one fraction per day. Hyperfractionation involves increasing the number of fractions and reducing the dose per fraction, typically with two or three fractions given per day, and randomised controlled trials have shown important improvements in outcome with such schedules. The EORTC hyperfractionation trial in head and neck cancer produced a 49% improvement in five year local control (absolute 19%) and a 33% improvement in survival (absolute 10%).[11] Continuous hyperfractionated accelerated radiotherapy (CHART, which includes reducing the overall treatment time as well as hyperfractionation) for treating lung cancer has delivered a 43% increase in two year survival (absolute 9%). For squamous carcinoma the increase in two year survival is 65% (absolute 13%).[12] Continuous hyperfractionated accelerated radiotherapy was conceived and evaluated in the UK, but it has not been generally implemented because of lack of resources.

Our calculations, based on the laboratory and clinical data available, suggest that an overall relative improvement in cancer cures of around 25% could be achieved simply by providing adequate radiotherapy facilities. The purchase of new linear accelerators for radiotherapy from the New Opportunities Fund announced recently is welcome and will help. However, many of the new machines will simply replace ageing ones; rather fewer will be additional, and there is no additional funding for the extra staff required to deliver the treatment (radiographers, physicists, and oncologists). A strategic review of radiotherapy resources, as the basis for a planned programme of national investment, is needed to address these important issues. Although further gains are to be expected from new radiotherapy technologies, such as conformal radiotherapy, the measures outlined above use existing technology, and all that is required is adequate resourcing.

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The rise in bacterial resistance

Is partly because there have been no new classes of antibiotics since the 1960s

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Almost since the beginning of the antibiotic era bacterial resistance has been seen as the major obstacle to successful treatment. Hardly any group of antibiotics has been introduced into clinical practice to which some bacterium has not developed resistance. Quantifying the impact of this resistance has often proved difficult, and misconceptions have often resulted from incomplete surveillance. Now that our surveillance methods are much better, we know that levels of antibiotic resistance are rising inexorably—as illustrated by this week's paper on trends in England and Wales (p 213).[1] Yet it has taken a long time to realise the extent of the problem, and there is still much that we need to learn about the mechanisms.

Resistance was often minimised as a problem simply because the problem was not known or recognised. At the end of the 1960s the surgeon general of the United States stated that "we could close the book on infectious diseases." Although those words seem naive now, at the time they were said the emergence of resistance did not seem to affect therapeutic options. Certainly, *Staphylococcus aureus* had become resistant to benzylpenicillin and was showing some resistance to methicillin, but it remained sensitive to gentamicin and thus infections could be treated.[2] Most of the bacteria responsible for community infections remained sensitive to the myriad of antibiotics available to treat them, and the surplus of available antibiotics masked the problem of emerging resistance.

At the start of a new century, some 30 years later, things look very different. We are facing a potential treatment crisis for some infections, with an escalating rise in resistance that we have difficulty in controlling.[2] What has changed? At the end of the 1960s we did not realise that we would face the next three decades with much the same antibiotic groups as we had then. Antibiotic discovery and development had been exponential since the 1940s, but no new clinically useful structures were discovered after 1961, and almost all the drugs that have been launched since the 1960s are modifications of antibiotics that we already have. This meant that bacteria that had "learnt" how to resist one member of a chemical drug class did not have to learn much more to overcome its later modifications. If bac-

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teria were challenged with a new antibiotic class, there would be little chance of cross resistance. Resistance had clearly been controlled up to the 1970s by the many different chemical antibiotic classes available.

The late 1960s were also important for the introduction of organ transplantation. As these procedures became more successful, more aggressive antibacterial therapy was required to protect immunosuppressed patients against infections. This situation was exacerbated with the treatment of neutropenic patients. This massive increase in antibiotic use in hospitals did promote the acquisition of resistance in some well recognised hospital pathogens, such as methicillin resistance in staphylococci and vancomycin resistance in enterococci.

In reality, these labels are convenient markers. Methicillin resistant *S aureus* is resistant to aminoglycosides, often to fluoroquinolones, and indeed to all antibiotics except the glycopeptides, and there are reports that some strains are becoming resistant to these.[3] In fact, these multiresistant variants of *S aureus* often occur as epidemic strains. What we are apparently witnessing is the clonal spread of a few resistant bacteria, and they are not simply the original hospital staphylococci that have become resistant.[4] They often contain plasmids harbouring resistance genes, but these plasmids are carriers of resistance that often have "dumped" their resistance genes into the bacterial chromosome by transposition. Similarly, the so called vancomycin resistant enterococci are also multiresistant strains and they are often resistant to all antibiotics targeted against them. The bacteria often spread clonally, although some individual resistance genes may be imported on mobile genetic elements.[5–7]

We are also facing some resistant bacterial species that were never traditionally regarded as pathogens, such as *Acinetobacter baumannii*. This organism was sensitive to all antibiotics in the 1970s,[8] but now some strains can sometimes resist all antibiotics.[9] In the case of this bacterium, the propensity to carry resistance genes seems as important as the ability to produce defined pathogenicity factors. In patients previously treated with antibiotics in hospital, *A baumannii* is a much more prevalent cause of pneumonia than in patients receiving no antibiotics.[10 11]

Where do these multiresistant bacteria come from? We do not know if they are subpopulations with a predisposition towards resistance. We do know, however, that they often spread clonally and that this may have been facilitated by hospital designs that move patients closer together and rely on regular transfers of patients between different points of treatment. Cross infection is clearly a major contributor to the rise in resistance, and modern molecular typing techniques show widespread dissemination of single bacterial strains. As our knowledge of molecular biology increases and the bacterial genome projects advance, we may well find that certain multidrug resistant strains are quite distinct genetically from their sensitive counterparts. We will then be able to show whether our multiresistant bacteria evolve from strains commonly found in hospitals or whether the antibiotic blanket selects certain strains, which survive merely because of the propensity to carry resistance genes.

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Why can't GPs follow guidelines on depression?

We must question the basis of the guidelines themselves

The Hampshire depression project, published recently, was a large well designed randomised controlled study of teaching practitioners about the recognition and management of depression and using patient improvement as the outcome measure. Its results were disappointingly negative, failing to show any increase in recognition or patient recovery rates.[1] These findings herald the need for a major change in thinking about improving the management of depression in primary care.

Through the 1990s educational initiatives have been mounted to implement expert guidelines on depression—based on the promising results of a study of educating 18 general practitioners in Gotland.[2] A two day course on recognising and managing depression given by psychiatrists was followed by increased antidepressant prescribing and decreased use of tranquillisers. Admissions for depression and the suicide rate both went down. The costs of the exercise were only 0.5% of the savings on admissions.

Subsequently, consensus guidelines on recognising and managing depression appeared in the United Kingdom.[3] The Royal Colleges of General Practitioners and Psychiatrists mounted the "defeat depression"

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