operon. These studies accentuate the intriguing relationship between transcription and replication; the new work links the tumorigenesis-associated protein p53 with these ubiquitous cellular processes.

As increasingly sophisticated techniques to identify associated proteins become available, there will probably be an escalation in the number of proteins that can be shown to bind p53. But determining which associations are physiologically relevant for p53 function is not simple. It is unlikely that p53 can bind to all the cellular proteins listed in Table 1 at the same time. Clearly, either cell-type or cell-cycle specificity must be invoked to accommodate all these guests. It is essential to determine what percentage of cellular p53 is bound by each associated protein and how the portion that is bound affects p53 function.

This raises several unanswered questions about p53, concerning its true cellular function(s). Over the past several years a number of biological and biochemical activities have been ascribed to p53 (ref. 6 and Table 2). The existence of mature p53 'knock-out' mice suggests that p53 is not necessary for normal development. However, the increased incidence of tumours in these mice implies that p53 has a critical role in suppressing tumour growth, even in short-lived animals. From the study of human tumours, a related and unambiguous fact emerges: cells with inactivated p53 genes enjoy a selective growth advantage over their neighbours. The neighbours include neoplastic cells containing one or two normal p53 alleles, and the p53 mutant cells selectively proliferate, eventually expanding to form the dominant clone in the tumour.

So how does inactivation of p53 lead to this clonal expansion? Progress in this area depends on finding answers to the following questions. First, what induces p53 expression? In most cells, p53 is expressed at low levels, probably too low to exert a suppressive effect. In emerging tumours, *something* induces p53 expression to levels sufficient for growth suppression, and then (and only then) can an inactivating mutation of p53 endow a cell with a selective advantage, relieving the growth inhibition. Although exposure to high levels of radiation or other DNA-damaging agents has been shown to induce p53 expression in experimental systems, such high exposures obviously do not occur naturally. Second, is the p53-mediated growth arrest transient or permanent? Two different models for such growth arrest have emerged. In one, p53 mediates a transient G1 block, reversible after the p53 inducer is removed[7,8]. In the other, the p53 'arrest' is permanent, resulting in apoptotic death[9]. These two models have distinctly different implications.

Third, what is the mechanism underlying the growth arrest? Three models have been formulated. In one, p53 may bind to and stimulate the expression of genes that are directly responsible for growth suppression, and p53 would then function primarily as an activating transcription factor[10]. In the second, p53 may inhibit the expression of transcription of TATA-controlled genes in general[11], perhaps by binding to TBP or other transcription factors (see Table 1). Finally, p53 may bind to cellular origins of replication, interacting with key proteins involved in DNA synthesis (such as RPA) and thus inhibiting entry into S phase (or, perhaps, directing cells primed for S phase into apoptosis).

Table 2 Reported functions of wild-type p53

Biochemical functions
Binds DNA in a sequence-specific manner
Activates transcription from promoters with p53 DNA-binding sites
Represses transcription from a variety of promoters without p53 DNA-binding sites
Stimulates annealing of single-stranded DNA
Inhibits helicase activity
Inhibits DNA replication
Biological functions
Induces G1 growth arrest
Induces apoptosis following DNA damage
Inhibits tumour cell growth
Preserves genetic stability

Getting definitive answers to these questions will be difficult, but one clue is provided by p53 mutants. The mutants found *in vivo* have been selected, in the most relevant environment, for loss of p53 function(s) required for tumour suppression. In this regard, it is notable that many of the p53-associated proteins still associate with at least some mutant p53 proteins, and the simplest interpretation is that such interactions do not mediate p53 tumour-suppressive effects. Guests at the p53 inn will continue to come and go; such guests must be scrutinized by rigorous biochemical and genetic criteria before they are allowed to become permanent residents rather than friendly visitors. □

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DAEDALUS

Bendless delight

WATER pressure increases rapidly with depth, as divers know to their cost. A diver in deep water rapidly becomes saturated with pressurized air. If he returns too quickly to the surface, this air froths out of his blood and tissue like champagne when the cork is released. This is the dreaded 'bends'. Seals and dolphins breathe air as we do, yet dive and ascend as rapidly as they wish. How do they avoid the bends?

Daedalus recalls that bubbles like crystals, form in a liquid only in the presence of microscopic initiating 'nuclei'. Some arctic fish survive below freezing point by means of a protein inhibitor that deactivates the nuclei needed to form ice-crystals. So, says Daedalus, seals and dolphins must have evolved an inhibitor against air bubbles. It may deactivate the nuclei themselves, as alkalis do to the nuclei of steam bubbles (which is why alkaline solutions boil so irregularly). Or it may be surface-active, covering the bubble surface with a gas-impermeable monolayer which stops it growing. DREADCO biochemists are now analysing the blood of seals and dolphins in search of this natural bubble inhibitor. It will probably be a simple protein.

The diving fraternity will welcome the new product. One simple injection of DREADCO's Nobub®, and a diver will be able to dive and ascend as freely as a seal or a dolphin. He will be able to shoot down to the depths, do his work, and shoot up again, without tedious delays for depressurization. But Daedalus is taking the idea further. Imagine, he says, a swimming bath whose water was itself loaded with Nobub. A compressor unit could saturate the water with tens of atmospheres of pure oxygen, and it would just stay in solution. It could be made available to swimmers by means of a mouthpiece or nasal spray, loaded with a Nobub-antagonist. Water entering the swimmer's nose or mouth would then fizz violently, disengaging enough oxygen for him to breathe. But Daedalus soon realized that the right amount of salt in the oxygen-loaded water would make it isotonic and fully compatible with human tissue, like medical saline. The swimmer could then simply breathe the water itself, as a fish does.

DREADCO's breathable Nobub bath will bring a wonderful new delight to its patrons. They will be able to float freely at any depth, buoyant and weightless, in warm water that they can breathe. Suspended so perfectly, they will enjoy the ultimate in total muscular relaxation. Even swimming lazily around will seem more like that euphoric, magical dream of flying. David Jones