviving the high-dose for longer periods, as did the population of interstitial cells, whose migration evidently serves to replace alveolar macrophages that disintegrate under their load or are carried proximally by ciliary activity. Despite the ingestion of or proximity to plutonium particles, macrophages retain their phagocytic capacity and are much less susceptible to the effects of irradiation than type II cells. Fibrosis was not a feature.

The time-dose relationship of the cellular events is epitomized in the table. Type II cells react to a wide variety of irritants and, although not necessarily specific, the features now described appear to be a particular consequence of irradiation especially by plutonium.

Plutonium induced changes in alveolar cells

	Quantitative		Qualitative	
	Low dose	High dose	Low dose	High dose
Type II epithelium	++	++	+→++	++→++++
Type I epithelium	nil	++	nil	nil
Alveolar macrophages	nil	++++	++	++→++++
Interstitial cells	nil	++++	nil	nil

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Effects of some oligopeptides, consisting of aromatic amino acids, on the excitability of an identifiable giant neurone of an African giant snail (*Achatina fulica* Férussac)

H. Takeuchi and A. Sakai[1]

Department of Neurochemistry, Institute for Neurobiology, Okayama University Medical School, Okayama (Japan), 17 March 1977

Summary. L-Phe-L-Tyr and L-Lys-L-Phe-L-Tyr showed a marked inhibitory effect (not chloride-dependent) on the excitability of an identifiable giant neurone (the TAN) of Achatina fulica Férussac, while L-Tyr-L-phe, L-Tyr-L-Tyr, L-Phe-L-Phe, L-Lys-L-Phe and Z-L-Phe-L-Tyr (Z-: carbobenzoxy) had no effect.

In a previous paper[2], a marked inhibitory effect of a tripeptide (L-Lys-L-Phe-L-Tyr), produced as a fragment of physalaemin (a hypotensive endecapeptide from an Amphibian skin[3,4]), on the excitability of a giant neurone (the TAN, tonically autoactive neurone), identified in the suboesophageal ganglia of Achatina fulica Férussac, was reported. In the present study, the effect of dipeptides and tripeptides, structurally related to L-Lys-L-Phe-L-Tyr, was examined on the same neurone, to determine the essential structure of these substances to produce the inhibitory effect.

Material and methods. The experimental material used and the electrophysiological methods employed have been precisely described in previous papers[5–7]. The TAN (tonically autoactive neurone) of Achatina fulica is excited by 5-hydroxytryptamine and physalaemin and inhibited by dopamine, GABA and acetylcholine. Most dipeptides and tripeptides examined in the present study (table) were obtained commercially. In order to determine whether the inhibition caused by some peptide is dependent on chloride ions, the inhibitory peptide was tested in the chloride free condition. To remove the chloride ions from the extracellular fluid of the dissected ganglia, the isotonic acetate (chloride free) solution was continuously perfused around the ganglia for at least 15 min.

Results and discussion. Experimental results obtained are summarized in the table. L-Lys-L-Phe-L-Tyr and

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