Jean-Claude Horiot: the innocent inquisitor

➜ Interview by Anna Wagstaff

In 1972 Jean-Claude Horiot left a wonderful research job in the US to join a cancer centre in Dijon that was too small to conduct clinical trials on its own. He teamed up with similar centres, and in so doing laid the basis for cooperative research and helped end a culture in which medics and hospitals answered to no-one for the quality of their work.

You led the development of international cooperative clinical research, which groups like the EORTC have used to great effect in the past 25 years. What prompted you to undertake this mammoth task?

JEAN-CLAUDE HORIOT When I graduated as a radiation oncologist in the late 1960s, only a handful of very large institutions, such as the cancer institutes in Amsterdam or in Villejuif, were carrying out clinical research. They were very elitist, and having done my medical training here in Dijon, I knew I had no chance of going into research in Europe.

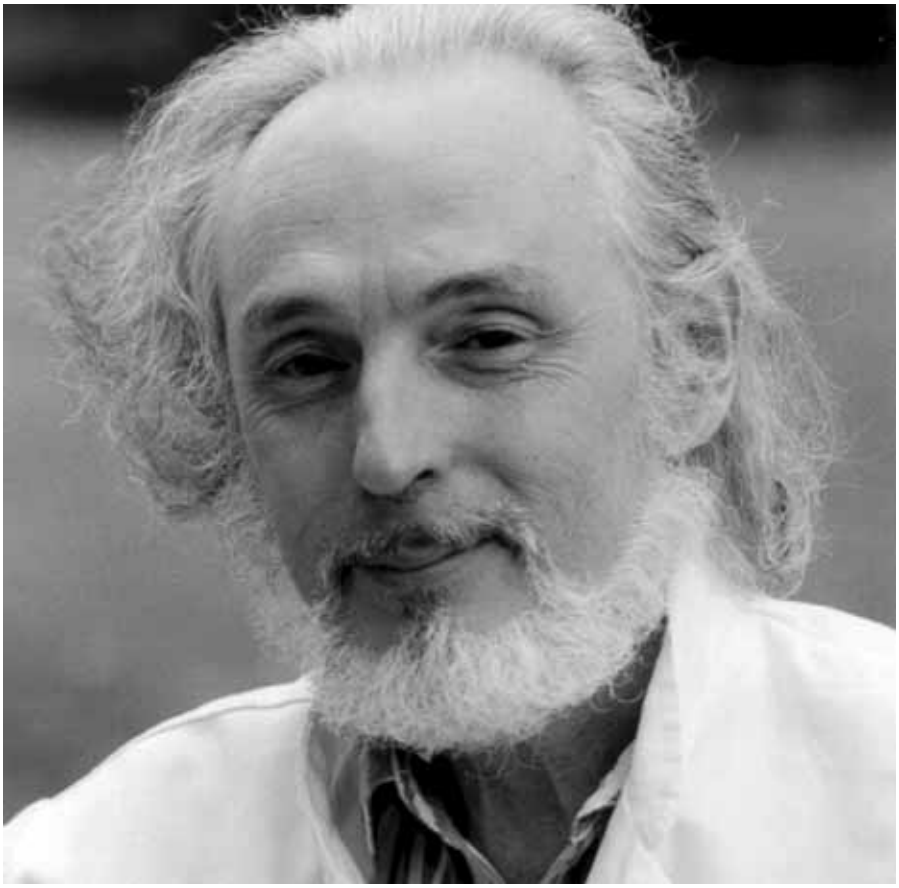
So I decided to build my career in the US. After gaining the US-equivalent qualifications, from MD upwards, I joined the MD Anderson hospital in Houston, and had a wonderful time doing clinical research, where basic, translational and clinical research were all carried out under one roof. But then an academic position opened up in my own city, Dijon, and I decided I would challenge the only candidate – who was from Paris. And to my great surprise, I was nominated.

In 1972 I found myself back in Dijon with an academic position and the remit I had always wanted – to develop research. But I was in a medium-sized centre that was not nearly big enough to carry out clinical research of any weight – at least not on its own.

I was convinced that cooperation between hospitals of this sort of size was the only way to get the necessary critical mass to carry out meaningful clinical research.

This is when I came across the European Organisation for Research and Treatment of Cancer [EORTC], which was exactly what I needed to accomplish what I wanted to do.

The great encounter I made there was with another man of my age, Emmanuel van der Schueren – 'Manu' – who went on to become one of the great builders of European oncology, not only creating the European Society for Therapeutic Radiology and Oncology [ESTRO], but also promoting cooperation between different oncology disciplines, for instance through the establishment of the Federation of European Cancer Societies [FECS]. He was Belgian and



They said we had helped them convince their directors to invest in more staff or better equipment

had trained in Leuven, but had spent some years at Stanford University, California, MD Anderson's great rival in radiation oncology.
We became great friends, and much of what I contributed to building European cooperative research, was done hand in hand with him.

European cooperation is dreamed of more often than achieved. How did you set about realising your goal?
JEAN-CLAUDE HORIOT The first step was to create a radiotherapy group within EORTC, which we did in 1974. Until then, radiotherapy had only existed as a subgroup of the radio-chemotherapy group, which was mostly involved in Hodgkin disease.
After this, we rather innocently invented the concept of 'quality assurance' in research trials. We wanted to include centres in many different countries in a single protocol, so we had to find a way to check that the data gathered in each centre was accurate and reproducible. We had to be certain, for instance, that 1 rad (the unit of radiation dose in those days) in Amsterdam was the same as 1 rad in Leuven, Dijon, Milan, Gothenburg and Lisbon. I visited all the partici-

Quality assurance has greatly reduced late tissue radiation injuries and accidents

pating centres as part of a team of physicists and clinicians, and we measured the beam qualities and equipment parameters. We checked the methodologies as well as the quality of the equipment, because there was a lot of scope for variation, resulting in inconsistencies.

This was the first time a peer review system had ever been used to evaluate practice as opposed to academic papers. Doctors believed what they did was an art, and could never be checked by anyone else. We were warned that we would be seen as an inquisition and that no institution would give access to a team of 'self-promoted inspectors'. Fortunately, these predictions turned out not to be true. One reason may be that we never claimed our measurements were right and others were wrong. We just wanted to ensure that the data we were pooling from many centres were consistent.

We banished the word 'error' from our language, using previously defined consensual parameters to define variations in measurements as minimal, minor or major. Centres with major deviations had to stop patient entry until they regained compliance. Sometimes it was a problem of human competence and sometimes their equipment was not good enough. Many centres told us later that we had helped them convince their hospital directors to invest in more staff or better equipment, as they were able to say: "Look you have refused us for years, and now we are not good enough to participate in European cooperative trials."

It took just two years to eradicate major deviations and demonstrate that we could all speak the same language. From the first published reports on quality assurance, the process was totally legitimised and established. These principles, which were first developed for research, are now used routinely in radiotherapy units throughout the world.

Did this process apply to radiotherapy alone?

JEAN-CLAUDE HORIOT Once the methodology was proven, everyone recognised the benefits of external independent review, and wanted to participate. Shortly after we had proved the concept, Manu and I were asked to chair the first EORTC Quality Assurance Committee, with the task of developing similar procedures in other disciplines, working with surgeons and medical oncologists to analyse the sequences and parameters in a given procedure or treatment. The process was completed by the mid-1990s and quality assurance is now applied in all areas of oncology research and clinical practice.

You can see the beneficial effects. With better radiotherapy resulting from quality assurance, the incidence and severity of late tissue radiation injuries have considerably decreased, and accidents such as transverse myelitis have been almost eradicated.

Was the quality assurance system enough to allow you to run trials on the scale you were looking for?

JEAN-CLAUDE HORIOT It was a learning process. Our intention had been to use the EORTC radiotherapy group to promote radiotherapy research,

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Manu (Emmanuel) van der Schueren, a founding father of ESTRO and FECS, who died of cancer at the age of 56. He shared Horiot's experience of research in the US, and the two of them worked together to build the foundations of European collaborative research

slowed down for several years in cervix, prostatic and rectal cancers. Even though the organ groups were not necessarily doing radiotherapy research themselves, they still didn't want anyone else to initiate trials outside of their group and their conditions. They were trying to assert some kind of 'ownership' over these types of cancer.

By the mid-1980s, we'd proved that we could do our own trials and get internationally recognised results. It became clear that working with joint protocols was in everybody's interests, and this is how we have been working for the last 15–20 years, with remarkable outcomes in head and neck, breast, prostate, rectum and brain tumours. We have learnt so much about the importance of cooperation. Today we have no problems even with trials involving multiple modes of treatment, such as various combinations of radiotherapy and chemotherapy, and possibly surgery and/or an organ-oriented specialty as well.

Another important lesson we learnt, by trial and error, is the importance of high-quality dialogue before deciding on a protocol, because research takes time and it is vital to make sure that you are asking the right questions. We cannot have an indefinite number of really good ideas in a normal life, and we have to select very carefully the topics we want to address in research trials.

Some private doctors may not have mentioned radiotherapy, as they cannot do it at their own clinic

but we soon realised improving technical aspects of radiotherapy was too restrictive and we had to promote pivotal trials for all solid tumours benefiting from radiotherapy. Such research had to be done in very close cooperation with surgeons, medical oncologists and organ specialists.

In the beginning, some of the organ oriented research groups were reluctant to work with us, and tried to deny us the right to initiate trials in 'their' area. For instance, in the mid-1970s and early 1980s, EORTC cooperative research was

When you initiate a trial, it takes anything up to two years to define it, write it, have the concept validated by a peer review process, and then deal with the onerous legal requirements. If it is a large phase III trial, you may need to recruit up to 5000 patients, and this can take another five years. Then it may take an additional three years before you can analyse the results. Which means that once you have asked a question, you will rarely get the answer within eight or ten years. You have to ask the right question, or the answer may

With Sweden's Queen Silvia, then Honorary President of the EORTC. Horiot led the EORTC first as Secretary General and later President between 1994 and 2000

be obsolete by the time you get it, and you will have wasted a tremendous amount of time, energy and money.

For instance, we did a lot of research into optimal fractionation (the number and timing of radiotherapy sessions). Up until the mid-1970s, treatment was given once a day, five days a week, as if someone believed that tumours don't develop on weekends or at night. So we started from biological data, showing that the concept of fractionation should be modified, depending on the speed of proliferation of the tumour and normal tissue, and on the type of tumour and tissues. We showed that treating the patient twice a day was better than once a day, and that using multiple fractions per day made it possible to reduce the overall treatment time significantly. It took 20 years to reach these results.

It was very interesting research, but it was also a very hard lesson, because although these results were very positive – for instance in head and neck cancers we could improve local control by 20% – it never came into standard practice. During the second decade of our trials, similar improvements were achieved by adding chemo- to radiotherapy, and this was a far more practical alternative as it is nearly impossible to treat patients with radiotherapy twice a day – you would need twice the equipment and personnel. So we had spent 20 years demonstrating that the concept was right, but it was barely applicable.

The concept could have been very important. If only we had been able to recruit enough patients to prove the point in five or six years, it would have been very useful in curing a large number of patients and helping to justify the case for strengthening radiotherapy departments.

Would you say that rivalry between surgeons, medical oncologists and radiotherapists is now a thing of the past?

JEAN-CLAUDE HORIOT In cancer institutes, we knew from the early 1970s that what is needed is not a choice between one type of intervention and another, but a multidisciplinary approach. People who work or were trained in cancer institutes cannot imagine working in any other way.

The trouble is that only a minority of patients are treated in cancer hospitals. In France, 80% are treated in general hospitals or private clinics, where the multidisciplinary approach has taken much longer to be established. However, this is changing, and under the National Cancer Plan for 2003–2007, a multidisciplinary approach is mandatory. If a patient is treated outside this system, individual doctors or entire institutions could lose the right to treat cancers.

The National Cancer Plan also gives patients the right to be told about all treatment options. Many patients with prostate cancer, for instance, opt for treatment by radiotherapy rather than surgery. In the past, some private physicians may not have mentioned this option, because they cannot carry out the treatment at their own clinic. But

Europe must hold its own in research or pay commercial prices for every new tool and treatment

There is the ethical price of having the human genome developed and patented purely in the US

the principle of informed consent has now been extended to all cancer patients, so it is much harder for clinicians to get away with this. As patients become better informed, all practitioners know they need to demonstrate that they work to the same high standards as the best cancer institutes or university hospitals.

Are there wide variations in the quality of radiotherapy available within and between the countries of Europe?

JEAN-CLAUDE HORIOT First-class radiation oncology is practised in most European countries, although not every patient in those countries may have access to the best management. The major problem, depending on where you are, is unacceptable delays or limited access to innovative techniques because of staff shortages, outdated equipment, or both.

With the latest techniques, it is not so much the machinery as the software and regular upgrading that is the real expense. Intensity-modulated radiotherapy, for instance, needs a very special multi-leaf collimator (that aligns the particle beam), activated to modify not only the field size but the fluence (rate of particle flow) of radiation to each spot. It is a very sophisticated technique involving enormously complex calculations and equipment monitoring, and you therefore need some extremely powerful software, renewed every year or two years. These techniques also require a huge amount of preparation time from radiation physicists and oncologists, in order to tailor the radiation to each individual patient. So the big difference nowadays is not so much the variation of knowledge as the amount of time one can give to a patient who can benefit from that technique.

The trouble with radiotherapy – and this applies equally to surgery – is that there is no equivalent to the pharmaceutical industry, which can discuss with bodies such as the European Medicines Agency [EMEA] and national health systems to reach agreement to use and fund a novel approach in a rational way. As a result, patient access to innovative radiotherapy can vary a great deal not just from one country to another, but from one institution to another, and even sometimes from one patient to the next within the same institution, which I feel is an ethical problem.

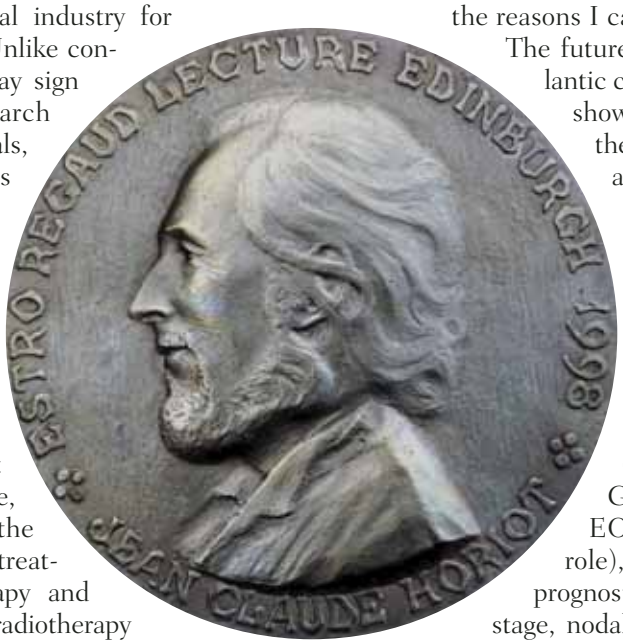
Do you see a time when the countries of Europe will be able to pull together in a coordinated research effort as happens in the US?

JEAN-CLAUDE HORIOT The US benefits from a federal approach. In Europe, under the principle of 'subsidiarity' research is defined as a national goal, and the EC only contributes to what each country cannot organise.

This was the trouble with the Clinical Trials Directive. We had hoped that European legislation on research would help the conduct of international clinical trials, by streamlining legal requirements. As we now know, not only did the Directive endorse the need to spend huge resources satisfying the legislation of each country with a participating centre, but some more European rules were introduced in addition to the national ones. The cost of clinical research has increased to a point where EORTC has to set strict priorities. As a result, some projects originating from EORTC groups have to be developed outside the organisation unless they are top priorities or have adequate funding.

The EORTC, which is by far the largest European group conducting cancer research, gets no support from the EC; it is treated like any other 'expert group' with the right to tender for projects drawn up by the EC. The preparation of an application requires an enormous amount of effort and money and the result is sometimes not

worth the game. We cannot define what we want to do, we cannot choose our partners, and we have to match the funding provided by the EC. In practice, the EORTC has to depend largely on the pharmaceutical industry for most of its funding. Unlike contracts the industry may sign directly with research institutions or hospitals, the EORTC always retains control over how we collect, analyse and publish the data, which is priceless. However, the industry will only fund trials that fit their marketing strategy, which means that if we want, for instance, to research into the difference between treatment with radiotherapy and surgery compared to radiotherapy alone, we have to find funding from other sources, because it is of no interest to the pharmaceutical industry.



Cast in bronze. This medal commemorates Horiot's ESTRO Regaud honorary lecture, delivered in 1998

Many member states hardly invest in clinical cancer research at all, and when they do, the funds tend to go to national projects. This is also true of most cancer charity money. Some research groups are worried about activating European trials in case they jeopardise their chances of getting national funding. This is where the US does so much better than us, and it is very disappointing.

You paint a gloomy picture. Are there any reasons for optimism about European cancer research?

JEAN-CLAUDE HORIOT Europe has to hold its own in research if it is to avoid having to pay commercial prices to access every new tool and treatment. More importantly, there is the ethical price of allowing the techniques, agents and procedures derived from mapping the human genome to be developed and patented purely within the commercial context of US research.

European research has a lot going for it, such as the quality of the relationship between doctors and patients, which is far more constructive and less litigious than in the US, and is one of the reasons I came back.

The future really lies in transatlantic cooperation, which was shown to amazing effect in the Glivec [imatinib] trials in metastatic GIST tumours [gastro-intestinal stromal cell sarcomas], which went from phase I to phase III in less than two years. The current 'planetary trial' TRANSBIG (Breast International Group, in which EORTC plays a major role), comparing classical prognostic indicators, such as stage, nodal status and hormonal receptors with innovative biological parameters, such as genomic profile, is an excellent reason to remain optimistic: 5000 patients to be accrued in 3 years by 39 leading institutions from 21 countries, which stands to benefit a hundred thousand women per year worldwide.

Looking to the future, everything we've learnt about the extraordinary complexity of the regulation of cancer growth makes it increasingly unlikely that a single specific mechanism can result in the discovery of a 'magic pill'. Surgery and radiotherapy will continue to be crucial in early cancer, and the slow but very regular progress we're making in stopping cancer growth for long periods in metastatic patients may revive indications for radiotherapy and/or surgery on these 'sleeping disease spots'. This is a very lively research field and Europe is playing a dynamic role. With a predicted shortage in these two disciplines, my message to all young oncologists is that there are tremendous opportunities to add your talents to the European research effort.