the repeated postal circulars suggested by O'Brien *et al* be better received? If muscular dystrophy cannot easily be kept uppermost in the mind of the family doctor who might never encounter a case, screening may be the only way to prevent unacceptable diagnostic delays.

One possible solution is to include clinical medical officers more actively, to permit them to obtain blood samples for creatine kinase assay, and to suggest that they screen all those boys (3% of the male population) who are (or were) unable to walk at 18 months—plus those who have unexplained motor and speech delay or who are unable to run or jump at 2 years. They might have to test 5% of boys altogether, but probably the rate of diagnosis would potentially approach that of neonatal screening. The 18 month rule alone would pick up 40-50% of cases.[3] Success would depend on a high proportion of children being seen at $1\frac{1}{2}$-$2\frac{1}{2}$ years of age, however, and both health visitors and clinical medical officers might have to rethink the timing and thoroughness of their efforts to recall children for examination if there was developmental delay at this age. Techniques of blood spot testing for whole blood creatine kinase[7 8] would mean that only a finger prick or heal prick would be necessary; high results could be checked later with a venous sample. The benefits of giving clinical medical officers access to laboratory screening methods have been disputed, but this is one example where it seems potentially important. Perhaps one or more regional health authorities could pioneer an experimental scheme for comparison with the Edinburgh neonatal screening project and develop the techniques and the lines of referral for expert diagnosis and counselling, which would be essential to the success of such an endeavour.[1]

For the present, however, the responsibility for recognising Duchenne muscular dystrophy in time to prevent a greater family tragedy rests with every doctor who is asked "Why isn't he walking properly?" The answer requires careful observation of the child in action and the willingness to check the serum kinase activity whenever there is doubt.

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Oncogenes and multistep carcinogenesis

Spectacular successes always attract criticism, and a legitimate criticism of recent advances in our understanding of the genetics of human cancer has been that they depend on a gross oversimplification of an extremely complex process. It is the simplicity of the approach, in part, that has made it so compelling (simplicity, that is, in principle: in practice it is based on very high technology molecular biology).

The technique is to extract the DNA from tumour cells, cleave it into roughly gene sized pieces, and reintroduce the fragments into cultured mouse cells. Any fragment that induces cancerous changes in the mouse cells may then be presumed to have played a part in the induction of the original tumour. This was the method used by two American research teams, late last year, to incriminate a specific mutant gene in a human bladder carcinoma.[1 2] What made the result a landmark in cancer research was the link it established between human cancer and not just one gene but a group of 15 or so that were already implicated in tumorigenesis on other grounds.[3] The genes in question had originally been identified as the oncogenes responsible for the tumorigenic effects of the RNA tumour viruses of animals; and the possibility of a link with human cancer had only recently come to light with the discovery of homologous genes (proto-oncogenes, as they were called) in normal human cells.

The tumorigenic gene extracted from the bladder carcinoma cells turned out to be a mutant of one of the cellular proto-oncogenes—specifically, a gene named *ras* after the rat sarcoma virus in which it was originally discovered. And at that point molecular biologists began to foresee the possibility of a genetics of human cancer based on mutants of a relatively small number of identified cellular genes.

But even at the height of the euphoria generated in scientific circles by these genuinely remarkable discoveries sagacious commentators were pointing out uncomfortable discrepancies between the laboratory picture of tumorigenesis and the real thing.[4]

In particular, though a single mutant gene is apparently sufficient to transform the cultured mouse cells, epidemiological analysis has made it clear that several independent mutations must be required to transform a normal human cell. The answer to this paradox is generally believed to lie in the nature of the cultured mouse cells—a cell line known as NIH 3T3, which is very far from normal and may well already have undergone most of the steps required for tumorigenesis. Indeed, the mutant *ras* gene extracted from the bladder carcinoma cells will not transform more nearly normal cells. A second weakness in the chain of evidence linking viral oncogenes with human cancer is that despite their precarious claim to normality the NIH 3T3 cells cannot be transformed by any of the other 14 odd oncogenes, against which the evidence has thus remained circumstantial.

Both of these embarrassing gaps in the oncogene story have now been plugged by a series of experiments, reported recently in *Nature*,[5 6] that have begun to make the molecular biologists'

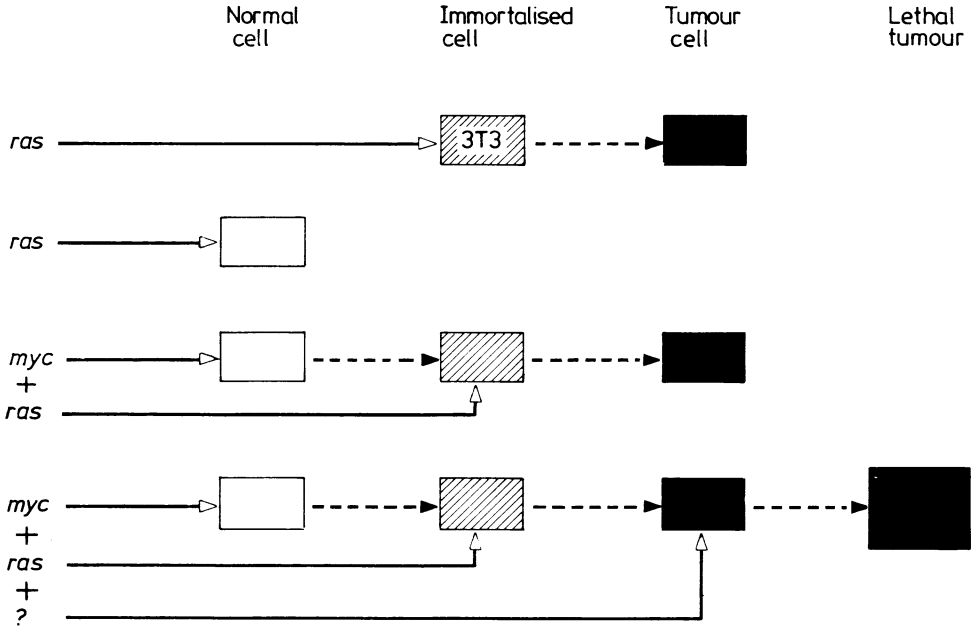
simplified view of tumorigenesis look substantially more like the epidemiologists' more complicated one.

In essence, the experiments have shown that, though a single species of activated oncogene is not sufficient to make a normal cell tumorigenic, a combination of two different ones will do the trick. The laboratory model of tumorigenesis thus begins to look more like the multistep process that occurs in real life and has been extended to embrace at least one more oncogene. In fact it has done even better than that. One of the most impressive aspects of research on oncogenes has been the way in which it has enabled apparently unrelated causes of cancer to be understood within the same general framework. For example, animal RNA tumour viruses and mutagens seem to be acting through the same genes, and moreover some tumour specific chromosomal translocations occur at breakpoints suggestively close to the site of cellular oncogenes and may induce changes that result in their activation.[7] The most recent experiments—which were the independent work of Earl Ruley, a young research biologist at the Cold Spring Harbor Laboratory in New York, and a team working at the Massachusetts Institute of Technology with Robert Weinberg, who was one of the first to discover the *ras* mutant—have enabled one more agent causing cancer to be slotted into the emerging framework, bringing with it associated insights into the nature of the changes normal cells must undergo en route to the cancerous state.

The agents in this case are the DNA tumour viruses of animals, the genetic basis of whose effects has until now had no known relation with those of the oncogene bearing RNA viruses. Detailed laboratory analyses carried out over several years have shown that DNA tumour viruses require two separate genes to complete the tumorigenic transformation of normal cells in culture. One of the genes simply enables the cells to go on growing indefinitely; the other induces changes in the shape and behaviour of the cell that seem to be associated with the loss of any remaining constraints on growth. Broadly, the two classes of gene, which have been identified in polyoma virus and adenovirus, are categorised as immortalising and transforming. Ruley reasoned that the NIH 3T3 cell line, which is a long established laboratory line, is already immortal and the mutant *ras* oncogene might therefore be acting as an equivalent to one of the DNA virus transforming genes. He was able to confirm that idea quite simply by introducing the immortalising gene from adenovirus together with the *ras* gene into normal rat kidney cells and producing full tumorigenic transformation.

Weinberg, in a more extensive series of experiments, took the same general idea a step further by showing not only that the *ras* gene can substitute for the transforming genes of DNA viruses but that a second identified oncogene can substitute for their immortalising genes. The second gene that he and his colleagues used in their experiments was an oncogene named *myc* (after the avian myelocytomatosis virus from which it was isolated), the cellular version of which is implicated in some human leukaemias because of its association with tumour specific translocations. Neither *myc* nor *ras* on its own is capable of inducing tumorigenic transformation of normal cells in culture—but both together proved able to produce cells that would form tumours in appropriately treated mice.

Further support (of a less precise kind) for the principle that tumorigenesis through whatever agent may require an immortalising and a transforming step comes from a third series of experiments, also reported in *Nature*,[8] in which chemical carcinogens were used to immortalise hamster cells before the ubiquitous *ras* gene was introduced to complete their transformation.



This leaves a strikingly coherent picture that is none the less still incomplete. For example, the tumours formed from the cells cotransformed in Weinberg's laboratory by *myc* and *ras* are not lethal: they stop growing at about 2 cm in diameter. Presumably lethal tumorigenesis requires at least one more step. In fact, as has been pointed out before,[4] it would be surprising if experiments on this principle did provide a complete picture of tumorigenesis, since by their nature they can detect only dominant genes and there is evidence that at least some of the genetic changes underlying some tumours are recessive.[8] The surprise is in the extent to which this and other lines of research have continued to converge on the recently identified cellular oncogenes—a recent instance being the discovery that a known growth factor produced by some

tumours is the product of one of the cellular oncogenes.[9 10] It may, after all, be possible to reduce a complex clinical problem to a system simple enough to be analysed by a mere laboratory scientist.

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Inner cities: time for a cure?

Two years ago a *BMJ* leading article[1] stated that "inner cities have some of the worst social and medical problems combined with some of the poorest primary care." Shortly afterwards the Acheson report on Inner London was published, giving hope that the government might be prepared to finance reform and restructuring of primary care in the most deprived parts of our cities.[2] These hopes have now been dashed by the cutbacks in National Health Service expenditure. Yet the problems remain: in the wake of the Acheson report other studies have confirmed the social and environmental problems facing doctors who choose to work in these areas.[3–6]

The use of the generic term "inner cities" has not helped —indeed, it has almost a pejorative ring to it. In reality the problems vary from city to city, from borough to borough, and even from street to street. Attempts to ascribe one cause or prescribe one solution to the multiple and complex problems produced by varying environments and circumstances are doomed to failure. Sensational treatment by journalists of the various medical and social aspects of inner city problems has made matters worse—while professional and political idealists have pursued their own particular philosophies with little regard to logic or the consequences.

In London, for example, the problems are said to include the numbers of elderly singlehanded doctors, practices with a small list size, unsuitable premises, and lack of available staff, together with a considerable lack of interest in supporting primary care by some planning authorities and teaching hospitals. Wood has shown that these are not the main problems in Manchester, where the prime difficulty is attracting young doctors to the area.[6] I have found that, though several common threads run through the pattern of problems in different cities, each needs to be considered on its own merits and with regard to local resources.[4]

Medical, social, and environmental factors may all contribute to the difficulties facing providers of primary care in our cities. The medical factors include elderly doctors, list size, the Medical Practices Committee's recruitment policies, low practice income, non-availability of doctors out of hours, overseas doctors, attitudes of teaching hospitals, lack of a primary health care team, high psychiatric-social caseload, and a poor public image. These are likely to be aggravated by the social factors—a high proportion of the population being mobile (but with many elderly patients living alone), single parent families, high rates of crime and unemployment, and concentrations of ethnic minorities; and the physical setting is likely to be decaying with inadequate or inappropriate urban development programmes and a lack of accommodation suitable for primary care.

These problems have been allowed to develop and then to persist as a consequence of medical inertia or indifference, political dogma affecting rational urban development, and a chronic lack of financial resources. The leading article quoted above went on to state that "the traditional buttresses of primary care [are] the acute hospital and social services." The attitude this statement reflects may explain why some of the problems have arisen. In most parts of Britain general practitioners would not consider themselves to be buttressed by the hospital or social services—indeed, quite the opposite. These and other attitudes will have to change if inner city problems are to be solved.

Of course, the personal examples of success by some doctors and administrators shine brightly in the otherwise drab uniformity of inaction and discouragement, but these are few. Medicopolitically the profession has little to be proud of. For example, until recently the policies of the Medical Practices Committee successfully blocked the appointment of young vocationally trained doctors to vacancies in inner city practices. Successive governments and local authorities have carefully ignored facts or difficulties which did not fit in with their own particular policies, and resources have not been made available—or have been, but only very slowly.

By contrast, those departments of general practice which have become actively concerned with the provision of inner city care have improved the standards of the practices with which they work. The establishment of two more chairs of general practice in London is very welcome (provided they are given the necessary resources). Yet the average general practitioner perceives academic general practice as being remote from reality. This impression could be effectively disproved if the departments united to coordinate their efforts to raise standards of care uniformly throughout Britain. The profession and the public have to acknowledge that two standards of primary care are now being offered to our population. In recent years the General Medical Services Committee and the Royal College of General Practitioners have worked closely together on several important issues, and they could cement their new relationship by taking the initiative for action. With the university departments of general practice they would make a powerful triumvirate that should be able to propose general policies for solution of the various problems—though these policies would need modification according to local circumstances—and persuade general practitioners to adopt them.

Clearly in its current mood of cut and freeze the DHSS has swept away all thought of acting on the Acheson report.[2]