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NEWS...NEWS...NEWS

Movement of staff in an enlarged EU

Few health professionals moved from the new to the original Member States in the first months after enlargement of the European Union (EU), according to Professor James Buchan (Queen Margaret University College, Edinburgh, UK). However, he predicted increasing levels of migration over the coming months and years.

''It is not a level playing field,'' he told delegates at a conference on *The Health Implications of an Expanded EU: threats or opportunities for the UK and Europe?* (Royal College of Physicians, London, 10th March, 2005): ''Countries have very different things on offer.''

A survey of physicians in Lithuania, Hungary, Poland and the Czech Republic conducted in 2003 (*Open Society*, 2003) found that almost 10% of physicians in Hungary and the Czech Republic were seriously considering a move, and had taken active steps to find out more about the procedure. Many more – 50% of doctors in Czech Republic, and 25% of those in Lithuania – had given some consideration to working abroad.

The UK has a long history of employing foreign doctors and has traditionally relied on many from Ireland and the Indian subcontinent. However, current pledges by the UK Government to increase the workforce have led to mechanisms to encourage doctors to come. Among nurses, there has been a more pronounced influx since 1998, mainly from outside the EU: the Philippines, South Africa and India providing most nurses.

The key question, Professor Buchan said, is what happens at an aggregate level if large numbers of health professionals move. The accession states typically have fewer doctors per head of population, but the difference is not extreme. The situation for nurses is much more marked. In 2001, Finland had 2171 nurses per 100,000 population; Hungary in 2000 had 281.

The effect of recruitment is starkly apparent in regard to sub-Saharan Africa. Malawi, for instance, can afford to train 100 nurses per year, and does so. In the last few years 60–70 per year have registered for work in the UK. ''The UK alone has accounted for nearly all the new nurses that Malawi can train in a year,'' Professor Buchan said.

The situation is complex, and requires a balance between the freedom of individuals to move to better their own circumstances and the effect at aggregate level. The World Health Assembly has come up with a protocol to encourage ethical international recruitment, and a Commonwealth Coalition has been signed by 22 countries – not including England, Australia or Canada. ''The 3 major recruiters have backed off,'' said Professor Buchan.

Younger health professionals are most likely to move, and their loss has most impact on smaller countries and specialties, such as anaesthesia. ''Do we allow this to happen? Or moderate and codify it?'' He said the World Health Assembly is pushing the issue higher up the agenda, aiming to reduce the negative side of staff mobility.

Health gains in Poland

An unexpected and dramatic improvement in health indicators occurred among States preparing for accession to the European Union (EU) in the 1990s, according to Professor Witold Zatoski (Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland). At the same conference, he said health gains had been seen in cancer, cardiovascular disease and infant mortality.

Changes in life expectancy in Poland rose by 4.1 years among men and 3.1 years among women during the 1990s, following 30 years of stagnation. The rising trend in cancer mortality among men was halted, and mortality from lung cancer among men started to decrease. Cardiovascular mortality fell by about 30% throughout the 1990s.

Potential reasons for the health gains include a reduction in smoking. The Polish tobacco control law came into force in 1995 and smoking declined among men of all ages, and among older and younger women (excluding those in their 40s and 50s).

Dietary changes included an increased consumption of vegetable oils in the 1990s, and decreased consumption of butter. Since the early 1990s, Poland has had a higher ratio of dietary polyunsaturated/saturated fats than Britain. Twice as much exotic fruit was consumed in Poland in the 1990s as in the previous decade.

Professor Zatoski said there could be ''many explanations'' for the improvements seen.

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New outcome predictor for pancreatic cancer

Up-regulation of the S100A6 protein may be an early event in the development of pancreatic cancer, researchers say. Furthermore, elevated levels of the protein in cell nuclei could affect clinical outcome.

UK and German researchers analysed the expression of S100A6, also known as calcyclin, in benign, malignant and pre-malignant pancreatic ductal cells (*Cancer Research* 2005, **65**, 3218-3225). Staining was more intense in the 60 malignant cell samples than in the 32 benign cell samples. In malignant cells, staining was higher in the nucleus than in the cytoplasm.

Univariate analysis revealed a significant decrease in survival time for patients with high levels of nuclear, but not cytoplasmic, calcyclin. No association was found between nuclear calcyclin expression and other variables, including tumour size or grade, nodal metastases, resection margin and vascular invasion.

Nodal metastases and resection margin involvement were also associated with poor survival, but multivariate analysis suggested that nuclear calcyclin is a significant independent indicator of survival.

Among 96 samples of pancreatic intraepithelial neoplasms (PanIN) taken from 46 patients, the 1a lesions showed a general absence of calcyclin staining. There was a progressive increase in the proportion of positively stained panINs with increasing PanIN grade, in particular, an increase in the frequency and intensity of nuclear staining.

Researcher Dr Eithne Costello (Cancer Research UK Clinical Centre, London, UK) said, ''We do not know whether calcyclin is a marker for pancreatic cancer growth, or whether it is an actual underlying cause promoting the growth and spread of pancreatic cancer.'' She said the identification of the protein is an important step in understanding pancreatic cancer. Its role in pancreatic cancer and its contribution to the rapid progression of the disease now need to be determined.

Anti-tumour effects of immunosuppressant drug

Kaposi's sarcoma, often diagnosed in kidney transplant recipients, may be eliminated by the same drug that helps prevent rejection of the transplanted organ, Italian researchers say (*N Engl J Med* 2005, **352**, 13:25–31).

In the study, 15 patients taking a cyclosporine regimen to prevent organ rejection were diagnosed with Kaposi's sarcoma. Within 3 months of switching these patients to the immunosuppressive drug sirolimus (Rapamune), all were shown to be completely free of the cancer both clinically and histologically.

Kaposi's sarcoma is usually restricted to the skin in transplant recipients and, depending on the form and extent of the lesions, can be fatal. Transplant recipients are 500 times more likely than the general population to develop the condition, probably because of the immunosuppressants. The usual approach is to reduce or even discontinue immunosuppression, which may cause the skin lesions to regress but also carries a risk of organ rejection.

The patients in the study were receiving cyclosporine and mycophenolate mofeil. On diagnosis of Kaposi's sarcoma, this treatment was stopped and patients given sirolimus therapy. Within a month, the cutaneous lesions began to disappear in 12 of the 15 patients; after 3 months, all patients were clear. There were no episodes of acute rejection and 6 months on from the end of the study, no return of Kaposi's sarcoma in the patients treated with sirolimus.

In their report, the researchers note increasing evidence that sirolimus has an anti-neoplastic action independent of its immunosuppressive effect. The anti-tumour activity could be due to its anti-angiogenic effect, mediated by a reduction in VEGF and its Flk-1/KDR receptor on endothelial cells. This is likely to be important in Kaposi's sarcoma, given the pivotal role of the VEGF system in its pathogenesis. However, several enzymes along the signalling pathway inhibited by sirolimus play a role in the development and progression of different cancers.

One of the researchers, Professor Francesco Paolo Schena (Bari University, Italy) said, ''The new discovery means that we have an alternative immunosuppressive therapy to offer our patients, which protects their transplanted kidney from rejection and inhibits the progression of this type of skin cancer.''

The report concludes, ''This dual role of the drug may prove important in other situations in which transplant recipients are at high risk for tumour recurrence or primary cancer.''

New mutation in myeloproliferative disorders

Swiss and Italian researchers have identified a mutation which appears in a high proportion of patients with myeloproliferative disorders (*N Engl J Med* 2005, **352**, 1779–1790). The mutation could form the basis for a new molecular classification of the disorders, and is also a potential target for the development of new therapies.

The researchers identified a region (9pLOH) including the Janus kinase (*JAK2*) gene in 244 patients with myeloproliferative disorders. In patients with 9pLOH, *JAK2* had a homozygous guanine-to-thymine transversion, causing phenylalanine to be substituted for valine at position 617 of *JAK2* (V617F).

Of 128 patients with polycythemia vera, 83 (65%) had V617F. The same mutation was found in 57% of patients with myelofibrosis and in 23% of patients with essential thrombocythemia. It was found only in haemopoietic cells and must be an acquired somatic mutation.

An accompanying editorial (*N Engl J Med* 2005, **352**, 1744–1746) noted that, normally, such consistent findings still require independent confirmation, but ''such confirmation is already available from both sides of the Atlantic. Research groups in Paris, France; Boston, USA; and Cambridge, UK have identified the same mutation in patients with myeloproliferative disorders, albeit with varying frequency. ''There can be little doubt that the observation is real and likely to be of major importance,'' the editorial notes.

Questions remain, such as how the mutation contributes to the pathogenesis of the disorders, and how the same mutation could cause 3 more or less clinically distinct entities. But the editorial concludes, ''At the very least, this newly identified molecular lesion will form the basis of a new classification. But it seems likely that patients will also eventually derive substantial benefit from the discovery.''

EUROFILE

Time for European action on public health?

The European Union (EU) has had little influence in public health to date, and limited funds for implementing initiatives. This is set to change, however, with the greater emphasis on health in the new constitution, coinciding with the enlargement of Europe.

There is a long way to go for the EU to become an effective force, according to Dr. Bernard Merkel, head of unit at the European Commission (EC)'s Health and Consumer Protection Directorate-General (DG): ''If you look at current treaties, our role and powers in terms of public health are very limited indeed''. At a conference on *The Health Implications of an Expanded EU: threats or opportunities for the UK and Europe?* (Royal College of Physicians, London, 10th March, 2005), he said, ''The EU is simply a construct of various Member States and it is very much the Member States' governments who decide what the EU will do and what resources we will have to do it.''

It is ''not an accident'' that Europe has such a minor role in public health, he said. ''The idea of the EU having any role at all in health is a relatively recent notion''. Europe's first foray into health was in cancer, prompted by President Mitterrand's illness, and this was followed by a European AIDS programme. Health was specifically referred to in the Maastricht treaty in 1992, but national Governments have remained reluctant to allow the EU any real influence on their countries' health systems.

The new European Constitution, however, ''represents quite a fundamental shift and development'' in

EUROPE'S ROLE IN PUBLIC HEALTH IS VERY LIMITED

health, Dr Merkel said. It describes ''a sense of well-being'' of citizens – a broad definition of health – as a fundamental aim. It has been accompanied by increases in funding, ''but we are starting from a very low base,'' he said.

For example, a Public Health Centre in Stockholm is to have an additional 70 staff which is to be welcomed, but it is tiny compared with the 9000 working at the Centers for Disease Control (CDC) in the US. European public health is small in national terms, and even in relation to the overall EU budget: DG Research is 100 times the size of DG Health, though within the research budget there are considerable funds for health research.

If DG Health has a limited role in promoting active policies, it is able to take legislative measures. Even here, though, legislation which impacts on

DG RESEARCH IS 100X THE SIZE OF DG HEALTH

health – such as the European Working Time Directive (EWTD) – is usually taken not from the point of view of promoting health, but to improve the way the single market works. Regulation of health products is still regarded as an industrial issue.

At the same meeting, Professor Martin McKee (London School of Hygiene and Tropical Medicine, UK) suggested that the new member states may be more willing than the original 15 to bring health services explicitly within the scope of EU law, so that the health consequences can be considered. They may also be more inclined to strengthen further the EU's role in public health. ''The 10 accession countries have a say in what happens in Europe and in all European member states,'' he said, ''But they do need to make their voices heard.''

The new member states are potentially more vulnerable to the challenges of an expanded Europe, he said. Under the Communist regime, labour was cheap and the accession countries have inherited weak health infrastructures. They are now likely to lose health professionals to wealthier countries, and may suffer disproportionately from EU laws such as the EWTD.

For the present, a European public health strategy is being developed following a consultation in 2004 involving Member States, health organisations and non-governmental organisations. The main points to come out of it were:

- A need for a coherent public health strategy, which is not contradicted by other EU policies. For example, anti-tobacco policies are undermined by a common agricultural policy which continues to subsidise tobacco farming.
- DG-Health should be more proactive in health promotion, disease prevention and risk analysis. It should consider lifestyle approaches and interventions in childhood, in ageing populations and so on.
- DG-Health should be less bureaucratic and less inclined to working in a top-down manner. More participation and consultation is required and over-ambitious projects without the resources to back them up should not be launched.

As a result of the consultation, a new strategy document is being drawn up and is due to be launched soon. This will cover the next EU financial budgeting cycle, from 2007 to 2013. Health protection will be the key feature, Dr. Merkel said, with a focus on surveillance and on specific diseases which play a role in the overall disease burden in Europe. One aim will be to help national health systems provide more and better health information, a key to which is compatibility and consistency of data collection. There is a need to work on improving civil society participation, to help develop nascent organisations, and a need to work much more closely with the World Health Organisation and other international agencies.

Professor McKee said that the EU will enlarge further and the future will be different from the present. ''There are opportunities but there are also threats. We must seize the opportunities,'' he said. ''If we don't, we will frankly have nobody but ourselves to blame.''

Helen Saul

Malaria gene linked to prostate cancer incidence

A study suggesting a link between a gene mutation that protects against malaria and the high incidence of prostate cancer in African-American men was presented by Alex Lentsch (University of Cincinnati College of Medicine, OH, USA) on April 5, 2005, at the American Society of Investigative Pathology sessions at Experimental Biology 2005, San Diego, CA.

In the USA, prostate cancer has a 60% greater incidence and a twofold higher mortality in African-American men compared with white men. Lentsch noted that 70% of African-American men lack expression of the Duffy antigen receptor complex (DARC), and investigated whether this deficiency could represent an epigenetic factor that predisposes African–American men to prostate cancer.

DARC is expressed on erythrocytes and vascular endothelial cells. It binds to angiogenic chemokines released by prostate tumours and is the erythrocyte receptor for malarial parasites. A genetic mutation in *DARC* evolved long ago in African–American men as natural selection against malaria infection.

''The study results confirm that DARC on red blood cells binds and clears angiogenic chemokines secreted by prostate cancer cells in culture and that this clearance reduces the ability of the cancer cell secretions to attract vascular endothelial cells'', claims Lentsch. ''Gene deletion of DARC results in much faster tumour growth associated with increased intratumour levels of angiogenic chemokines'', he adds.

John Carpten (Translational Genomics Research Institute, Phoenix, AZ, USA) and Rick Kittles (Ohio State University, Columbus, OH, USA) caution that the findings could be a result of population stratification'', but are worth substantial follow-up''. Testing for DARC on erythrocytes in people at high risk of prostate cancer could provide information about tumour aggressiveness.

''We now plan to investigate if antichemokine treatments could effectively slow the development and progression of prostate cancer'', concludes Lentsch.

Laura Thomas

This story originally appeared in Lancet Oncol 2005, **6**, 266.

High-risk women 'reluctant' to take tamoxifen

Fewer than one in five US women who were considered eligible to take tamoxifen, agreed to do so after being told of its risks and benefits, a study found. Concerns over the drug's adverse effects were the primary reason for refusal.

Researchers from the University of California, USA, interviewed 255 women with significant risk factors for breast cancer (*Cancer 2005 DOI: 10.1002/cncr.20981*). The interview included an evidence-based education session about the risks and benefits of tamoxifen and a follow-up evaluation of their knowledge about the drug and about their decision.

Women seriously overestimated their breast cancer risk, perceiving they were at 10 times their actual risk. Even so, 70.9% described their risk as low or average.

After the education session, only 17.6% of women over 50 who were potentially eligible to take it, agreed to do so. Very few changed their minds as a result of the educational session.

The decision to use or not use tamoxifen was independent of actual breast cancer risk. Concerns about adverse effects or low self-perceived breast cancer risk were significant reasons for not using tamoxifen.

Those from low socio-economic backgrounds and those most confident of its benefits in reducing breast cancer risk and osteoporotic fractures were most inclined to take tamoxifen.

''Many high risk women are unwilling to consider tamoxifen even with extensive education about its potential benefits and harms,'' the authors conclude.

Approval for capecitabine...

The European authorities have approved capecitabine (Xeloda) for use as an adjuvant treatment in patients with colon cancer. The decision follows results (*Proc Am Soc Clin Onc, JCO* 2004; *22: 14S # 3578*) from the phase III X-ACT trial (Xeloda in Adjuvant Colon Cancer Therapy).

The X-ACT trial demonstrated that capecitabine is at least as effective as the standard treatment – intravenous 5-FU/LV – in terms of disease-free survival. Further, it is an oral treatment and patients receiving capecitabine needed an average of 8 hospital visits, compared with 30 visits for those treated with 5-FU-LV.

Capecitabine is already approved for use in patients with advanced colorectal or breast cancer.

... and positive opinion for temozolomide

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) has issued a positive opinion recommending approval of temozolomide (Temodal) for first-line use in the treatment of patients with newly-diagnosed glioblastoma multiforme (GBM). It is currently approved in the European Union (EU) for the treatment of patients with malignant glioma such as GBM or anaplastic astrocytoma, which has recurred or progressed after standard therapy.

The positive opinion is based largely on efficacy and safety data from a Phase III study conducted by the European Organisation for Research and Treatment of Cancer EORTC) and the National Cancer Institute of Canada (NCIC). It included 573 patients with newly-diagnosed GBM and found a significant improvement in overall survival among those treated with temozolomide plus radiotherapy, compared with those who received radiotherapy alone (*NEJM* 2005, **352**, 987–996).

Temozolomide is an oral, cytotoxic alkylating agent. The most commonly observed adverse events associated with its use included decreased appetite, headache, constipation, nausea, vomiting, hair loss, rash, convulsions and fatigue. Low white blood cell and platelet count were also observed.

PODIUM

Towards grass-roots harmonisation

Jacques Demotes-Mainard is a neurologist and Professor of Cell Biology at University of Bordeaux Medical College, France. Since 2001, he has been Director of the Centre d'Investigation Clinique (CIC), INSERM, a hospital-based academic clinical research facility. He is also the co-ordinator of the European Clinical Research Infrastructures Network (ECRIN).

Professor Jacques Demotes-Mainard

What is ECRIN?

ECRIN is designed to promote high quality standards in European clinical research, and a bottom-up harmonisation of training, tools and practice. It is funded by the European Union (EU)'s 6th Framework Programme and is based on the interconnection of national networks for clinical research. The consortium currently includes 8 national networks in 6 countries: Denmark, France, Germany, Italy, Spain and Sweden.

When was it set up?

The first meetings were held in 2003, and our first proposal was accepted by the EU in April 2004. Since then, we have held meetings in each of the countries involved and have described the current state of clinical research network infrastructure. In February 2005, we held a meeting in Brussels, *Towards integration of clinical research infrastructure in Europe*, which was an opportunity to compare networks, look at the bottlenecks in European clinical research and set up 3 working groups.

What will the working groups do?

The first working group is devoted to the ethics and regulation of clinical trials, and adverse event reporting. The second will look at methodology, data monitoring and management. And the third at operating procedures, audits devoted to ensuring the quality of clinical trials. Once they've reported we will look at communicating their findings to academic scientists and researchers, and to industry.

We are also planning to develop a set of services to support the sponsor of transnational clinical trials. The services will be offered through ECRIN at a national level and will help bridge the fragmented organisation of European clinical research.

What sort of services will be offered?

A representative in each country will facilitate the interaction with local ethics committees, easing problems with language and with the process of ethical review. Interaction with competent authorities is complicated because of the divergence in local regulations governing Clinical Trials, especially those which fall outside the scope of the Directive, such as radiotherapy or surgical trials. We'll help with this interaction, and with the reporting of adverse events and pharmacovigilance. Another service will facilitate dispensing and distribution of the drug under study. Further, we'll provide help in organising the movement of biological samples across borders; and in data management and data monitoring, which has to be performed in the local language.

It sounds as though ECRIN is attempting to repair some of the damage caused by the Clinical Trials Directive

The Directive has had an impact on the services we intend to offer, but many of the problems associated with conducting clinical research in Europe were apparent before the Directive came in. The Directive was an attempt to harmonise procedures, from the top down, but the national laws written to implement it differ and there is a need for harmonisation at grass roots level. It is now very difficult to perform clinical trials in Europe.

What place will cancer research have within ECRIN?

ECRIN is a non-specialist infrastructure which will be able to support studies in any medical field. Individual centres connected by the network may of course be specialised but the network itself is non-specialist. Cancer is a special case in that it is the only field which already has its own clinical trials organisation, EORTC. We don't want to reinvent EORTC, but we are in contact with the organisation, which is supporting us. Our model is different, in that we are not looking to have a centralised database, or headquarters, and we will not ourselves sponsor trials. Instead, ECRIN is a network, which will support trial sponsors – from academia or industry – and allow clinical research which crosses borders to continue.

What is ECRIN's role in the new Member States?

We have contacts in the individual countries. The problem is that, though they have networks of investigators, there are few centres with the infrastructure for conducting multicentre clinical research. Our first step within these countries is to stimulate the development of national networks for clinical trials in all medical specialties. Then we can include them within ECRIN. We will help them to develop these networks, and by the time this happens, the standard operating procedures will be in place so that they will become effective very rapidly. The idea of creating infrastructure networks is recent – they were only developed in France and Germany in 2000–2001 – but it has not been developed in the new Member States, and many large clinical trials are moving there.

Why isn't the UK involved in ECRIN?

Clinical trials in the UK are organised within specialty-specific networks: there's a cancer network, a paediatric network, an HIV network and so on. ECRIN's services are for studies in any field. However, a clinical research network co-ordination centre is being developed to coordinate all the specialty-specific networks. We hope this will be a good way for us to connect to the UK.

What is the next step?

We're waiting for EU Commissioner's decision on our second application, to see whether all or parts of our proposal have been accepted. We should know by July 2005, but our working groups are already up and running.

For further information, see www.ecrin.org