

would be hard. The results of the trial of universal neonatal screening in the Wessex region (1993-6) should help to evaluate the benefits and difficulties of this strategy for a large population. Whatever the outcome, later testing will be needed for those children with acquired hearing loss, who account for 6-7% of all hearing impaired children at age 5.² Parental concern should always lead to diagnostic testing, and the school entry "sweep" test of hearing (a modified pure tone audiogram) should be performed.¹

The consensus statement discusses the advantages and disadvantages of the current methods of screening newborn infants. Auditory brainstem responses are highly sensitive, detecting nearly all children born with appreciable deficits, but some false positive results occur in babies with normal hearing. The testing needs scalp electrodes and trained staff and is time consuming. Transient evoked otoacoustic emissions are low intensity sounds produced by the inner ear, which can be measured with a sensitive microphone placed in the ear canal. The test for them is less invasive and can be performed in a shorter time than auditory brainstem responses, and staff can be trained more easily. It is also sensitive but has more false positive results than those obtained with tests of auditory brainstem responses, resulting in a heavy follow up workload and unnecessary parental anxiety. The consensus panel recommends that newborn screening of transient evoked otoacoustic emissions is performed, with those infants who fail going on to additional

tests with auditory brainstem responses, but it does so without having the results of large population based studies showing that this strategy is practical, especially given the heavy workload placed on the follow up services.

The National Institutes of Health consensus will probably increase the pressure for universal neonatal screening in Britain. But before any model of screening is introduced two things are necessary: thorough evaluation in the context of our postnatal wards and neonatal units and the provision in each area of comprehensive audiological diagnostic and treatment services. Screening is of no value without facilities for follow up.

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p53: a gene for all tumours?

Provides profound insights into the basic molecular mechanisms of cancer

Of all the dominantly acting oncogenes and recessive tumour suppressor genes, the p53 gene is by far the most frequently mutated in human cancers.¹ Recent experiments have shown how these mutations affect the structure and function of this remarkable gene, which is emerging as one of the few truly central players in the tumorigenic process.² The hope is that such experiments may eventually provide better treatments for many types of cancer.

The p53 gene, on chromosome 17p13.1, encodes a nuclear phosphoprotein of 393 amino acids, which acts as a transcription factor. Several domains of the sequence are extremely highly conserved between different species, and most of the point mutations observed in human cancers map to these regions. Somatic mutation of the p53 gene occurs at both alleles in 50-80% of spontaneous human cancers from a wide variety of histological types, but germline mutations of p53 also play a part in inherited predispositions to certain types of cancer. In the Li-Fraumeni syndrome, which is a rare, heritable condition, family members who are highly susceptible to a range of malignant cancers before their early 30s inherit non-sense or missense mutations in one p53 allele. Cells from unaffected members do not carry any mutation. The inheritance of a single (recessive) mutation allows normal development but greatly increases the risk of cancer because only a single somatic mutation is required in any cell to reduce its genetic complement to homozygosity for loss of p53.

What is the function of p53? Transgenic mice lacking functional p53 genes develop normally (so p53 protein cannot be essential for life) but invariably develop cancers at 3-6 months, showing that p53 is a central control point for passage through the cell cycle.³ Similarly, in normal cells with DNA

damaged by ultraviolet or γ irradiation, progression through the cell cycle is blocked at G1 coincident with a sharp rise in the levels of p53 protein. During the subsequent arrest of growth, repair of DNA is completed before the cells proceed into S phase "in which their DNA is replicated." If, however, genomic damage is excessive the cell undergoes programmed cell death—apoptosis⁴—which requires p53 protein.^{5,6} Cells expressing mutant p53 protein, however, do not pause in G1 but continue straight into S phase before repair of DNA is complete. p53 protein has therefore been described as the "guardian of the genome" as it prevents entry into S phase unless, or until, the genome has been purged of potentially damaging (that is, transforming) mutations.⁷ In addition, because many chemotherapeutic drugs kill tumour cells by inducing apoptosis, loss of p53 protein function may also directly decrease the cells' sensitivity to such cytotoxic agents, enhancing the clinically dangerous emergence of drug resistant populations of cancer cells.⁸

Other experiments have shown that p53 protein acts as a transcription factor in the nucleus controlling gene expression, whereas mutant p53 protein no longer binds DNA.² At least some of the genes that p53 protein regulates may therefore promote repair of DNA or terminal cell differentiation, including apoptosis.¹ Mutations of p53 protein would prevent the transcriptional activation of this array of cell protective genes, allowing the cell to progress unchecked through repeated cell divisions.

Mutations in p53 either prevent production of protein or generate mutant proteins that have lost their normal function.⁹ In addition to an inability to suppress cell division, many mutants express a gain of function which actively

promotes the tumorigenic potential of cells lacking endogenous p53 protein. Missense mutations can generate mutant p53 protein, which is more stable than wild type p53 protein and can sequester normal protein into inactive oligomeric complexes.^{2,9} Such mutant proteins effectively act like the oncogene products of the DNA tumour viruses, which also form complexes with p53 protein (and other tumour suppressor proteins) to abrogate its cellular activity.¹⁰ In cervical carcinomas positive for human papillomavirus the E6 oncogene of human papillomavirus types 16 and 18 binds to p53 protein in infected cells to promote tumorigenesis.¹¹ A further class of mutation has recently been described in some breast cancers, in which p53 protein is sequestered in the cytoplasm rather than being transported into the nucleus, thereby preventing it from functioning in its correct cellular compartment.¹²

More recently, both mutant and wild type p53 protein has been shown to form complexes with the product of a cellular proto-oncogene called mdm-2.¹³ High concentrations of mdm-2 prevent normal p53 protein from activating gene transcription, so the transforming action of an oncogene (mdm-2) might be explained by its ability to inactivate the product of a tumour suppressor gene (p53). Cancers have indeed been described that are normal for p53 but in which mdm-2 is overexpressed¹⁰—the number of tumours that involve dysfunction of p53 protein may therefore be even greater than studies of mutation in the p53 gene alone suggest.²

Screening for mutations of p53 is already of diagnostic and prognostic value for patients with cancer and families at increased risk of cancer, although such information brings with it profound socioeconomic and ethical implications. Whether p53 can be a viable therapeutic target remains to be seen. Eventually, it may be possible to deliver normal copies of p53 to tumour cells in vivo to induce apoptosis¹⁴ or differentiation¹⁵ or even to restore sensitivity to cytotoxic

agents,⁸ although considerable theoretical and practical difficulties remain.¹⁶ Pharmaceutical intervention may target the altered conformation of mutant proteins so that the function of p53 in normal cells is left unaffected.

The p53 gene blurs the previously sharp conceptual division between the oncogenes and the tumour suppressor genes both functionally (certain mutant p53 proteins can be dominantly transforming) and also mechanistically (by its interaction with known viral and cellular oncogenes). p53 therefore seems likely to yield profound insights into the basic molecular mechanisms of cancer.

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Information management and patient privacy in the NHS

Confidentiality must be better protected, probably by statute

Last year the NHS Management Executive launched an ambitious project to unify health service information systems.¹ Its aim is to set free all the health information currently imprisoned on isolated systems throughout the health service and allow it to travel to wherever decisions are being made. The benefits of sharing information across the health service are undeniable. General practitioners, specialists, and other health professionals will no longer have to conduct consultations without notes or investigation results; purchasers will have the information they need to contract accurately for services; and audit will be easier, quicker, and more streamlined. The strategy could also, however, make it far more difficult than it is now to protect patients' confidentiality and privacy. So far these problems have attracted little attention from most NHS professionals.

A seminar organised by the BMA's information technology working group heard last week that most doctors are not only ignorant of the strategy's implications for privacy but also unaware of the objectives of the strategy itself. A survey done in April this year by the management executive showed that only a fifth of general practices knew it existed.² Few of the speakers and even fewer of the invited audience could name

even one of the strategy's five key principles, a reflection of the management executive's failure to make NHS professionals aware of the strategy.

The essentials are that by 1995 everyone in the country will be identified by a new NHS number. This will be recorded along with other personal information—name, address, date of birth, sex, and registered general practitioner—in one of a set of administration registers. Each administration register will hold details on everyone living in a particular geographical area and they will all be linked. The local register will provide the core data for local general practice lists, hospital administration systems, and family health service association registers, removing the need for each system to duplicate patient data. And when patients move outside their local area the linkage of all administration registers will allow a distant hospital or practice to access the patient's details. Eventually a nationwide computer network will be in place allowing family health service associations, district health authorities, general practitioners, community units, hospitals, and others to share patient information. Clinical details, including signs, symptoms, diagnoses, and prescribed treatment will be coded from a nationally agreed thesaurus based