Where will new drugs come from?

2010 was a bleak year for new drug development. Figures released by the European Medicines Agency (EMA) show a substantial decline in the number of approved drugs for human use in 2010, based on evaluations of marketing authorisation applications. Only 38 positive opinions were issued and 41 applications were finalised by October, 2010. The figures could yet increase by the end of 2010 but seem unlikely to match those of 2009, when there were 117 positive opinions and 125 finalised applications. Additionally, some highly anticipated new drugs proved to be expensive failures in 2010, including ocrelizumab for rheumatoid arthritis and systemic lupus erythematosus, several disease-modifying treatments for Alzheimer's disease, and motavizumab for prophylaxis of serious respiratory syncytial virus disease.

The declining trend has been a growing concern within the drug industry as well as among clinicians and drug regulators. When wrapping up his 10 years as chief of the EMA, Thomas Lönngren criticised the drug industry, saying that of the estimated US$85 billion spent globally each year on drug research and development (R&D), around $60 billion was wasted when one calculated how few new molecular entities were produced. He also pointed out that the industry failed to invest enough effort into developing drugs where there is the greatest need—for key and unmet areas of public health—such as infections with multidrug-resistant bacteria and disorders of the CNS.

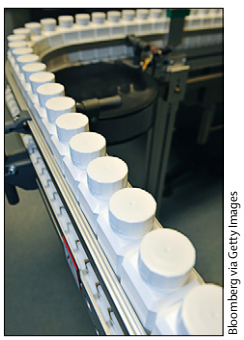
Despite ballooning research spending and great progress in science and biotechnology, why is there still an innovation deficit? Undoubtedly, drug discovery is a big challenge, as for every new drug that is approved on average $1 billion is spent on research, 10 years of development are required, and nine of every ten drugs fail. With the blockbuster pipeline drying up, increasing drug development costs, and higher regulatory standards for drug approval, innovation has become even more difficult.

It is unlikely that big drug companies will keep spending more highly on R&D. On the contrary, budgets are likely to be scaled back in the present high-cost, ever low-yield environment. As Andrew Witty, Chief Executive of GlaxoSmithKline, told *The Economist*, "shareholders are not prepared to see more money invested in R&D without tangible success. If anything, based on a rational allocation of capital, R&D should now be consuming less resource." To boost innovation and break the R&D bottleneck at a time when money is tight, perhaps the right question to ask is not how much investment is needed, but how can efficiency be improved by avoiding waste and failures?

One prescription is to transform the unsustainable R&D model. At present, too many steps are pursued by academia and industry without effective collaboration, which can lead to expensive mistakes. The failure of promising drugs for Alzheimer's treatment in clinical trials questioned the validity of a single potential drug target for this condition, and called for research into multiple disease targets. Another lesson learned is that companies should share their experiences to avoid repeating errors. As similar planning and methodological problems occur in different trials, more collaboration between drug companies and clinical researchers could lead to more standardised randomised trial protocols, reduced errors, and decreased costs. Indeed, big companies have realised the importance of cooperation, as partnerships with academics, biotechnology companies, and even competitors are being strengthened gradually. Merck, Eli Lilly, and Pfizer have planned a joint Asian Cancer Research Group that will help speed up research on new drugs to treat gastric and lung cancers in the region.

There are also other important roles in the drug discovery ecosystem, such as drug discovery by academics, which provides balance between the dominant drug companies' focus on the major diseases of affluence and unmet needs in the developing world. Moreover, the industry is dependent on universities' basic scientific research achievements to help fill the drug pipeline. What is missing at the academic level is a network of people with heterogeneous talents from a range of disciplines such as clinical pharmacology, cell biology, and genetics, who can work together to bridge the translational and interdisciplinary divides.

Finally, governments must ensure sufficient funding for research into new medicines, especially for curiosity-driven science. Basic research might not have an immediate effect on medical treatments, and because of the short-term nature of research based on academic review cycles and shareholder dividends it is always difficult to get adequate funding. However, history shows us that in many instances it is such "untargeted" research that has led to major scientific advances. ■ *The Lancet*



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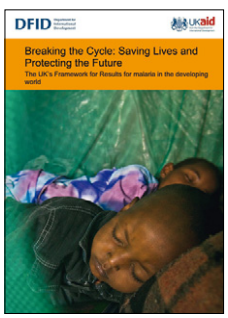
For the **EMA's monthly figures on centralised procedures for human medicines** see http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/12/WC500099566.pdf

For **Andrew Witty's comment in *The Economist*** see http://www.economist.com/node/17493432.

Two new year resolutions for DFID



DFID

For **Breaking the Cycle: Saving Lives and Protecting the Future** see http://www.dfid.gov.uk/Global-Issues/Emerging-policy/Malaria/

For **Choices for women: planned pregnancies, safe births and healthy newborns** see http://www.dfid.gov.uk/Global-Issues/Emerging-policy/Reproductive-maternal-newborn-health/

The UK's fiscally austere coalition government has—so far—sought to protect spending both on health and overseas aid. The budget for the Department for International Development (DFID) is expected to rise substantially from an annual £7·8 billion to £11·5 billion over the next 5 years. Two policy initiatives have now been launched, on malaria and on maternal and child health.

For malaria, the aspiration is to halve deaths from the disease in at least ten developing countries by 2014–15. Efforts will be concentrated on countries with a high disease burden, namely India, Burma, and 16 countries in sub-Saharan Africa. Up to £500 million is to be spent yearly by the end of the 5-year period (the UK's estimated spend on malaria activities in 2008–09 was £139 million, including contributions to the Global Fund and other agencies; total global spending on malaria reached US$1·94 billion in 2009). Investment will go not only to proven interventions such as bednets, artemisinin-combination therapy, and indoor residual spraying but also to development of services to reach poor and remote areas. There will be assessments in 2013 and at the end of the 5 years.

A 2009 review recommended an increase in DFID's spending on reproductive, maternal, and newborn health, with the ultimate goal of supporting progress towards Millennium Development Goals 4 and 5. The new strategy commits to a doubling of the UK's investment in women and children's health (over the period 2008–12, sustained thereafter until 2015). Specific aims include saving the lives of 50 000 women and 250 000 babies by promoting safe deliveries, and extending effective methods of family planning to 10 million more families, by 2015. Although details of budgets and priorities are yet to be agreed, again there will be monitoring of outcomes in 8–12 focus countries.

Sustained, targeted, and accountable investment by the UK in the health of people in developing countries is welcome. But before we can fully endorse the new DFID strategy, we need to know what is being cut to accommodate these new priorities. ■ *The Lancet*

Binayak Sen's conviction: a mockery of justice

AFP/Getty Images

See **Editorial** *Lancet* 2009; **373:** 1146

On Jan 4, the day this issue of *The Lancet* went to press, Binayak Sen should have been celebrating his 61st birthday. Instead, found guilty of treason and sedition by a court in the central Indian state of Chhattisgarh, Sen is facing the bleak prospect of a life behind bars. It is an inhumane sentence for a committed humanitarian, whose life before his imprisonment was devoted to improving the health and welfare of some of the most marginalised and poverty-stricken people in India—the Adivasi. This work led to Sen becoming the first Indian recipient of the Jonathan Mann award for Global Health and Human Rights in 2008.

From the outset the charges against Sen reeked of political motivation—a reaction to Sen's tireless documentation of human rights abuse at the hands of the state. He was accused, on the flimsiest of evidence, of acting as a courier for the imprisoned Maoist leader Narayan Sanyal. The subsequent trial, spanning more than 3 years, was Kafkaesque. Its conclusion is a travesty.

Reaction to the ruling was swift, with the Indian press unanimous in their criticism of the court's decision. Amnesty International described Sen as a prisoner of conscience, while a statement signed by over 80 prominent academics worldwide decried the sentence as savagery. *The Lancet* adds its voice to this chorus of condemnation.

In April, 2009, we called for the Indian Government to intervene in the case, and ensure that justice be done. An injustice can still be overturned by India's supreme court. If it is not, the already profound damage done to India's credentials as an upholder of human rights will be damaged for years to come. Where the state failed to provide for its poorest citizens, Sen stepped in to give them health care and to champion their rights. His reward: to be convicted under a section of the penal code first introduced by the British to quell political dissent, and later used to convict Mahatma Ghandi. On his conviction, Ghandi argued that the administration of the law had been "prostituted consciously or unconsciously for the benefit of the exploiter". The conviction of Binayak Sen shows that, in parts of modern India, precious little has changed. ■ *The Lancet*

Caution needed for country-specific cancer survival

In *The Lancet*, Michel Coleman and co-workers present changes in survival of patients with breast, colorectal, ovarian, and lung cancer in six countries (UK, Sweden, Norway, Australia, Canada, Denmark). The researchers used adequate data to examine trends in incidence, mortality, and survival from 1990 to 2007.[1] The merit of this paper is its ability to display relative survival together with incidence and mortality trends.

The paper opens by stating: "Survival is a key index of the overall effectiveness of health services in the management of patients with cancer." Effectiveness can be understood as the contributions of early cancer detection and of the quality of patients' management. However, the interpretation of survival data is a major challenge. The panel summarises factors that can influence the survival of patients with cancer. When countries are compared, because of the complexity and intricacy of factors influencing survival statistics (including the fact that health systems differ in many ways), many factors not associated with performance can influence variations in survival.

Administrative limitations in cancer registration have been suggested to explain the lower survival rates of patients with cancer in the UK; such limitations include registration of date of recurrence instead of date of diagnosis and absence of registration of some long-term survivors.[2] Such critiques have been challenged for the Scottish data,[3] which were not included in the UK data used by Coleman and co-workers. Furthermore, in Denmark, where cancer registration is compulsory and of high quality, survival statistics are similar to those observed in the UK. However, the large Thames Cancer Registry in England reported that the estimated completeness of case ascertainment in 1990–2001 was 85·0% for breast cancer and 87·8% for colorectal cancer.[4] In Finland, a country with longstanding compulsory cancer registration, these figures were 98·5% and 98·8%, respectively. Lack of ascertainment mainly concerns long-term survivors. Hence, even though cancer registration is constantly improving in the UK, one cannot dismiss that gaps in case ascertainment in England might be responsible for a proportion of the survival differences when comparisons are made with those countries having nearly complete case ascertainment, for example Sweden.

Survival differences could be due to differences in exposure to cancer risk factors. For instance, obesity is associated with breast cancers of worse prognosis that are less sensitive to treatment.[5] The prevalence of obesity in adult women around 2000 was 20% in the UK and 9% in Sweden,[6] a difference that might play a role in the dissimilarity in breast cancer survival.

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Adjustment of cancer survival statistics for stage at diagnosis usually leads to a substantial decrease in survival differences between areas,[7–9] indicating that variations in cancer stage are a factor of considerable variation in survival. Detection of a cancer at an earlier stage or when the primary tumour is still small could allow for more efficient treatment, often leading to mortality reduction and improved survival. Early detection might improve survival in the absence of any effect on mortality for two reasons. First, early detection could simply increase the time between diagnosis and death, without modifying the fatal outcome but increasing survival (lead-time bias). Second, earlier detection methods, such as mammography, often find slow–progressing

***Panel:* Factors that can influence cancer survival statistics**

Incidence-related factors

- Earlier detection of cancer from which patient will die (lead-time bias)
- Detection of non-life-threatening cancer (length-time bias and overdiagnosis)
- Detection of cancer precursor lesions (eg, CIN lesions of cervix, colorectal adenomas)

Cancer incidence data (cancer registries)

- Cancer definition (eg, classification used)
- Population coverage
- Completeness of cancer case ascertainment
  - Registration of newly diagnosed cases
  - Cases registered after death from cancer and unknown date of diagnosis (death certificate only)
  - Registration of cancer recurrence instead of cancer diagnosis

Patient-related factors

- Age*, sex*, genetic background
- Socioeconomic status, education
- Race, ethnic origin
- Comorbidity
- Mortality from other causes (competing causes of death)*

Risk factors (eg, environment, lifestyle, use of drugs)

- Population prevalence
- Influence on cancer incidence, on cancer mortality, or both

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Cancer-related factors
- Stage at diagnosis
- Anatomical site of cancer
- Cancer capacity to invade surrounding and distant tissues

Health-system factors
- Ability of early detection methods and screening programmes to prevent cancer occurrence and/or occurrence of advanced cancer
- Alertness of health professionals (attention to signs and symptoms possibly associated with cancer)
- Availability, access to, and quality of:
  - Diagnostic methods
  - Histological diagnosis
    - Classification of cancers
    - Classification of non-invasive cancer as invasive cancer
  - Treatment
  - Supportive care
  - Follow-up care

Organisational efficiency
- Speed and quality of work-up of positive early detection (screening) tests, clinical signs, and symptoms
- Referral to specialised services
- Health facility's patient load
- Multidisciplinarity

CIN=cervical intraepithelial neoplasia. *Factors controlled for with use of relative survival statistics.

organ-confined cancers, most of which would not have become clinically apparent and life-threatening (over-diagnosis).[10,11] Increased detection of indolent cancers will increase incidence without changing mortality, driving survival statistics towards higher values (length-time bias).[12,13] For instance, in 2000–07, the 5-year relative survival of Norwegian patients with breast cancer was greater than the rates of the UK and lower than that in Sweden in Coleman and colleagues' paper; however, in 2000, breast cancer mortality in Norway was close to that in Sweden and after 2003, it was lower. Invitation to mammography screening started about 12 years later in Norway than in Sweden,[14,15] possibly indicating that the higher survival in Sweden could be due to earlier and more intense screening, resulting in greater screen-detection of small non-life-threatening cancers. To establish how early cancer incidence contributed to differences in survival, stage-specific incidence rates need to be compared.

The comparison between Norway and Sweden indicates that survival is not always consistent with incidence and mortality. A further example is the 5-year survival of patients with colorectal cancer, which was 15% lower in the UK than in Sweden in 1995–99. This difference decreased slightly to 11% in 2005–07 but it remained the worst among the six countries. In 1985, colorectal cancer mortality was 36% higher in the UK than in Sweden. After a constant drop, this figure reduced to 1% in 2007 and was lower than mortality observed in the four other countries. Incidence curves remained broadly parallel. The quasi-constancy of the differences in 5-year survival data does not at all reflect the kinetic of mortality trends. Even more than for breast cancer, colorectal cancer survival statistics depict a demoralising stagnating lack of effectiveness in the UK health system, while mortality data provide strong evidence that efforts deployed over the past two decades are paying off. Discussion of reasons underlying the contrast between mortality and survival is beyond the scope of this commentary and would require additional data. However, colorectal cancer data show that, contrary to what is claimed by Coleman and co-workers, mortality is not a function of both incidence and survival.

To compare possible determinants of survival between countries, high-resolution studies retrospectively collect clinical information on stage at diagnosis and on treatment.[16] To what extent these studies in their current design will help to explain differences in survival is still unclear. For instance, the largest European population-based study collecting information on stage, diagnostic procedures, and treatment for patients with breast cancer diagnosed mainly in 1996–98 showed that Swedish patients received less radiotherapy and less chemotherapy than did patients from other countries;[17] in particular, older Swedish patients were largely undertreated. These findings are surprising, in view of the high survival of Swedish patients with breast cancer. By contrast, Allemani and colleagues reported data that correlates well with the observation that, from 1989 to 2006, breast cancer mortality in Sweden only moderately declined, especially in older patients.[18]

When factors likely to influence survival statistics are similar across medical facilities, or when data on these factors are available, survival statistics might bring insights into the respective roles of detection and treatment.[19] When comparing countries, however, as certain studies have started to do,[20,21] country-specific cancer survival data should always be considered together with both incidence and mortality data, and one should always consider the

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