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A boost to communications in Europe

A new website is to play a key role in improving cancer communications throughout Europe. The website, *www.eurocancercoms.eu*, is funded by a Euro 1.2 million grant from the European Commission's FP7 programme, and is to be at the heart of the drive to establish a single, efficient network for Europe (*see PODIUM with Professor Gordon McVie, EJC News, Issue 11, 2009*).

Eurocancercoms was initiated by the European Institute of Oncology and Professor Umberto Veronesi is the principal investigator. It will be led by ECCO and ecancermedicalscience, with Professor Richard Sullivan, head of the European Cancer Managers' Forum, as project manager.

Professor Eggermont, president of ECCO, said, 'Cancer survival is unacceptably variable in different European countries. A previous study (EUROCAN+PLUS) identified poor communication between all those involved in cancer care as one of the main reasons for these poor outcomes. Eurocancercoms aims to address these problems by creating a 'one-stop shop' for the whole cancer community from scientists to patients.'

Eurocancercoms will look at issues surrounding the communication and dissemination of cancer information across Europe, identify bottlenecks and suggest solutions. It will:

- examine the flow of information between basic scientists and other healthcare professionals
- identify barriers to successful dissemination of cancer research results
- establish searchable databases for clinical trials and guidelines and make them available to all involved in cancer care, including patients
- use internet-based technologies to link the whole cancer community
- develop policies for promoting dissemination of cancer science across Europe.

Professor Sullivan said the project is 'a marvellous opportunity' to understand the key issues in cancer communication 'and to create novel ways of getting information out to both the professionals and the patients'.

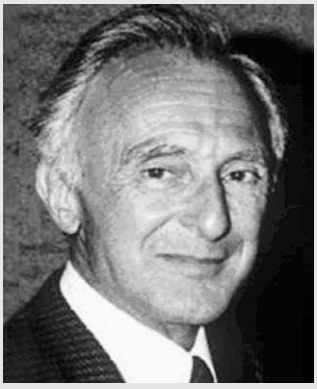
'We need to understand 21st century communications, particularly electronic communications. For instance, at the moment the way we communicate with patients is still the classical method of putting leaflets in doctors' surgeries; but patients are not picking these up any more; they are going online and finding information on the web and through social networking sites.

'People are changing and electronic resources are the future. We are working in a different world and the way that we work has to reflect this.'

Cancer, the environment, and a (critical) friend remembered

A new series of conferences on environmental causes of cancer has been set up in honour of Dr Lorenzo Tomatis, former director of the International Agency for Research on Cancer (IARC), who died in September, 2007. The range of subjects covered at the inaugural meeting (Turin, Italy, June 4–5, 2009) – and the resultant debate – reflected his wide influence on the field.

There were presentations on occupational cancer, childhood cancer, nutrition, cancer in developing countries and prevention. 'What I found most remarkable about this conference was that Lorenzo Tomatis seemed to be there all the time,' said delegate Professor Lucio Luzzatto (Instituto Toscano Tumori, Firenze, Italy). Most speakers 'seemed implicitly to ask themselves what he would have had to say about the latest set of results or about the next research plan.'



Dr Lorenzo Tomatis

Professor Paolo Vineis (Imperial College London, UK) who, along with Professor Rodolfo Saracci (formerly at IARC, Lyons, France), co-ordinated the conference, said that even the keynote

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Cross-protection from HPV vaccine

An international phase III trial found that the Cervarix vaccine against human papillomavirus (HPV) provided significant cross-protection against pre-cancerous lesions other than those containing HPV types 16 and/or 18.

The study, HPV 008 PATRICIA (Papilloma Trial Cervical cancer in young Adults) involved 18,644 women aged between 15 and 25 years from countries across Europe, Asia-Pacific and Latin and North America. They received either Cervarix or a control hepatitis A vaccine.

In women who complied with the trial protocol (87% of the sample), the vaccine provided 92.9% protection against pre-cancerous cervical intraepithelial neoplasia (CIN) 2+ associated with HPV 16 or 18. (*Lancet 2009; doi:10.10.1016/S0140-6736(09)61248-4*).

The vaccine also provided significant cross-protection against pre-cancerous lesions not containing HPV types 16 and/or 18. The additional efficacy could translate into approximately 11–16% extra protection against cervical cancer, the researchers said, with the effect mainly driven by protection against HPV types 31, 33 and 45.

Lead author Professor Jorma Paavonen (University of Helsinki, Finland) said, 'The results re-affirm confidence in vaccination as a primary preventative measure against cervical cancer when use alongside screening.'

A commentary, 'HPV vaccine for all' went further, suggesting that the current targets for vaccination – girls and young women aged 11–26 years – are too small a subgroup to limit the spread of the virus: 'The only efficient way to stop the virus is to also vaccinate the other half of the sexually active population: boys and men.

'The goal to eradicate sexually transmitted carcinogenic viruses can be jointly carried by women and men, and could be accomplished within a few decades,' it concluded (*Lancet 2009; doi: 10.10.1016/S0140-6736(09)61247-2*).

Mammography: 'a close call'

Mammography is one of medicine's close calls, 'a delicate balance between benefits and harms', according to Professor Gilbert Welch (Dartmouth Institute for Health Policy and Clinical Research, Vermont, USA). Writing in response to a paper which found that one in three screen-detected cancers is over-diagnosed, he said that different people in the same situation 'might reasonably make different choices'.

'No right answer exists, instead it is a personal choice,' he said (*doi:10.1136/bmj.b1425*).

The systematic review was carried out by Karsten Jørgensen and Peter Gøtzche (Nordic Cochrane Centre), and examined data from the UK, Canada, Australia, Sweden and Norway. It covered 7 years before screening, and 7 years after screening was fully implemented in each country.

The review found an increase in incidence of breast cancer closely related to the introduction of screening. Little of this increase was compensated for by a drop in incidence among older, previously screened women. The review estimated a rate of over-diagnosis of 52%, meaning that this proportion of cancers would have remained dormant, regressed, or grown so slowly that the woman died of other causes before it caused symptoms (*doi:10.1136/bmj.b2587*).

'NO RIGHT ANSWER EXISTS, INSTEAD IT IS A PERSONAL CHOICE'

Professor Welch suggested that the information that would influence most women's choice would be the trade-off between the number of deaths from breast cancer avoided and the number of cancers over-diagnosed. Estimates vary between a ratio of one death avoided to 2 women over-diagnosed; up to a ratio of one to 10. Improvements in the precision of these estimates 'are sorely needed', he said.

'THE TIME HAS COME FOR A RANDOMISED CONTROLLED TRIAL TO TEST HIGHER THRESHOLDS'

Furthermore, he said that over-diagnosis is a function of the mammographer's threshold to recommend biopsy. 'The time has come for a randomised controlled trial to test higher thresholds, such as only recommending biopsy for breast masses larger than a certain size,' he concluded.

Racial disparities in survival

Black women diagnosed with breast cancer have a greater chance of dying from the disease than white women, US researchers say (*J Natl Cancer Inst 2009;101:993–1000*).

Using the Surveillance, Epidemiology, and End Results (SEER) program, they investigated 250,000 diagnosed between 1990 and 2003. They found a statistically higher hazard of death in black, compared to white women, especially in the first few years after diagnosis.

'Greater emphasis should be placed on identifying the reasons for these increased hazards among black women and on developing new therapeutic approaches to address this disparity,' they wrote.

Another study in the same issue (*J Natl Cancer Inst 2009;101:984–92*) found that even when African American patients received the same care as all other patients their survival rates were lower for breast, prostate and ovarian cancers. They were equivalent for other major cancers.

The findings suggest that the survival gap is most likely to be due to an interaction of tumour biology, hormonal environment and inherited variations.

'Taken together, the two studies and others do not suggest that blacks have a different kind of breast cancer, but rather that there are multiple kinds of breast cancer and a higher proportion of black breast cancer patients have the worst kind,' an accompanying editorial stated (*J Natl Cancer Inst 2009;101:970–1*).

Cancer, the environment, and a friend remembered... *(continued from page one)*

address was provocative when the speaker, Professor John Cairns (Oxford University, UK), suggested that almost nothing is known about the mechanisms of carcinogenesis.

'There was disagreement, which is good for a scientific conference. When there's too much agreement it means that the audience aren't personally involved,' Vineis said. 'It was a lively event; Lorenzo would have enjoyed it.'

Tomatis was born in Sassoferrato, Italy in 1929, and qualified in medicine at the University of Turin. A few years later, he moved to work at Chicago Medical School with Dr Phillipe Shubik – a leader in the field of experimental chemical carcinogenesis – and started a line of research that he fully developed in the late 1950s and 1960s.

Professor Paolo Vineis

He and his group administered nitroso-compounds to rats and mice and noted the increased frequency of tumours in their offspring. 'This was pioneering work,' said Vineis. 'It meant that the effect of chemical exposure can be passed on to successive generations; it is important in public health.'

Trans-generational research did not take off initially, lying relatively dormant for years. Vineis: 'It has become fashionable now because of some interesting experiments in epigenetics. Researchers are showing that dietary differences can lead to epigenetic changes in offspring; that diet may alter the functionality, not the structure, of DNA. This is of course different from mutations induced with chemical carcinogens.'

Tomatis, however, continued the broad theme of this work on returning to Europe in 1967 to join IARC, where he set up the chemical carcinogenesis unit. 'Experiments in toxicology, predicting the effects of chemicals on humans, led to strict measures in factories about many exposures, ranging from aromatic amines to vinyl chloride. Overall, I believe these experiments prevented many thousands of cancers,' said Vineis.

Tomatis will be most widely remembered for setting up IARC's distinguished Monograph series which grew out of his Programme on the Evaluation of Carcinogenic Risks. The first was published in 1972. 'The Monographs are not original experimental work; they are systematic evaluation of existing research literature by working groups. The 'Cochrane collaboration' does something similar but the Monographs pre-date it by nearly 30 years,' Vineis said. Saracci added: 'The Monographs represent an early example of the now current 'evidence-based' approach in medicine and public health. A salient feature is that all available evidence, from experimental and epidemiological studies, is critically scrutinised and contributes to the overall evaluation of risk for humans.'

'The Monographs are universally regarded as the ultimate authority on their individual topics', said Luzzatto. 'Probably never has a single person – namely Tomatis himself – through his scientific rigour, his incredible dedication, and his unique ability to catalyse whenever possible consensus on a sound scientific ground, contributed so much to a successful venture of this nature.'

As director of IARC from 1982 to 1993, Tomatis continued to champion the Monograph series but was influential in diverse fields. He was sensitive to the problems of developing countries, and, for example, set up the Gambia Hepatitis Intervention Study, involving a countrywide hepatitis vaccination of all newborn children and a cancer registration scheme. It will allow evaluation of the effectiveness of vaccination in preventing primary liver cancer.

Another interest was social inequalities in developed countries. 'He was very worried about the lower survival among lower social classes,' said Vineis. 'He felt that IARC should play a role in identifying inequalities and in developing a strategy to address them.'

Professor Rodolfo Saracci

Beyond his academic work, Tomatis was a published novelist in Italy. His first novel, *Il Laboratorio (The Laboratory)*, was based on his research activities and was, Vineis says, extremely critical of Italian universities. 'It was also funny; he described characters at the university with much humour.'

He wrote several more novels, and a collection of short stories was published after his death. In keeping with his own scientific integrity, Vineis said, some of the stories strike a more serious note, taking on topics such as conflicts of interest and attempts by the chemical industry to influence the interpretation of data in IARC Monographs. 'Tomatis was himself acutely aware of how economic and social forces influence research,' Saracci said. He 'thought that, as there is no good scientific experiment without specification and control of conditions, so there cannot be good science without a keen reflection on and control of the societal factors that condition its practice. Only with this premise are scientists able to maintain the independence of their research'.

As the Turin conference ended on an upbeat note, Saracci said that Tomatis would probably have been characteristically low-key in response. 'Lorenzo would have said the meeting was fine but perhaps next time we can do even better, and – at any rate – he would be happy to attend it'.

The Lorenzo Tomatis Conference on Environment and Cancer is expected to become a biannual event. It aims to bring together all those involved in cancer research, to foster communication between different specialities and groups, and to encourage researchers to take a broad view of the questions they are addressing.

Is paperwork suffocating British clinical research?

Concerns are being raised by a growing number of British academics that bureaucratic overload is stifling their ability to undertake clinical research, compromising the future of this activity in the UK, and ultimately doing patients a disservice.

Researchers complain that UK interpretation of the European Clinical Trials Directive (ECTD) has led to the requirement of a detailed protocol (which might reach 100 pages in length) and the answering of over 40 questions on a form spanning 28 pages. An Investigative Medicinal Product Dossier, which might also be 100 pages long, is also required to detail the stability and toxicology of the product to be tested. If the product is to be used in humans for the first time, stability and toxicology studies are necessary from independent laboratories. Even low-risk clinical research, such as imaging trials involving radio nucleotides, must go through the same channels. Many research groups claim that the gathering of information, required testing, and writing of these documents can take months.

'DELAYS – SOMETIMES OF YEARS – ARE NEGATIVELY AFFECTING RESEARCH CAREERS'

Approval must also be obtained from the National Research Ethics Service (NRES), which means addressing over 100 questions in a 50-page document. Site-specific approval may also be needed if the trial is to be done outside of the National Health Service (NHS). If a trial involves radioactive compounds, approval is required from the Administration of Radioactive Substance Advisory Committee, which involves another 40 questions.

The research and development committees of the hospitals involved have to give approval, which may require further supporting material. A legal, although not necessarily financial, sponsor must also be sought – often a charity or university. These sponsors usually require documentation satisfying their own safety concerns.

Stephen Mather (Institute of Cancer, London, UK) believes that delays – sometimes of years – are divesting British clinical researchers of their edge, negatively affecting research careers, and possibly discouraging potential clinical researchers from entering the field. 'Research is highly competitive and all about getting there first these days,' he explains. 'Although other European countries are in theory supposed to comply with the same European Directive, in practice they interpret it much more flexibly, which means in many cases they are able to take advantage of exemptions.'

Kent Woods, Chief Executive of the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) is sympathetic to researchers' concerns, but explains, 'As a general principle, UK does not [add requirements] that are not in [a] directive. Nor did we in this case. Even so, universities and NHS organisations have had much development to do in order to handle their roles under the new legislation. It has not been easy for them, often not their highest corporate priority, and much frustration and delay has been experienced by researchers as a result.'

Efforts are being made, however, to deal with administrative bottlenecks to trial approval. For example, prior to the ECTD, the UK had a tapestry of local research ethics committees that took an undetermined time to give their opinions. Now a single research ethics committee has been formed and has a 60-day limit to deliver a verdict.

Janet Wisely, Director of the NRES, explains that a single electronic form now deals with applications to all the necessary bodies in one go. 'January 2008 saw the launch of the Integrated Research Application System (IRAS) which provided another marked improvement, with the standard ethics form being adapted to provide a single dataset from which applications could be made for regulatory approvals within the UK, including ethics, MHRA, and [research and development] management approvals.

'Where partners require essentially the same information, they have agreed to request this in a common format so that researchers only need to answer the question once.'

Many researchers, however, complain that the workload required to get to the point where an application can be made – IRAS or not – remains a problem. Moreover, research and development committees are commonly identified as more serious bottlenecks.

Unfortunately, the forthcoming cuts in research funding and the huge financial shortfall experienced by the NHS may be the motivator to find solutions that please everyone. Filling out forms is not a cost-effective use of researchers' time, and firing more support staff would only increase costs.

'EXPEDITING APPROVALS MIGHT HELP STEM THE FLOW OF RESEARCH MONEY OVERSEAS'

Moreover, expediting approvals might help stem the flow of research money overseas: 'It would make the UK a more attractive place for big [pharmaceutical companies].' says James Cassidy (Glasgow University, UK). 'Right now we are seeing an exodus to Eastern Europe and India. Pharmaceutical companies still like UK quality and the reputational value of having UK investigators, but are less and less willing to tolerate delay and high costs.'

Such is the concern over delays that a group known as the Sensible Guidelines for Clinical Trials Working Group was due to hold its second meeting in Oxford, UK; September 5–6, 2009. Organised by the Clinical Trials Service Unit at Oxford University, in conjunction with Duke University (USA) and McMaster University (Canada) – showing that UK academics are not alone in their concerns – the meeting will discuss the main areas preventing the efficient initiation and conduct of randomised trials, and discuss ways of overcoming these problems (*for more information contact sensibleguidelines@ctsu.ox.ac.uk*).

Clearly, if there is a real danger of the future of clinical research being compromised, then researchers, approval bodies, and policy makers need to foster better partnerships to develop more effective and efficient integrated solutions as soon as possible.

Adrian Burton

The full version of this article appeared in Lancet Oncol 2009;10:749–50.

PODIUM

Pezcoller Award for Scientific Leadership

Dr Françoise Meunier was head of the infectious diseases department at Institut Jules Bordet, Brussels, before moving to EORTC in 1991. She has led the organisation since then and her 'outstanding contribution as a scientific leader and mentor' gained her the 2009 Pezcoller-ECCO Recognition for Contribution to Oncology. She is due to give a plenary lecture at the joint ECCO 15–34th ESMO Congress (Berlin, September, 2009).

You had a high-flying academic career; why did you make the shift into management?

I was extremely happy in my academic work researching invasive fungal infections in cancer patients; I'd always said I would die at the Bordet! But Professor Henri Tagnon (who was instrumental in setting up the EORTC in 1962, and a former president) suggested the move. I was motivated by my admiration of EORTC, which I had been aware of since medical school, when I spent a lot of time at the Bordet (where the EORTC was then housed). It was one of the only hospitals where I saw clinicians with the intellectual rigour and scientific integrity necessary to say to patients, 'We don't know the best treatment, but if we enter you in an EORTC trial we hope to find out.' We were educated to put patients on a protocol and it was an approach I greatly appreciated.

What were your first impressions?

The EORTC had moved out of the Bordet in May 1990; when I arrived as director in April 1991, we had 28 staff, and I realised that we needed to expand to be better able to cooperate in independent clinical research but also to benefit from a unique network of key opinion leaders in oncology who were already involved in drug development outside of EORTC. I suggested to the board that we bring together academic trials and partnerships for drug development. This was very new.

At the same time, France had new legislation on clinical trials (that eventually led to the European Clinical Trials Directive) brought in by Senator Huriet. I realised that EORTC would have to adapt its processes if it were to continue to operate in France, where we had a lot of trial participants.

It was more than a full time job. In parallel with my managerial responsibilities, I set up a new EORTC group for invasive fungal infections, and I continued with my scientific responsibilities until 1995, when the board appointed me the first director general. Since then, I've been fully focused on management.

You received the Pezcoller award for your mentoring skills

It is a great honour and major recognition for EORTC. I am proud of the team here. They understand the vision and the noble mission of EORTC and are motivated to work in this environment. We have a certain, somewhat idealistic, approach and want to help define more effective or less toxic treatments for a dreadful and frequent disease.

I have always enjoyed great support from EORTC presidents and board members.

How has the organisation developed?

We have increased the expertise of our staff, and we have created a unique clinical research infrastructure, which is multidisciplinary not just from the medical point of view, but also in incorporating the administrative and legal support necessary to conduct complex clinical trials at international level involving translational research, imaging and biobanking. We now have 170 staff and 5000 patients are included in EORTC trial each year.

We collaborate closely with major international partners, such as through our annual tri-partite meetings, EORTC-NCI-ASCO and EORTC-NCI-AACR, but also with many national research groups through intergroup studies.

Changing rules and regulations – such as the Clinical Trials Directive – have meant that we've had to adapt, but we will survive. Regulators are slowly realising that if we want to maintain the capacity for excellence in Europe, there will have to be changes. It may still take a few years – longer than we'd wish – but I am confident we will find a pragmatic solution.

What challenges does EORTC face?

The major challenges we're addressing are developments in modern cancer clinical research including imaging, translational research and quality assurance. We understand more about the molecular mechanisms involved in cancer, it's totally different from comparing treatment A to B; more complex and expensive.

We also must motivate younger oncologists. EORTC has been sustained for more than 40 years by a generation who lived through its creation. Now we need to give younger oncologists opportunities to conduct high quality, internationally-recognised pan-European trials. EORTC is now a full partner in the Flims meetings – the forum in which young oncologists learn how to write trial protocols.

Optimal cooperation and coordination with national groups are also needed to avoid duplication of effort. We should do everything possible to make sure that the benefits of European research – our huge resources of commitment, expertise – and track record are not diluted through unnecessary local politics and competition.

Helen Saul