oxygen vacancies. In the latter case, the actual carriers are lattice ions, which are much heavier than electrons. The scaling characteristics of these metal–oxide–metal devices are not discussed by the HP team, but they should, in principle, be quite good because the oxygen vacancies will probably have to drift only a few angstroms under the applied electric field.

The suggestion that heavier particles might be preferred for nanoscale devices may seem counterintuitive because lighter particles can be moved about much faster than heavier particles. However, it is difficult to confine electrons in a very small space because they can tunnel out quite easily. Moreover, response times for atoms can be rapid if they only have to move a short distance. 'Nanoionic' devices have already attracted the attention of several research groups[3–5]. In the 'atomic relay', for instance, a nanoscale gap is opened and closed by the movement of a small number of silver atoms, and the switching time in such devices is expected to be about 1 ns (ref. 4).

A number of memory concepts based on ion-migration effects in solids are currently being explored and they show potential to overcome the scaling limits associated with traditional electron-based memories[5]. A common characteristic of all devices whose operation relies on the movement of both ions and electrons is that they require materials that are not typically used in semiconductor devices. This suggests that innovation in nanoelectronic devices is strongly dependent on materials research.

As a final note, although one may argue in favour of two-terminal devices such as those developed by the HP team[6], the electronic circuit community might be interested in extending this device concept to three-terminal devices with gate electrodes (Fig. 1a). In principle, one could devise a three-terminal device in which the barrier height was regulated by charge, as in conventional devices, but in which information was carried by different and heavier charged particles. Such an approach could limit the 'OFF' state currents that arise in devices with feature sizes of ~1 nm because the heavier particle would be much less prone to tunnelling and over-the-barrier transitions than electrons.

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NANOTOXICOLOGY

The asbestos analogy revisited

Direct injection of long multiwalled carbon nanotubes into the abdominal cavity of mice produces asbestos-like pathogenic behaviour. What does this finding mean for nanotube safety?

Agnes B. Kane and Robert H. Hurt

are at Brown University, Providence, Rhode Island 02912, USA.

e-mail: Agnes_Kane@brown.edu; Robert_Hurt@brown.edu

The possibility that carbon nanotubes would show asbestos-like behaviour in the human body was raised ten years ago with a call for appropriate research[1]. Exposure to asbestos is known to cause mesothelioma — cancer of the lining of the lungs (pleura) and abdominal cavity (peritoneum). The nanotube and asbestos analogy relies on several points of material similarity: small fibre diameter, long length and chemical stability in physiological environments (biopersistence). There are also differences between these two fibrous materials, such as their chemical composition and surface properties, so the validity and usefulness of the nanotube and asbestos analogy have been unclear. Two recent studies provide important new insight into the possibility that carbon nanotubes may indeed induce mesothelioma — a disease that is rare in unexposed populations and is thus a sensitive marker for asbestos exposure.

On page 423 of this issue[2], Ken Donaldson of the MRC/University of Edinburgh and co-workers in the UK and US report that long multiwalled carbon nanotubes (MWNTs) injected directly into the abdominal cavity of mice induce inflammation, formation of nodular lesions called granulomas and early fibrosis or scarring in the mesothelial lining. Shorter nanotubes had much less of an effect, as did carbon black nanoparticles used as a non-fibrous reference material. A seven-day exposure did not induce mesothelioma, but the distribution and severity of these early inflammatory and granulomatous lesions are similar to those induced by long fibres of brown asbestos (amosite), which is known to induce significant toxicity and carcinogenicity in longer-term animal studies.

Another recent study[3] by Jun Kanno of the National Institute of Health Sciences in Japan and colleagues from the Tokyo Metropolitan Institute of Public Health shows that MWNTs, also injected into the abdominal cavity of mice, induce malignant mesotheliomas in p53+/– heterozygous mice — a common genetically engineered mouse model. These mice are a useful laboratory model because they are sensitive to asbestos and can rapidly develop malignant mesothelioma following repeated exposure to asbestos fibres.

Using commercial MWNTs from the same suppliers as Donaldson and co-workers, the Japanese team observed granulomas and fibrosis in the mesothelial lining as well as tumours in 88% of the MWNT-treated mice after 25 weeks, in comparison with 79% in mice injected with crocidolite, a particularly potent form of asbestos. Minimal mesothelial reactions and no mesotheliomas were produced by the same mass dose of (non-fibrous) C_{60} fullerene. The authors conclude that asbestos fibres and MWNTs may have similar carcinogenic potential on the basis of their fibrous geometry, biopersistence and ability to generate tissue-damaging free radicals.

Both of these reports identify key physical properties of carbon nanotubes that may be relevant for potential toxicity

and carcinogenicity: fibre length and biopersistence. Fibrous materials longer than 10–20 μm cannot be completely engulfed by macrophages, which are 'housekeeping' cells that take up and clear fine particles inhaled into the lungs or in the pleural or abdominal cavities. Incomplete uptake or 'frustrated phagocytosis' of long asbestos fibres (Fig. 1a) or MWNT bundles/ropes impairs macrophage-mediated clearance and stimulates release of free radicals, inflammatory mediators and growth factors from these target cells. Asbestos fibres themselves may amplify free radical production through catalytic reactions involving iron[4] originating from the asbestos fibre itself or deposited on its surface after contact with physiological fluids[5].

Repeated exposure to such long, biopersistent, surface-active fibres will result in persistent release of inflammatory mediators leading to recruitment and activation of additional inflammatory cells (Fig. 1b). The normal defence mechanism against foreign materials is accumulation of activated macrophages and multinucleated giant cells to form a granuloma. If the foreign materials are resistant to degradation and cause persistent generation of tissue-damaging free radicals, then granulomas can become sites for recruitment of fibroblasts, deposition of collagen scar tissue, and in-growth of new blood vessels. Free radicals also cause DNA damage and mutations in proliferating cells that are the precursors of mesothelioma. This combination of free radical-induced tissue damage and inflammation provides a favourable microenvironment for tumour development and progression[6].

Taken together, these two pioneering studies provide scientific evidence for an asbestos-like pathologic response to carbon nanotubes, at least in certain cases, which will probably increase societal concern about nanotube health effects. It would be premature, however, to declare carbon nanotubes a major risk factor for mesothelioma in humans, for several reasons.

First, it remains unclear whether nanotubes will reach the mesothelial lining in sufficient numbers following inhalation, as this requires initial penetration to the deep lung followed by translocation across the air sacs into the pleura. Asbestos fibres can navigate this complex pathway, but data on nanotubes are still scarce[7]. A more complete 'gold standard' for testing fibre carcinogenicity is a chronic inhalation assay using a range of doses in two rodent species[8], but this approach may be too expensive and complex to be carried out on a wide variety of nanotube types.

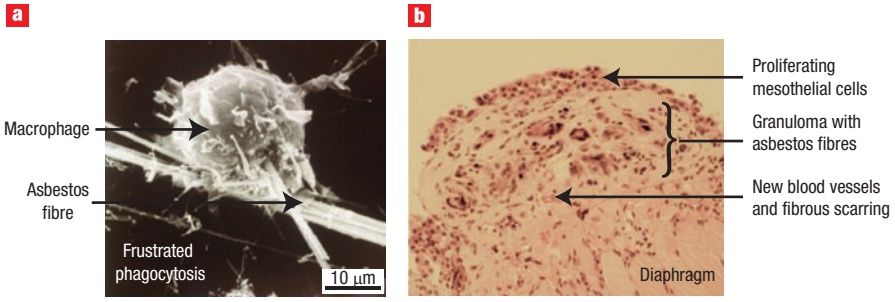

Figure 1 Exposure to asbestos fibres leads to development of malignant mesothelioma. **a,** A scanning electron micrograph of 'frustrated' or incomplete phagocytosis of long asbestos fibres leading to impaired clearance. **b,** Granuloma on the abdominal lining. Histologic sample of a cross-section of the diaphragm between the abdominal and pleural cavities. Injection of crocidolite asbestos fibres into the abdominal cavity induces formation of a lesion known as a granuloma, covered by proliferating mesothelial cells. Repeated injury to the mesothelial cells is accompanied by DNA damage, in-growth of new blood vessels and fibrous scarring around the granulomas. This chronic inflammatory microenvironment promotes tumour development.

Second, the biological mechanism in question is triggered by geometry, but the 'effective' nanotube geometry sensed by cells is determined by aggregation state, which may include bundles, ropes, spherical balls or free tubes. Moreover, the actual geometry is experiment-dependent and governed by the environmental and processing history of the samples (see Table 1 in ref. 2). In real human exposure scenarios, the actual physical form of nanotubes that are presented to internal target tissues such as the mesothelium remains unknown.

Third, the genetically engineered mice in the study by Kanno and co-workers are susceptible to induction of foreign body tumours (formed by solid carcinogenic materials) and work is needed to confirm the diagnosis of mesotheliomas in that study as distinct from foreign-body tumours[9].

Fourth, although carbon nanotubes are generally believed to be chemically stable, there are insufficient data in physiological environments to establish biopersistence over long time periods, which in the case of some types of asbestos (amphiboles including amosite and crocidolite) can exceed years or decades.

Finally, the recent findings are quite specific for this particular subclass of long, unfunctionalized MWNTs and it is difficult to extrapolate to other nanotube types. The nanotube material family is quite diverse in geometry, chemical composition and surface properties, especially considering the many new modes of chemical surface functionalization that have become common practice in nanotube processing.

This last point offers a ray of hope. Identifying key material features linked with toxicity (here, fibre length) can suggest new and more precisely targeted approaches to nano safety. For example, future product development may prefer short nanotubes when they are compatible with the application, and where long tubes are absolutely required — for instance, to form percolating networks that impart electrical conductivity to polymers — more stringent exposure controls might be deemed necessary.

In the case of asbestos, rigorous toxicological testing has been able to identify the physical and chemical properties responsible for lung toxicity and carcinogenicity, and this knowledge was used in the development of asbestos substitutes that show minimal toxicity in animal[8] and human epidemiologic studies[10]. In the case of carbon nanotubes and other engineered nanoproducts, we are still within a 'window of opportunity' to develop safe material design and manufacturing strategies before commercialization becomes widespread.

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