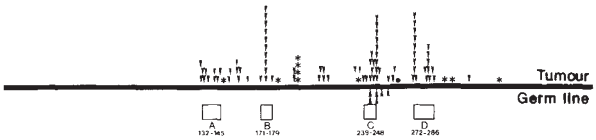

Mutations in the human *p53* gene. The thick bar represents the 393 codons of the gene. Arrowheads represent missense mutations, asterisks denote nonsense mutations (due to deletions or point mutations) and closed circles represent splice–junction mutations. The mutations above the line have been documented in sporadic tumours (see ref. 11 for sources); those below the line have been shown to occur in the germ line of Li–Fraumeni patients[1,2].

the effect of inherited *p53* gene mutations; yet the median age of tumour development is over 30 years, and the median number of lifetime tumours is less than two. From the cell's (not the patient's) point of view, inherited *p53* mutations are incredibly weak tumour initiators.

This weakness is even more curious in light of the putative dominant-negative nature of the mutations described above. Perhaps some *p53* gene mutations are less dominant-negative than others; indeed, from recent studies in several laboratories it would seem that there are significant differences in the biological and biochemical activities of various mutant proteins. Interestingly, the mutant *p53* gene products in normal cells of Li–Fraumeni patients are apparently less stable (and therefore expressed at lower levels) than those previously analysed in sporadic tumours[1]. But it is more likely that the low expression of the inherited mutant proteins reflects the cell type in which expression was assessed rather than the mutant type. And in fact some of the same mutant *p53* genes observed in Li–Fraumeni patients have previously been observed to encode high levels of stable proteins in the tumour cells of sporadic cancer patients. The striking positional clustering of the Li–Fraumeni mutations between codons 245 and 258 suggests however that the inherited mutations do indeed have some unique properties compared to most of those observed in tumours (see figure).

The new findings also illustrate an emerging concept in cancer gene research. Inherited *p53* gene mutations are clearly the initiating event in the tumorigenic process of Li–Fraumeni patients, occurring 10–30 years before the onset of malignancy. In many human tumours, however, *p53* gene mutations have been shown to represent late events in the neoplastic process, occurring 10–30 years after the initiation of neoplasia. There is thus a 30-year interval over which such mutations can exert an oncogenic effect. This emphasizes that it is not the time of occurrence of mutations, but rather their accumulation, that is most important in tumour development. In Li–Fraumeni patients, *p53* gene mutations occur first and other mutations follow. From the lower than expected incidence of cancer in these families, it would seem that several additional mutations, not just loss of the wild-type *p53* gene, must occur before malignancy ensues. In the general population, these additional mutations occur first and *p53* gene mutations follow. The end result is identical, though, regardless of the order of the mutations.

Li–Fraumeni syndrome is rare — fewer than 100 families suffering from it have been identified. But what are the boundaries of the clinical features caused by mutations in *p53*? The clinical expression of many inherited diseases can vary widely depending on the mutation, the environment and the inheritance of other genes. It is clear from previous studies that *p53* gene mutations in most cancers are somatically acquired. It is possible, however, that a small percentage of such mutations (under 5 per cent) is inherited. This percentage may be higher for selected patient subsets, such as young women with breast cancer. If the inherited *p53* gene mutations are limited to the fewer than 0.001 per cent of breast cancer patients with classical Li–Fraumeni syndrome, this inheritance will have few practical implications for the general population. If, on the other hand, inherited mutations are found in a greater proportion (even as few as 1–5 per cent), screening for them will become a serious issue for public health policy.

The new results also have considerable historical implications. All of the recent work on *p53* gene mutations in humans can be directly traced to research on specialized and sometimes obscure experimental model systems. These older studies have now led to a key clue to the pathogenesis of many of the most common forms of human malignancy. In our increasingly goal-oriented research environment, the p53 story, particularly its origins in basic research, may well be worth re-telling. □

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DAEDALUS

Aromatic air

LAST week Daedalus proposed synthesizing benzene in a magnetic field. Each ring molecule would then have a magnetic flux line threaded through it. Since the benzene ring acts as a room-temperature superconductor, through which flux lines cannot pass, the molecules would then be permanently linked to the flux lines like loose beads on a string.

Daedalus now muses that all benzene has been synthesized in a magnetic field anyway: that of the Earth. Any shipment of the compound must drag a little of the Earth's field with it. This of course explains the appalling navigational record of oil tankers and toxic-waste vessels: the benzene content of their cargo disrupts their magnetic compasses. It also suggests a novel global communication system. For benzene synthesized at one site and released as vapour would not diffuse randomly away. It would drift up the magnetic flux line leaving the Earth at that point, arch through space, and curve down again towards the 'conjugate point' where that flux line meets the other hemisphere. The benzene molecules threaded along the flux line would act as a sort of one-dimensional gas, and should therefore transmit sound. Being unable to spread out, this sound should travel along a flux line without attenuation.

DREADCO acousticians are already travelling to the magnetic conjugate points of major oil refineries and heavy-chemical installations. They reckon that benzene vapour released over the years will have saturated the connecting flux lines already, establishing a sonic channel. They will locate the exact conjugate point by listening for industrial noise echoing out of the empty sky; they will then shout back. The changing bandwidth and propagation time of the channel will give fascinating insights into the path, distributed benzene-loading, and high-altitude fluctuations of that particular flux line.

Daedalus is even inventing benzene molecule astronomy. Benzene released from a very northerly chemical works would ride the Earth's flux lines far into space. A shout or pulse of compressed benzene vapour launched up such a line should return an echo for each discontinuity it encountered. The high-altitude magnetosphere, the Earth's magnetotail stretching away from the Sun, the shock front where its field hits the solar wind, could all be studied from the relative comfort of some Northern tank farm or plastics factory. Some lines of force must even intersect the Moon, so that its changing distance could be measured by a sort of benzene-molecule sonar. The speed of sound is so low that it would take hours or days for the echoes to return. Distances established in this way would be correspondingly precise.

David Jones