

## Improving the health of the world's poor

*Communicable diseases among young people remain central*

Several prominent reports have recently called attention to the world's health transition,<sup>1-5</sup> a process associated with reductions in fertility and improvements in overall health. As the transition progresses death and disability among infants and children from communicable diseases tend to decline in importance relative to problems resulting from non-communicable conditions at older ages.

The transition has proceeded furthest in the developed countries, but it has also occurred in the developing world. Recognising this, many observers have begun thinking in terms of a double burden of disease in developing countries.<sup>6,7</sup> The first is the "unfinished agenda" of communicable diseases in the young, which dominated professional thought in the decade after the World Health Organisation's 1978 Alma-Ata conference on primary health care. The second is the "emerging agenda" of non-communicable diseases at older ages resulting from the health transition. Such thought has recently resulted in calls for a shift in attention toward the emerging agenda.<sup>8,9</sup>

In assessing these calls we need to be aware of their equity implications. The emerging agenda is unquestionably important for the world's poor. However, it is much less important for the poor than it is for the rich. It also continues to be less important for the poor than communicable diseases in infants and children, despite the gains that have been achieved. As a result, any shift in emphasis from the unfinished to the emerging agenda would move away from problems that are most important for the poor towards those that are more important for the better off.

Non-communicable diseases were responsible for most (56%) deaths in the world in 1990.<sup>5</sup> But a closer look at the figures shows that these deaths were unevenly distributed across social class. For example, non-communicable diseases caused a notably smaller percentage of deaths (34%) among the poorest 20% of the world's population and a much higher percentage (85%) among the richest 20%. The situation for communicable, maternal, and perinatal diseases was the reverse: they caused 33% of deaths overall but 56% among the poorest compared with only 8% among the richest.

When these mortality figures are adjusted for disability the interclass differences increase, reflecting the fact that non-communicable diseases are far from alone in causing sickness as well as death. Similarly large differences also exist in age of death and disability, with the poor falling ill and dying at a much earlier age than the better off. Other research points to inter-

class differences within countries that are similar to the global variations.<sup>10</sup>

In the world as a whole, certainly, non-communicable diseases have increased in importance. What is not clear is the extent to which the poor have shared or will share in the overall gains that have brought enormous improvements for the emerging middle and upper classes in many countries. Whatever the future brings, however, today's policies cannot avoid taking today's conditions into account. And for those concerned with the poor a central feature of today's conditions is the fact that the health problems of the poor differ significantly from those of the better off.

These differences point to a need to move well beyond the aggregate figures that have thus far dominated discussions of disease burdens. If the poor are to benefit from the disease burden approach the approach will have to be used to identify the problems that are most important for them and that differentiate them from the rich. The packages of cost effective poverty oriented health interventions resulting from such an application will vary from setting to setting. In most places such packages will almost certainly include at least some components dealing with non-communicable diseases among poor adults and elderly people. Undoubtedly room also exists for further research to identify more effective, inexpensive interventions against such diseases. But, overall, governments and agencies using a burden of disease approach to improve the health of the poor, and to reduce rich-poor disparities, should expect to give a much more central place to further reducing infectious diseases among young people than is suggested by current assessments.

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## The trouble with bone allograft

*We need a safe, abundant alternative*

Allogeneic bone is the most commonly grafted tissue.<sup>1</sup> Its applications are expanding in all aspects of orthopaedic surgery, notably in the restoration of bone stock in patients undergoing revision hip replacement or surgical treatment for bone tumours. This expansion has occurred despite concerns about the supply and safety of allogeneic bone grafts and the complications of the procedure.<sup>1-6</sup> In the absence of an alternative, however, demand has begun to outstrip supply.

Bone tissue for allograft is obtained mainly through the donation of femoral heads from primary hip replacement. Guidelines have been developed which stipulate strict criteria for donation.<sup>3-7</sup> As a result, up to 50% of potential donors are excluded. The remainder are tested for antibodies to HIV-1, HIV-2, and hepatitis B and C viruses. Tests for HIV and hepatitis C virus should be repeated 180 days after the harvest, and grafts are discarded if they test positive or if test procedures are not satisfactory. In addition, about 18% of harvested femoral heads are contaminated with bacteria or fungi.<sup>4</sup> For revision hip surgery, each acetabular reconstruction requires two to four femoral heads, and most bone banks in England are reporting difficulties meeting demand. In Scotland the supply of femoral heads has been virtually exhausted (Lumley SP, Galea G, British Association of Tissue Banks meeting, Lancaster 1996).

Some centres are therefore using cadaveric donation, formerly a source of large grafts reserved for specialist centres. This source is unpredictable and places extra demands on staff and the next of kin. Adequate standards of asepsis are often not achievable at the time of harvesting, and bacterial contamination rates are higher than for live donation.<sup>4</sup> Similarly, cadaveric donors cannot provide repeat tests for viral antibodies, yet about 1 in 1000 British heterosexual men outside London carries HIV.<sup>8</sup> Unlike blood donors, cadaveric donors are not self selected. Screening histories have to be obtained from relatives. They may be incomplete, and the risk of viral infection remains unknown.<sup>5</sup>

The main complications after bone allograft are infection, fracture, and non-union. In a recent review of 718 large allografts the complication rate was 46%.<sup>2</sup> Rates increase with the size of the graft and the complexity of the procedure. They also reflect the success of graft incorporation. This depends on the intrinsic bone forming properties of the graft, the bone forming potential of the host, the graft's mechanical stability, and the surface area of the host-graft contact. Despite an understanding of the function of many iso-

lated proteins in the bone matrix, the bone forming properties of bone allograft are poorly understood. In most femoral heads such properties are probably minimal, and mechanical failure is an increasing problem.<sup>9</sup> Large grafts in general incorporate poorly, and fracture, non-union, and infection can be expected in 19%, 17%, and 11% of procedures respectively.<sup>3</sup> Morsellised allograft offers better results,<sup>10</sup> but applications are limited to those in which it can be adequately impacted to form a stable construction. Graft incorporation may in part depend on the patient's immune response, and antigenic disparity between donor and recipient has been cited as a disadvantage.<sup>6</sup> The immune response is directed mainly against cellular debris in the graft, but the bone matrix itself is also antigenic. It stimulates resorption of the graft, which can lead to rapid dissolution of the graft.<sup>11</sup> However, the relation between the patient's immune response and graft incorporation is not clear, and outcome remains largely unpredictable.

Bone allograft, particularly in its morsellised form, has proved valuable to countless patients for restoration of bone stock. However, it is not without its problems, and the shortage created by its widespread use is testimony not so much to its success as to the lack of a safe, abundant alternative.

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# Consumer participation in research and health care

## *Making it a reality*

The quality and relevance of much clinical research fall short of patients' needs.<sup>1</sup> Although there are many reasons for this, one is that clinical research has been delegated largely to the pharmaceutical industry, whose main motivation is its own economic welfare.<sup>2</sup> Another reason is that research priorities do not flow from a transparent process where the views of all the relevant stakeholders are equally considered. With very rare exceptions—the case of the AIDS advocacy movement is an exemplar—patients and consumers have no voice in how research is prioritised, funded, and monitored. Indeed, the presence of lay people on research ethics committees is common but there is a widespread belief that they are rarely influential.<sup>3</sup> Even among progressive scientists and health professionals, a paternalistic attitude still prevails. They do not believe that patients and consumers can improve the decision making process as, they say, consumers lack the necessary knowledge and skills. But successful efforts to shift the balance of participation are becoming a reality, even in difficult areas such as oncology.

In March, the First International Conference on Breast Cancer Advocacy convened in Brussels, under the strong leadership of the National Breast Cancer Coalition (United States), helped by organisations such as Association Nationale Contra el Cancer (Panama), Contre le Cancer (Belgium), Breast Cancer Care (England), Europa Donna, Israeli Breast Cancer Coalition, and UK National Breast Cancer Coalition. The main theme was how to make consumers' participation in research planning and healthcare delivery a reality. More than 250 breast cancer survivors, health professionals, and consumer advocates from 44 countries and six continents discussed for three days their own experiences and the difficulties encountered when they entered the scientific and policy making process. General issues (such as the status of breast cancer research and the biases that affect regulatory mechanisms for new drugs approval worldwide) were presented by scientific leaders. Specific workshops were organised to allow focused discussion and exchange of experiences, including consideration of how to mobilise and influence the media and how to influence legislation.

The Brussels conference was both the recognition of the success of the NBCC's Breast Cancer US Army Program<sup>4</sup> and the starting point for creating a truly international advocacy movement for breast cancer. The NBCC is a grassroots organisation, set up in 1991 and dedicated to ending the breast cancer epidemic through action and advocacy. While NBCC has spearheaded the effort to increase federal funding for breast cancer research in the United States, one of the most important changes that the coalition has brought about is the acceptance of the idea that breast cancer survivors must have a say when policies are formed and decisions about research funding are made.

The NBCC has created an innovative model of open communication and exchange of expertise with

the scientific community. Project LEAD (Leadership, Education and Advocacy Development) is a science training programme for breast cancer advocates. Project LEAD's goal is to empower activists to participate fully, however breast cancer decisions are made. Too often consumers are ill prepared or too intimidated by the process to speak up or ask questions. Project LEAD gives advocates basic scientific and leadership training so that they can effectively and responsibly influence decisions related to breast cancer research. Similar training and educational efforts to empower consumers and patients are being designed in Australia, Canada, and some European countries.

Even in Europe many research organisations are now beginning to work with patient groups that help set their agenda for future research, but there is still resistance to the idea that patients and consumers can fully participate. Some even worry that consumers will represent the views of special interest groups and could become strong lobbies easily manipulated by interested parties to advocate all care at any cost in an era where healthcare systems are struggling (at least in Europe and Australia) to be able to provide minimum necessary care to their populations.

As an international organisation putting strong emphasis on consumer participation,<sup>5</sup> the Cochrane Collaboration also took part in the Brussels meeting, and its newly formed Cochrane Breast Cancer Review Group was able to discuss its scientific endeavour and the challenge of establishing mechanisms for creative and productive patient and consumer involvement. The Brussels conference clearly endorsed the status of breast cancer advocates as equal partners with health professionals, scientists, and policymakers in preventing the disease, improving treatment, and ensuring better quality of care. Without such a partnership—difficult though it may be—research is unlikely to become more productive or relevant. The challenge is now for the medical profession to accept this message and develop alliances with consumers to move forward toward a wider recognition of the uncertainty and weaknesses of medicine and the biases in the process of setting research priorities.<sup>6</sup>

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# Adverse drug reactions: finding the needle in the haystack

*Pharmacovigilance is improving: now we need to ensure that patients benefit*

Patients need to be sure that the medicines they take are as safe and effective as possible. Concerns over a product's safe use must be discovered, evaluated, and acted on, and the results made available for patient care as expeditiously as possible. In this process spontaneous reports of adverse reactions play an important part, but the problem they present is that of finding needles—true adverse reactions—in large haystacks of suspicions.

There is no substitute for spontaneous adverse drug reaction reports for providing early signals of problems with drugs. The article in this week's issue by Lee et al shows that reporting by pharmacists can make a difference to the number of meaningful reports from hospitals (p 519).<sup>1</sup> Britain thus joins 36 other countries in the World Health Organisation's programme on international drug monitoring that accept reports from pharmacists. Britain is already in the top eight countries for reporting, with a rate of >200 reports/million inhabitants,<sup>2</sup> so what is the advantage of more reports? There is relative under-reporting from British hospitals compared with general practice,<sup>3</sup> so there is scope for new important information since adverse reactions to new drugs and those used in special disease categories are most likely to be seen in hospitals. Also serious adverse reactions cause hospital admissions.

Experience internationally with pharmacist reporting has been variable, both quantitatively and qualitatively.<sup>2</sup> The need for medical evaluation of a suspected adverse reaction can be a drawback because of the extra work, particularly if this necessitates correspondence after the first report is submitted (a problem that Lee et al avoided). At worst, the submission of more reports which are clinically unsubstantiated may simply add to the size of the haystack without providing any more needles.

The dilemma of spontaneous reporting is that, to make as sure as possible that nothing is missed, we ask for all (serious) suspicions to be reported: this inevitably means a large haystack. Actual reporting requirements vary between countries and include direct reporting by patients in some countries.<sup>2</sup> The result is that national regulatory and pharmaceutical industry databases are crowded with associations between drugs and reactions that have little value in raising new general concerns. Information technology has now made it possible easily to share information in the different databases throughout the world, but this has also exacerbated the problems with duplicate reports.

The problem of getting early and useful information out of this huge mass of data is one that has taxed members of the WHO monitoring programme since its inception. The Uppsala centre, which collects adverse reactions reported from all over the world, now has nearly 2 million records stored according to a

format established by the WHO programme. The centre has developed a data mining tool based on Bayesian, mutual information logic within a neural network<sup>4</sup> that allows the strength of all drug-reaction associations to be quantified. Effectively the whole database is being used as the control, so that any new positive drug-reaction association highlighted implies a significant difference from the global reporting experience: in this case the size of the haystack becomes an advantage.

Nevertheless, even a significant report is only a concern about a drug and a reaction: a direct causal relation remains unproved. Many other methods, such as toxicological testing and pharmacoepidemiology, may need to be used to determine the nature of the reaction, and reactions must be evaluated individually for their clinical importance before action is taken.<sup>5</sup>

Finally, although we have made progress both in finding adverse drug reactions and analysing them, has this benefited patients? There remains a gap between the development of pharmacovigilance knowledge and its use in practice. Some drugs are too widely used when there are safer alternatives<sup>6,7</sup>; others have been taken off the market when they still have a useful place<sup>8</sup>; and we are some way from satisfactory, open, communication, particularly with patients,<sup>9</sup> on benefit and risk in therapeutic choices.<sup>10</sup> The gaze of pharmacovigilance professionals has been preoccupied by gathering complete information and developing a more certain science. We must also be sure that individual patients benefit as much as possible from the information they, the patients, give us.

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