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# NEWS. . .NEWS. . .NEWS

## Recruitment problems

Women carrying BRCA mutations may be reluctant to join chemoprevention trials because they do not wish to be assigned to placebo. Recruitment of women at very high risk may now be insufficient to determine efficacy and future trials may need to be designed without a placebo arm, researchers say (*Lancet* 2001, **358** 889–890).

Over the past 8 years, women with greater than 40% lifetime risk of breast cancer who attend the Family History Clinic in Manchester, UK, have had the option of entering clinical trials. Two chemoprevention trials and a risk-reducing mastectomy (RRM) study have each enrolled about 10% of the women. This compares with more than half, 58%, who opted to enter a magnetic resonance imaging (MRI) screening study.

Recruitment for the International Breast Cancer Intervention Study (IBIS), which compares tamoxifen with placebo, has been "particularly disappointing", they say. Women at the highest risk are especially reluctant to join this study and the low recruitment "seems to be associated with a reluctance to be randomly allocated placebo," they say.

*"FUTURE TRIALS MAY NOT BE ABLE TO HAVE A PLACEBO ARM"*

A newer trial comparing raloxifene plus monthly injections with gosarelin with no intervention may be "daunting" because of the likely hormonal symptoms and amenorrhoea. "Design of the next definitive prevention study for women at high risk of developing breast cancer may need to consider randomisation without a placebo arm and inclusion of tamoxifen, which is generally well-tolerated," they say.

However, an editorial (*Lancet* 2001, **358**, 853) suggests that women could also be influenced by how they are asked. ''To persuade women to accept an equal chance of receiving placebo, the evidence that no available preventive strategy works has to be strong and to be properly presented,'' it states. They may also be more likely to take part if approached by women. Women should be involved at all stages of trial design and recruitment, it states.

## Nephrectomy 'standard care' in renal cancer

Adjunctive radical nephrectomy should be viewed as the standard of care for patients with metastatic renal cancer, following publication of results from an EORTC study (*Lancet* 2001, **358,** 966–970). An editorial (*Lancet* 2001, **358**, 948–949) says that the EORTC study, along with an American trial from the Southwest Oncology Group (SWOG 8949), show the value of a combined surgical and biological approach to metastatic renal cancer. They ''will deservedly be recognised as classic studies,'' it stated.

Radical nephrectomy alone was routine in the 1960s and 1970s, but it was later strongly discouraged after reports that rates of surgical mortality were far higher than those of spontaneous regression. However, the EORTC and SWOG studies now suggest that radical nephrectomy plus immunotherapy increases survival by 50–100%, compared with immunotherapy alone.

The EORTC study included 85 patients with a good performance score, an operable primary tumour and who were good candidates for immunotherapy. They were randomised to receive either interferon-alfa alone, or to have surgery before the immunotherapy.

The study found "an important survival benefit" for these nephrectomised patients. Median survival improved from 7 months in the control group to 17 months in the study group. However, response rated did not differ significantly between groups.

Nephrectomy reduces tumour burden and removes the source of new metastases, the researchers say, and may also improve quality of life by relieving symptoms, such as pain or haematuria. However, the timing and effect of nephrectomy merits further investigation, as does the search for active treatment regimens.

Results from the SWOG study are yet to be published, but the EORTC results are in accord with a preliminary report. On this basis, the researchers conclude, "We recommend tumour nephrectomy before immunotherapy as a standard treatment for metastatic renal-cell carcinoma patients who are suitable for this approach."

*"MEDIAN SURVIVAL IMPROVED FROM 7 TO 17 MONTHS"*

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## Walking and cycling "reduce breast cancer risk"

Regular physical activity may substantially reduce risk of breast cancer among postmenopausal women, say researchers from The Netherlands (*Cancer* 2001, **92**, 1638–1649). They found that walking or cycling for more than 90 minutes a day cut the women's risk by 24%, compared to those who did not exercise regularly.

The study included 62 537 women aged between 55 and 69 years. In 1986, the women completed a questionnaire on potential risk factors including physical activity, history of participation in sports, occupational history and dietary habits. In more than years' follow-up, 1208 new cases of breast cancer were available for case-cohort analysis.

Physical activity was inversely related to risk of developing breast cancer. Baseline activity, including cycling or walking, combined with gardening and doing odd jobs or sports, was protective. Daily activity of more than 90 minutes, compared to less than 30 minutes, reduced the risk of developing breast cancer by 24%. Daily activity of more than an hour, compared with less than 10 minutes, reduced risk by 19%.

Neither occupational physical activity, nor the number of hours spent sitting per day at work, were related to the risk. The researchers could find no specific period in women's lives, such as before or after menarche, or birth of their first child, during which there was a particularly strong link between involvement in sports and risk of developing cancer.

They call for more work into different aspects of physical activity. "Physical activity is one of the few modifiable, protective factors for breast carcinoma and there are many other important health-related reasons to promote regular exercise," they conclude.

## Improved survival from childhood leukaemia

Children with leukaemia are living longer than traditional estimates suggest, say German researchers. They say that new methods of survival analysis indicate that long-term survival rates are higher than those derived previously (*Cancer* 2001, **92**, 1959–1966).

"The type of analysis makes a major difference when one aims to derive the most up-to-date, long-term survival estimates for patients with childhood leukaemia," says Dr Herman Brenner (Dept of Epidemiology, German Centre for Research on Ageing, Heidelberg, Germany).

The prognosis for children with leukaemia has improved steadily over the last few decades as a result of significant progress in therapy. Traditional estimates of long-term survival rates do not take this progress into account because they tend to place heavy emphasis on survival experiences of patients diagnosed many years ago, when the prognosis was poorer. The new method, called period analysis, enhances survival estimates to ensure they reflect the survival experience of leukaemia patients in recent years.

Researchers examined survival rates for 8059 children included in the German Childhood Cancer Registry. They were aged up to 14 years and diagnosed with leukaemia between 1981 and 1998. Traditional estimates put overall 15 year survival rates for all leukaemia patients at between 62.5 and 66.7%. This compares with an estimate of 73% derived from period analysis.

The authors say their analysis shows that improvements in long term survival are "considerably greater" than has been previously reported. "This may help to relieve undue anxiety and depression among children with leukaemia and their families," they say.

*"PERIOD ANALYSIS REFLECTS MORE RECENT SURVIVAL EXPERIENCE"*

## Selection of endocrine therapy in breast cancer

Measurement of epidermal growth factor receptor (ErbB)-1 and ErbB-2 (*HER2/neu*) may be useful in determining the most efficacious endocrine therapy for women with breast cancer, according to a joint US–European study. Researchers found strong support for the role of these measurements in selecting between letrozole and tamoxifen (*J Clin Oncol* 2001, **19**, 3808–3816).

Researchers examined biopsies from more than 270 women randomised to receive either letrozole or tamoxifen as neoadjuvant therapy for 4 months before primary surgery. The women were postmenopausal and had oestrogen and/or progesterone receptor positive tumours. They were ineligible for breast-conserving surgery.

Overall, patients who received letrozole had a superior outcome to those on tamoxifen and more went on to have breast conserving surgery. However the difference was most marked for tumours that were positive for ErbB-1 and/or ErbB-2 plus oestrogen receptors. Women whose tumours had these markers had an 88% response rate with letrozole, compared with 21% with tamoxifen.

An accompanying editorial (*J Clin Oncol* 2001, **19**, 3795–3797) says the paper is important and that the aromatase inhibitors are emerging as superior choices for the first-line treatment of hormone-responsive breast cancer in the metastatic and neoadjuvant setting. But it says: ''More data are required before ErbB-1 and ErbB-2 measurements should be used to select endocrine therapy in routine practice.''

The editorial calls for improved quality control in the measurement of oestrogen and/or progesterone receptors, the traditional factors known to be useful. "We must not forget that these results have important implications for every patient we treat."

# AWARDS AND APPOINTMENTS

## Cancer Scientists win Nobel Prize

Sir Paul Nurse (Imperial Cancer Research Fund, ICRF, London, UK), Dr Tim Hunt (ICRF, London, UK) and Dr Leland Hartwell (Fred Hutchinson Cancer Research Center, Seattle, USA) have been jointly awarded the Nobel Prize in Physiology or Medicine for 2001. Announcing its decision, the Nobel Assembly at the Karolinska Institute, Stockholm, said the Laureates have made ''seminal discoveries concerning the control of the cell cycle.''

*Sir Paul Nurse and Dr Tim Hunt*

"They have identified key molecules that regulate the cell cycle in all eukaryotic organisms, including yeasts, plants, animals and humans. These fundamental discoveries have a great impact on all aspects of cell growth. Defects in cell cycle control may lead to the type of chromosome alterations seen in cancer cells. This may in the long term open new possibilities for cancer treatment," the Assembly said.

Dr Hartwell, director of the Fred Hutchinson Cancer Research Center, worked with baker's yeast and in 1970–1971, isolated yeast cells in which genes controlling the cell cycle were mutated. He went on to identify more than 100 genes specifically involved in cell cycle control, the cell division cycle (*cdc* genes). One of them, the 'start' gene, controls the first step in the progression through the G1-phase of the cell cycle.

Sir Paul Nurse, director general of ICRF, worked with a different type of yeast and identified the gene *cdc2* which controls transition from G2 to mitosis. Later he found that *cdc2* has a more general function and is identical to Dr Hartwell's 'start' gene. His 'eureka moment' came in 1987, when he discovered that this gene is also present in human cells. In doing so, he had shown that the underlying mechanism controlling cell division is common to all living things, from yeast to frogs to humans. The gene is now known as cyclin dependent kinase 1 (*CDK1*).

Dr Tim Hunt, head of Cell Cycle Control at ICRF, discovered the first cyclin molecule in the early 1980s. Cyclins bind to CDK molecules and thereby regulate CDK function. His discovery was made using the sea urchin, *Arbacia*, as a model system. He noted that the protein was degraded periodically in the cell cycle; this is an important control mechanism. He later discovered cyclins in other species and today around ten different cyclins have been found in humans.

Sir Paul said, ''Naturally I am thrilled to win the Nobel prize, particularly as the prize celebrates its centenary this year, but this is a team effort and it is important to realise that this achievement was made possible by the efforts of the many researchers I've worked with over the years.''

Dr Hunt also paid tribute to his team at ICRF. He said the research, ''has opened up a new chapter in cancer research and it is fantastic that this has been recognised in this way. The knowledge we have gained about how cancer cells work should lead to exciting new therapies for cancer patients in the future.''

The discoveries are important in understanding how parts of chromosomes are rearranged, lost or distributed unequally between daughter cells. It is likely that such chromosomal instability is the result of defective cell cycle control. Genes for CDK-molecules and cyclins can function as oncogenes; CDK-molecules and cyclins also collaborate with the products of tumour suppressor genes such as p53 and Rb during the cell cycle.

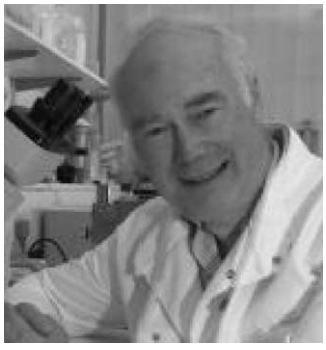
The Nobel Assembly said that findings in the cell cycle field are about to be applied to tumour diagnostics and that they may in the long term open new principles for cancer therapy. "Most biomedical research areas will benefit from these basic discoveries, which may result in broad applications within many different fields," it said.

*"IT'S A TEAM EFFORT, MADE POSSIBLE BY THE EFFORTS OF MANY"*

The Nobel Laureates will each receive an equal share of the prize of 10 million Swedish Krona. Nobel prizes are traditionally presented on 10 December, the anniversary of Alfred Nobel's death.

## Lasker Award for Knockout Mice

The 2001 Albert Lasker Award for Basic Medical Research was awarded jointly to Mario Capecchi (University of Utah, USA), Martin Evans (Cardiff University, Wales) and Oliver Smithies (University of North Carolina, USA) for their part in the development of the knockout mouse.



*Martin Evans*

The Lasker Awards are the most prestigious honours for medical research in the US. The 2001 Basic Award honours the three scientists who developed a technology, based on mouse embryonic stem cells, that allows the creation of designer strains of mice in which virtually any gene can be disabled. These new laboratory models enable academics to test ideas, and the pharmaceutical industry to test drugs, in ways that were not previously possible.

*"THEY HAVE REVOLUTIONISED THE STUDY OF HUMAN HEALTH"*

Dr Evans, working originally with Dr Matt Kaufman at Cambridge University, UK, first isolated embryonic stem cells, multi-purpose cells whose DNA could be manipulated to create any mutation of interest. He then developed mouse embryonic stem cell technology to make designer mice, capable of transmitting their altered genetic material to their offspring. Meanwhile, Drs Capecchi and Smithies demonstrated that they could alter any gene in a cell by replacing it with a modified version. Their work combined led to the creation of a mouse with a specific genetic change in all of its cells.

Presenting the Award at the Pierre Hotel, New York City on 21 September 2001, Dr Ira Herskowitz, one of the judges, said that Drs Capecchi, Evans and Smithies "have created a magic wand by which it is possible to modify any mouse gene with exquisite precision". They "have revolutionised the study of human health and disease."

## Klausner to leave NCI

Dr Richard Klausner has resigned his post as Director of the US National Cancer Institute (NCI). He has become the first president of the new Case Institute of Health, Science and Technology (CIHST), according to The Blue Sheet (12 September 2001).

Dr Klausner resigned in September, saying in a letter to the Bush Administration, ''It has been a privilege and an honour to head one of the world's great scientific institutions dedicated to the advancement and application of science aimed at reducing the burden of one of humanity's feared diseases.'' He continued, ''I appreciate the extraordinary support of your administration for me, for the NCI and for biomedical research.''

The deputy director, Dr Alan Rabson, said he had watched with great pleasure as Dr Klausner ''progressed from a research fellow in my division to become the most creative and imaginative director in the history of NCI.'' Dr Rabson is acting director of NCI while a permanent replacement for Dr Klausner is found.

CIHST is wholly backed by the Case Foundation, set up by Steve Case, chairman and founder of AOL Time Warner, and his wife Jean. It aims to develop partnerships with academic, philanthropic, for-profit and other organisations; funding pilot projects; and launching and funding new initiatives not specific to any single disease.

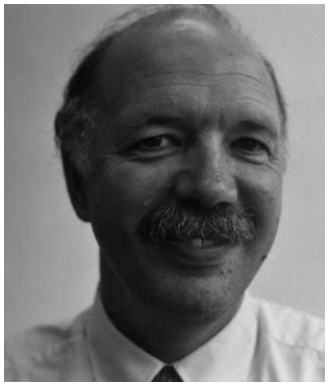
*Dr Richard Klausner*

*"THE MOST CREATIVE DIRECTOR IN THE HISTORY OF NCI"*

Dr Klausner has been at the National Institutes of Health for 22 years. He was appointed NCI director by the then President Bill Clinton in 1995. He is to continue to run a research laboratory within NCI as an unpaid 'special volunteer', in addition to his work at the CIHST. He has indicated that his main reason for resigning as Director was the opportunity to focus, within a think-tank environment, on breaking down boundaries between biological, physical and information sciences.

# INTERVIEW

*Professor Pieter de Mulder works at the University Medical Center, St Radboud, Nijmegen and is Chairman of the Nijmegen Academic Oncology Center. He is a member of the Dutch Working Party on Head and Neck Tumours. At EORTC, he is Vice-Chairman of the Biotherapeutic Development Group and Chairman of both the Chemotherapy Committee of the GU group, and of the Quality Assurance Committee. His main research interest is in immunotherapy.*



*Professor Pieter de Mulder*

**Where did you train?**
I trained at Nijmegen at the hospital where I have been ever since.

**Who inspired you?**
Professor Haanen, who trained me and who believed that the link between research and the clinic is crucial if there is to be progress. I wholeheartedly support his vision of building bridges between the two.

**Why did you choose to work in the field of cancer?**
Originally by chance, and because of the opportunities that came my way. But also because I appreciate the type of patient contact within oncology. Our patients are facing death and they lose their façade. If you can drop your own façade as well, you get real contact with real people. Even when things are going wrong, if they can see that you are honest and are trying your best for them, it can be tremendously rewarding.

**Did any other branch of medicine appeal?**
I wasn't born wanting to be a medical oncologist and probably would have enjoyed being a gastro-enterologist. But I have never regretted my choice.

**Might you have done something else altogether?**
I enjoyed the sciences at school and I liked having people around me. Medicine seemed a logical combination.

**What has been the highlight of your career to date?**
There are several. My 6 years as chair of the EORTC's chemotherapy group allowed me to get to know people from the US and across Europe and the collaboration was tremendous. At Nijmegen, building a laboratory with 15 basic immunologists, who specialise in melanoma and renal cell carcinoma and work closely with clinicians. Also, my very early involvement in the use of 5HT3 antagonists as anti-emetics. The first patient to receive it was continually sick. One simple infusion and the sickness stopped. It really was quite something. And finally, the fact that we have been able to bring the whole of oncology under one umbrella in our hospital.

**. . . and your greatest regret?**
Personally, either I don't have one or I've suppressed it effectively! Generally, I regret the diminished authority and independence that doctors now have. We work with managers, within budget restraints and increasingly have to deal with non-medical issues.

**If you could complete only one more task before you retire, what would it be?**
To ensure that my department is organised optimally so that our scientists can work to the best of their ability without being distracted by organisational things. I want the best for the group, I'm not looking to win the Nobel prize.

**What is your greatest fear?**
That the gap between the expectations of our patients and what we really can deliver is getting larger not smaller. Patients are much better informed and we have to spend a lot of time explaining that the situation may not be as black and white as they imagine. We can't do everything and this may not be the most effective use of our resources.

**What impact has the Internet had on your working life?**
The speed is fantastic, but information comes with a lot of noise. Things are turned around very rapidly, and I'm not sure this is always wise. In the past there was a lot more time to reconsider.

**How do you relax?**
I view every weekend as a short holiday. I draw and take photographs of buildings and architecture on Saturday mornings. I like cycling, reading, spending time in my garden and with my family. I don't find it difficult to relax. I know that I can't solve every problem and once I have done my best I don't go tilting at windmills.

**Who is your favourite author?**
I'm reading *Captain Corelli's Mandolin* by Louis de Bernieres at the moment. I appreciated *The Fountain Head* by Ain Rand, and Pat Barker's reflections on World War I. I also like to read biographies of achievers. I'm interested in why things turn out the way they do, how much is down to chance rather than to the person.

**What do you wish you had known before you embarked on your career?**
More about people's behaviour and how they interact. We have to work together to achieve anything, and the more you understand about people, the further you get.

**What piece of advice would you give someone starting out now?**
Do something you like and be honest about your motivations. If you are driven by money or other people's admiration, oncology may not be for you. If however, you like science and are interested in people, you're fascinated and humbled by biology, it may be.
Also—look around and learn as much as you can from other people, especially those with different experience or background.

**What is your greatest vice?**
Sometimes I'm not smart enough to pick up on the right clues. However, if you search carefully and don't find what you are looking for, that is as useful as a positive result. But it is satisfying when your idea is proved correct.