testosterone influences the development of prostate cancer, has led to the hypothesis that physical activity may protect against this cancer.[3] Though most studies suggest an inverse association between activity and prostate cancer, null and positive associations have also been shown.[3] These inconsistent findings may be explained by a variation in the detection of latent disease. Data are similarly discrepant for testicular cancer.[8 9]

Although physical activity improves pulmonary ventilation and perfusion, which may reduce both the concentration of carcinogenic agents in the airways and the duration of agent-airway interaction, the association of activity with lung cancer has received relatively little attention. Findings from most, but not all, studies suggest a negative relation,[1 3] with those of strongest design—prospective cohort studies relating repeated assessments of physical activity to subsequent lung cancer[10 11]—showing an inverse, dose-response association in men.

In the absence of randomised trials, confounding could be an alternative explanation for the apparent protective effect of activity. Individuals who are physically active may be different from their sedentary counterparts in genetic predisposition, dietary habits, and tobacco and alcohol use. Although several investigators report inverse associations between activity and cancer that are robust to statistical adjustment for these potential confounders, genetic predisposition has been little studied and dietary characteristics have been inadequately assessed. Furthermore, physical activity itself is often measured crudely, so misclassification, albeit non-differential, is likely to result.

In addition to the apparent role of physical activity in the primary prevention of some cancers, there is growing interest in its use in the treatment and rehabilitation of patients with cancer.[12 13] Physical activity may reduce the likelihood of recurrence and enhance survival through its capacity for improving bodily movement, reducing fatigue, and enhancing immune function. Studies are, however, hampered by small sample sizes, short follow up, selection bias, and variations in the stage of cancer at study induction. Thus, although initial results are promising, clearer conclusions depend on larger and better designed studies.

How can the clinician interpret these data on physical activity and site-specific cancers? Overall the evidence supports a potentially important protective effect of activity against colon cancer and probably breast cancer, with no association with cancer of the rectum. Notably, physical exertion does not appear consistently to increase the risk of any cancer. Further data relating activity to cancers of the endometrium, prostate, testes, and lung and to haematopoietic cancer[14] are required. The optimal permutation of mode, intensity, duration, and frequency of physical activity, and its association with cancer at different stages of life, is unclear. In the meantime, in light of the decreasing population prevalence of total physical activity, doctors should advocate moderate endurance-type activity, such as walking and cycling. As well as reducing the risk of chronic diseases such as coronary heart disease and non-insulin dependent diabetes, such physical activity does seem to protect against some cancers.

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Age related macular degeneration

New hope for a common problem comes from photodynamic therapy

Age related macular degeneration is the commonest cause of severe loss of central vision in people aged over 50 in the Western world.[1] The vision loss results from loss of function of the macula, the centre of the retina, which is responsible for central visual tasks such as reading, driving, and recognising faces. Macular degeneration has until recently been untreatable, but laser treatments have become available within the past few years that can halt progression of the disease and the consequent loss of vision in some patients.

The early stages of macular degeneration (usually without significant vision loss) include the formation of drusen,[2] which can be seen with the direct ophthlamoscope (after dilatation of the pupil) as small yellow deposits in the centre of the retina. Drusen are

BMJ 2000;321:1425–7

extremely common, detected in at least 10% of everyone over 65.[1] Although their cause is unknown, their progression is well documented.

Significant vision loss may occur from neovascular or non-neovascular abnormalities. In neovascular (sometimes termed "wet") age related macular degeneration, abnormal new blood vessels from the choroidal layer of the eye that nourishes the outer retina grow and proliferate with fibrous tissue within drusen material.[2] This choroidal neovascularisation causes acute loss of vision as transudate or haemorrhage accumulates within and beneath the retina, with permanent loss occurring as the outer retina (including the photoreceptors) becomes atrophic or replaced by fibrous tissue.[2] Although the haemorrhage, fluid, or scar tissue from the choroidal neovascularisation may be seen, the abnormal blood vessels themselves and early stages of fibrosis may not be seen easily on ophthalmoscopy but may be visualised on fluorescein angiograms of the retina.

In non-neovascular (or "dry") degeneration the pigmented layer of the retina and the photoreceptors overlying drusen become atrophic, and this is accompanied by slow loss of central vision, usually over a decade or two.[3] Most people who lose vision from age related macular degeneration, however, lose vision from neovascular complications.[1]

Two types of treatments have been shown to reduce the risk of vision loss in selected patients with neovascular complications. One, laser photocoagulation, uses thermal energy delivered under topical anaesthesia to burn the area of the retina occupied by choroidal neovascularisation. Several randomised clinical trials sponsored by the National Institutes of Health[4–6] have shown that photocoagulation could reduce the risk of severe vision loss for about 15% of patients.[7 8] The treatment is usually applicable to choroidal neovascular lesions that do not extend under the centre of the retina since photocoagulation will usually destroy any viable photoreceptors overlying the abnormal vessels.

However, most patients with neovascular macular degeneration present to an ophthalmologist with new vessels extending under the centre of retina. In such cases a new technique, photodynamic therapy using the drug verteporfin, has recently been shown in randomised trials to reduce the risk of moderate and severe vision loss.[9 10] Photodynamic therapy is a two step process. Firstly, a photoactivator, verteporfin, is infused intravenously. Then a laser is applied over the entire neovascular lesion. This activates the drug, which has concentrated within the neovascular lesion. The photoactivation presumably selectively destroys the lesion by creating reactive intermediates of oxygen such as superoxide and hydroxide radicals without damaging viable retinal tissue overlying the neovascularisation.[11]

Retreatment as often as every three months, averaging five to six treatments over two years, is needed to prevent significant growth. Tests using higher doses of light failed to stop regrowth but instead caused photoactivation in normal retinal blood vessels, leading to loss of vision. The clinical trials showed that photodynamic therapy with verteporfin could reduce the risk of moderate and severe vision loss from 61% to 33% at one year and from 69% to 41% at two years in patients with neovascularisation extending under the centre of the retina and predominantly classic appearances on fluorescein angiography—an appearance that has a high likelihood of growth and vision loss within months if left untreated. Fortunately, the drug appears to be safe. Some patients may notice some transient fluctuations in vision for a few days after treatment, and all patients need to avoid prolonged exposure to bright sunlight during the two day period of potential photosensitivity.

Perhaps 20% to 30% of the 200 000 cases of neovascular macular degeneration that present to ophthalmologists in the United States each year are candidates for prompt photodynamic therapy. Once extensive vision loss has occurred the treatment is no longer beneficial. It is important therefore to teach older patients with drusen who are at risk of developing neovascular macular degeneration to screen for the possible development of neovascularisation. The primary care physician has an important role here since drusen are usually asymptomatic.

Specifically, the physician needs to evaluate the retina for the presence of drusen or refer the patient to someone who can screen for drusen each year. Once drusen have been discovered the patient needs to be told to screen one eye at a time often, perhaps as often as each day, for possible signs of developing neovascularisation so that if it develops the patient can seek help quickly. Such screening includes checking straight lines, as on a piece of graph paper or between tiles in a bathroom. Any sudden development of blank spots or distortion of the lines may be a sign of neovascularisation. Since the development of neovascularisation in one eye is associated with a 50% chance of developing a similar lesion in the other eye,[12] it is critical to try to save vision in either eye since one does not know which eye will end up being the better seeing eye.

The advent of effective photodynamic therapy makes even more important than before the need for primary care physicians to identify and educate the many people aged over 50 who have drusen about the risk of developing choroidal neovascularisation. As the number of people in this age group will double over the next 25 years, the public health importance of age related macular degeneration will continue to grow.

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Stem cell research

The UK government should sanction carefully regulated research

Later this month the UK parliament is scheduled to vote on recommendations on stem cell research made in a report by the chief medical officer, Liam Donaldson.[1] The leading recommendation is that research using human embryos should be permitted to allow exploration of the nature and therapeutic potential of stem cells. The outcome of the vote may have repercussions well outside the United Kingdom for there is considerable controversy, both in the United States and Europe, about this form of stem cell research.

Research on human embryos up to a limit of 14 days is already permitted in the United Kingdom, under the 1990 Human Fertilisation and Embryology Act, in five specific areas. These include infertility and preimplantation diagnosis of genetic and chromosomal disorders. The chief medical officer's report proposes expanding the purposes for which human embryos may be used under the act, and it would cover research using stem cells derived by cell nuclear transfer as well as from "spare" embryos created during in vitro fertilisation procedures. Research would be permitted only under license from the Human Fertilisation and Embryology Authority, as is currently the case.

Extending the scope of research on human embryos does not on the face of it raise a fundamentally new ethical challenge. But it has put the spotlight back on this form of research. "A significant body of opinion is firmly opposed to any form of research involving embryos," Donaldson acknowledges, "because they believe that an embryo should be accorded full human status at the moment of its creation." What has generated fresh concern, however, is "therapeutic cloning," the popular but emotive name for cell nuclear transfer.

This technique entails removing the nucleus from a somatic cell and fusing it with a (donor) oocyte that has had its own nucleus removed. The cell is then stimulated to develop, and the stem cells are taken from the developing blastocyst. The advantage of this technique over deriving stem cells from "spare" embryos, umbilical cord blood, or aborted fetuses, is that the cells obtained are genetically identical to the donor and so rejection would be avoided.

Some believe, however, that sanctioning therapeutic cloning is a step too far. In a recent parliamentary debate the MP Ann Winterton said that "if we accept therapeutic cloning now it will lead on to reproductive cloning later." It is precisely because of this fear that the government, which has welcomed the Donaldson report, has said that it would introduce primary legislation to prohibit reproductive cloning.[2]

Over the past two years the therapeutic potential of stem cells has become more apparent, as a special issue of *Science* on stem cell research and ethics shows.[3] Research, mostly in animals, has shown that stem cells can be stimulated to develop into a wide range of cell types. This has raised expectations that in the long term they may prove to be an effective regenerative therapy for a wide range of disorders including Parkinson's disease, Alzheimer's disease, type 2 diabetes, myocardial infarction, severe burns, and osteoporosis.

A raft of recent research showing that adult stem cells may also be stimulated to produce new cell lines has generated much interest. The ethical dilemmas would be resolved if adult stem cells derived from bone marrow and other sources could be used instead of stem cells from embryos. The problem is that it is not possible to obtain adult stem cells from most tissues, and expert groups agree with the independent scientific academy the Royal Society "that it will be at least a decade and very possibly a lot longer (possibly ever) before scientists will be able to overcome the hurdles blocking the therapeutic use of adult as opposed to embryonic stem cells."[4]

As MPs ponder their decision they are not short of advice. Clear statements on the rationale for stem cell research and the case for sanctioning therapeutic cloning have been made by the Medical Research Council, the Wellcome Trust, the Nuffield Council on Bioethics, the British Medical Association, and the Roslin Institute, as well as the Royal Society.[5–7] The European Group on Ethics in Science and New Technologies has taken a rather more cautionary stance. It recommends pursuing the research but states that "the creation of embryos by somatic cell nuclear transfer would be premature."[8]

As MPs weigh up the evidence and the ethical concerns it is important to bear in mind that these cut both ways. Arguments against therapeutic cloning must be set not only against the scientific case for it but against patients' interests too. In the United States a coalition of groups of patients has argued for public funding for such research. Their view is encapsulated by the recent statement made by the UK Parkinson's Disease Society that "stem cell research involving therapeutic cloning is justified to improve patients' lives."[9]

BMJ 2000;321:1427–8