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Celebration of progress in childhood leukaemia

Childhood leukaemia may share a common cause with allergies and type I diabetes, according to Professor Mel Greaves (Institute of Cancer Research, London). Speaking at a public meeting to celebrate the 25th Anniversary of the UK Children's Cancer Study Group (UKCCSG, London, 5 July 2002), he said that a lack of infections in the first year of life may contribute to the development of all these diseases.

The so-called 'hygiene hypothesis' assumes that infections in babies prime the immune system and are critical for its proper development. A lack of infections at this early stage can lead to immune dysregulation, and, depending on genetic predisposition, to the development of a number of auto-immune diseases. In childhood leukaemia, problems arise when slightly older children start to mix more and encounter the common infections they avoided earlier. The infections may then provide a trigger for the development of leukaemia.

Some epidemiological work backs up this assumption. Professor Greaves said that other researchers have reported a birth-order effect, in which childhood leukaemia is more common among first children—who are more likely to avoid common infections as babies—than in those with older brothers and sisters. Conversely, children who attend playgroups and creches in their first year of life appear to have some protection from the disease.

However, for childhood leukaemia, this is only part of the story, he said. Childhood leukaemias are now thought to require two 'hits', with the first occurring in the womb. In acute lymphoblastic leukaemia (ALL), the first hit is thought to be a developmental accident affecting a chromosome. This is a common event. Professor Greaves: "For every child with leukaemia, 100 children have the first hit." The second hit is the delayed exposure to common infection.

New molecular genetic technology is allowing researchers to study genetic changes underlying cancers. It is becoming apparent that different subtypes of leukaemia have their own distinctive genetic changes, each caused by different assaults, he said. For example, a rare type of leukaemia which occurs a few months after birth is thought to be caused by exposure of pregnant women to certain chemicals. "We are using this technology to get to grips with the natural history of the disease, which was previously invisible because children are healthy until they develop leukaemia. Understanding the natural history will have an impact on epidemiological studies looking for causes. I am quite optimistic that we will be able to pin them down," said Professor Greaves. In future, treatment may be given according to the biology of the cancer, he said.

The two-hit model, with the first hit being common, is likely to be the same for other childhood cancers, said Professor Greaves, but research into brain and kidney cancers is less advanced. This is partly because the cancers are less common, but also because they pose more practical problems in research. "Blood is an accessible tissue," he said. Leukaemia has been a success story, with the outlook for children improving dramatically. "The disease was invariably fatal in the 1940s. Now it's 80% curable," he said.

Dr Sue Ablett, Executive Director of UKCCSG, said that the meeting, which included scientists, clinicians, charity groups and parents, celebrated recent successes, but also focused on problems and shortcomings. The lack of Government funding is a perennial problem: "So much of our work is funded by charities," she said. Childhood cancer lacks a clear position in the UK national health system, and is not clearly a part of the national framework either for children or for cancer. Other priorities include the provision

Dr Sue Ablett

of facilities for adolescents with cancer; the availability and development of drugs for childhood cancers; and long-term studies into the side-effects of cancer treatment, a particular issue for childhood survivors.

'We have made such a lot of progress in the past 25 years. But we're going to need improvements in funding, organisation and collaboration if children are to receive the best possible care," said Dr Ablett.

On a similar theme, see 'Population mixing and childhood leukaemia', Parslow et al., to be published in EJC later in 2002.

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Microarrays "predict survival from lymphoma"

Gene expression patterns may predict survival from diffuse large-B-cell lymphomas, an international research group reports. The joint European/US/Canadian Lymphoma/Leukemia Molecular Profiling Project has identified patterns that appear to relate to different subgroups of the disease (*N Engl J Med* 2002, **346**, 1937–1947). The subgroups may have different prognoses.

Survival following anthracycline chemotherapy in patients with diffuse large-B-cell lymphomas, the most common adult lymphoma, is only 35–40%. Attempts to improve survival may have been thwarted by the complexity of diffuse large-B-cell lymphomas, which may be a heterogenous disease. Indeed, two distinct types of lymphoma (germinal centre B-cell-like and activated B-cell-like subgroups), with different outcomes following chemotherapy, have been reported previously.

In the current study, researchers examined biopsy samples from 240 patients, and using 100 genes in a hierarchical clustering analysis, confirmed the identification of these two groups and also defined a third group that did not express either of the gene patterns associated with the previously identified subgroups. The germinal centre and activated groups differed with regard to translocation events. The former was exclusively associated with the t(14;18) translocation involving the *bcl-2* gene and amplification of *c-rel* on chromosome 2p. This group had a 5-year survival rate of 60% compared with 39% in the diffuse type subgroup and 35% in the third subgroup.

The three groups did not completely predict for survival in that there were some good prognosis patients in the activated subgroup. The authors then examined individual genes that predicted outcome and found four gene expression signatures. These are groups of genes that are expressed in specific cell lineages or differentiation stages or are expressed during a particular biological response. They used 17 identified genes to define a gene-based predictor that they then compared with the international the prognostic index. Both the gene-based predictor and prognostic index were independent prognostic factors. The small number of genes involved means that this technique could easily be developed for clinical application, they reported.

In an accompanying editorial, Dr Ian Magrath (International Network for Cancer Treatment and Research, Brussels) agreed that as well as enhancing diagnosis, the microarray analysis has the potential to influence therapy. However, he cautioned that this analysis could not be expected to identify all factors that influence the outcome of treatment. The study demonstrates the power of microarray analysis and represents an important step forward, but it remains to be seen whether a gene-expression predictor of prognosis will lead to advances in treatment. It may help in identifying high-risk patients in whom experimental therapy would be appropriate, but oncologists must decide what that therapy will be. "For now, treatment approaches remain essentially empirical," he said.

Emma Cannell

Iressa receives Japanese approval

ZD1839 (Iressa) has received its first approval, in Japan, for the treatment of inoperable or recurrent, non-small cell lung cancer (NSCLC). The decision was based on two phase II trials, IDEAL 1 and 2 (see *EJC* News, 2002, **38**, 1424). ZD1839, a selective Epidermal Growth Factor Receptor (EGFR) inhibitor, is also being considered for approval in USA, Switzerland and Australia.

HRT "poses breast cancer risk"

A major US trial into the risks and benefits of hormone replacement therapy (HRT) has been stopped early because of an increased risk of invasive breast cancer among participants. The study, which was run by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH), also found increases in coronary heart disease, stroke and pulmonary embolism.

The study (*JAMA* 2002, **288**, 321–333; full text also freely available at www.jama.com) included 16 608 women with an intact uterus, aged between 50 and 79 years. It was part of the Women's Health Initiative (WHI) in the US. The women received either a conjugated oestrogen/progesterone pill or a placebo. They were recruited by 40 US clinical centres.

The planned duration of the trial was 8.5 years; however, the NHLBI halted the trial after an average follow-up of 5.2 years. A small increase in heart attacks, strokes and blood clots had been detected in 2000 and again in 2001, but did not cross the predetermined boundary. However, a data review meeting on 31 May 2002 found the number of invasive breast cancers had crossed the safety boundary and the trial was stopped.

The group taking oestrogen and progestin combined had: a 41% increase in strokes, a 29% increase in heart attacks, a doubling of rates of venous thromboembolism and a 26% increase in breast cancer. Intriguingly, there was also a 37% reduction in colorectal cancer and a one-third reduction in hip fracture rates.

NHLBI Director Dr Claude Lenfant said the question of whether HRT would prevent heart disease was long-standing. "The bottom-line answer from WHI is that this combined form of hormone therapy is unlikely to benefit the heart. The cardiovascular and cancer risks of oestrogen plus progestin outweigh any benefits."

Commenting on the trial, Dr Lesley Walker, Director of Cancer Information at Cancer Research UK, said, "Women need to be aware of the risk of breast cancer and the newly-identified risk of cardiovascular disease found in this study when they weigh up the pros and cons of HRT with their doctors."

A second arm of the trial, which is comparing oestrogen alone with placebo, is continuing. A related editorial (*JAMA* 2002, **288,** 366–368) said, "It is reasonable to assume that to date, oestrogen alone may be safer than combination oestrogen/progestin."

EUROFILE

The overhaul of FECS

The Federation of European Cancer Societies (FECS), known to date as a successful conference organiser, is undergoing a process of rejuvenation to address its original purpose. The federation is being transformed into a dynamic network which is now on its way to becoming recognised as a platform for all the partners involved in oncology in Europe.

The shake-up is intended both to enhance relationships and interactions between FECS and its member societies; and to raise the profile of FECS at the European level. It is the responsibility of Ms Kathleen Vandendael, who joined FECS as Executive Director in the autumn of 2001. She has been encouraged by the FECS' Board of Directors, who she says have shown a 'strong willingness' to implement the changes.

The underlying themes of strengthening relationships, improving communications and increasing transparency were covered in the new mission statement (discussed in detail in *EJC News*, 2002, **38**, 12 1565) which also commits FECS and its member societies to promoting multidisciplinary care and continuing medical education; providing the best available information in oncology; and becoming recognised by the authorities as representing professionals, cancer leagues and patients' organisations throughout Europe.

FECS is a large organisation and reaching the goals in the new mission will take time. Many proposals were agreed at a strategic meeting in January 2001, but only became official at a Council meeting on 4 June 2002. Yet Ms Vandendael insists, "All of the changes are going in the same direction, and it's the right one."

A key amendment to the statutes, passed by the Council, will enlarge the board of Directors so that it includes a representative from all full member societies. "We want them to be involved in every step of the decision-making process," said Ms Vandendael. Similarly, the Council is to be extended to include sustaining members. They will not have voting rights but their presence at meetings will enhance relationships and interactions between the societies, she says. Another change in the byelaws will improve the representation of member societies on FECS' various committees.

The Council has offered affiliated membership to the Organisation of European Cancer Institutes (OECI), a network of 70 prominent cancer centres in 20 countries throughout Europe, including Eastern Europe. This gives FECS more direct access to information about public health in different countries. "If we want to influence public health policies in relation to oncology throughout Europe, we have to be in close contact with those familiar with what's going on at the national level," said Ms Vandendael.

FECS' established activities are continuing, and it will have organised six conferences in 2002: the European Breast Cancer Conference EBCC-3, EONS' Spring Convention, the ESSO Congress, EACR 17, the Flims workshop on methods in clinical cancer research, and the EORTC/NCI/AACR meeting. The Leonardo da Vinci Project, a 3-year study into continuing medical education in oncology in Europe, conducted for the European Commission, is on-going (see next issue, *EJC News* 2002, **38,** 14, for an update). FECS has also established, and is funding, special pan-European projects, which are multidisciplinary, and conducted in collaboration with member societies. The first to be given approval will study late outcomes of cancer treatment. Others in the pipeline include a training programme to improve skills to manage early breast cancer; and a survey of the status of medical oncology across Europe.

In order to raise the profile of FECS within European Institutions, Ms Vandendael has instigated meetings with key people within the European Commission and Parliament and with European and international organisations. For example, a FECS delegation met representatives of the European Commission's DG SANCO in June 2002. They discussed how the new Public Health Action Plan will address cancer-related issues. "It allowed us to explore how our members, the medical healthcare professionals, could help the Commission achieve its goals," said Ms Vandendael. After the meeting, FECS sent its proposal of support.

FECS has also sent an expression of interest to DG Information Society within the 6th Framework programme. It is for a project to create a telematic network pooling all existing expertise from different centres of excellence, in order to provide a treatment advice and quality assurance programme for individual cancer patients based upon microarray analysis and tumour characteristics.

DG Research has, for the first time, invited FECS to nominate up to 15 representatives to participate in a meeting in September 2002 entitled, 'Towards Greater Coherence in European Cancer Research.' Ms Vandendael 'It's a good sign and means that FECS is becoming more widely recognised.'

Meetings with Mrs Heidi Hautala, Chair of the Public Health Intergroup at the European Parliament are leading towards a hearing on unequal access to quality treatment and care across Europe, and related outcomes. Further, FECS is supporting ESMO's efforts to obtain recognition for medical oncology as a speciality, though it is likely to be 2 years before this Directive is fully approved.

All of these activities received strong support from FECS' member societies at the Council meeting. "My goal is to draw the attention of the authorities to what is going well, and to what is going wrong and needs improving. We should then involve the right experts from our societies to write position papers and participate in meetings with the authorities. This is the way we should function," she said.

Helen Saul

INTERVIEW

Professor Alan Craft is head of Child Health, University of Newcastle, UK. He is President of the International Paediatric Oncology Society (SIOP) and Co-chairman of the European Intergroup Co-operative Ewings Sarcoma Study Group. He is President Elect of the Royal College of Paediatrics and Child Health in the UK and a former Chairman both of the UK Children's Cancer Study Group and of the Medical Research Council Bone Sarcoma Committee.

Professor Alan Craft

Where did you train?

I'm self-trained in that there was no proper training in paediatric oncology in the 1970s. I spent 2 years at Newcastle, and 1 year on an MRC training fellowship at the Royal Marsden to get what training I have.

Who inspired you?

Fred Miller and Cyril Noble in Newcastle were good caring doctors who taught me the art of paediatrics. Cyril managed all leukaemia patients and I also learnt a lot of my early oncology from him. At the Royal Marsden, Tim McElwain was a larger than life professor of medicine who used to declare that "Rules are there to be broken". And then demonstrate how and why. He and Michael Peckham showed me the value of working in a multidisciplinary team. They brought two different disciplines together for the benefit of patients. It was inspirational.

Why did you choose to work in the field of cancer?

Purely by chance. As a junior doctor, a colleague who was looking after leukaemia patients got pregnant. I was told I would have to take on her patients for 6 months. By the time she came back, I was hooked. Simple as that.

Did any other branch of medicine appeal?

I was always interested in paediatrics and at the time, there were few sub-specialities. Paediatric nephrology and paediatric gastroenterology were emerging at the time and also appealed to me.

Might you have done something else altogether?

From the age of 14, I wanted to study medicine. I was offered a place to study dentistry, but I would have hated it.

What has been the highlight of your career to date?

Working with European colleagues, particularly Herbert Jurgens in Germany. We have worked together for more than 15 years on protocols for Ewing's sarcoma. It was initially an Anglo-German collaboration but recently the Americans have decided to adopt part of it, which is almost unheard of. We were surprised and flattered and it was a real highlight.

. . . and your greatest regret?

That we can't cure all our patients. In Ewing's sarcoma, and most childhood cancers, cure rates have gone from 35 to 75%, but that means there's still 25% we can't cure.

If you could complete only one more task before you retire, what would it be?

I'd like to establish a truly effective global paediatric oncology network to bring the best possible care, or at least some care to all the world's children. At the moment, 80% of the world's children receive none at all. I am president of SIOP and we are slowly taking paediatric oncology to the far corners of the earth. We have programmes for children in Africa and India, but it's difficult.

What is your greatest fear?

The politicisation of medicine which I think, unfortunately, is necessary. It is a great pity, but since health care is such a large industry, and we can't afford the best possible medicine for everyone, it has had to become political.

What impact has the Internet had on your working life?

I love e-mail; it has revolutionised my life. But I never use the Internet. It has meant that my patients are better informed, though, and they educate me.

How do you relax?

By running and doing the crossword. I have run 72 half marathons and 30 marathons in my career. The next is on Sunday, and an hour after I finish I'll be getting on a plane to Washington.

Who is your favourite author?

My favourite book is The White Spider by Heinrich Harrer, about attempts before the war to climb the imposing north face of the Eiger. It's a wonderful, inspirational book of triumph against adversity—just like paediatric oncology!

What do you wish you had known before you embarked on your career?

Nothing. I love the spirit of exploring the unknown. It would have been a pity to know it all before I started.

What piece of advice would you give someone starting out now?

Remember that your patient and his family are human and can only take so much. Listen to what they are telling you. Remember you have two eyes and one mouth and you should communicate in that ratio.

What is your greatest vice?

What is a vice? I have a small one in my current tool shed and am hoping to do better when I retire.