



Bob Pinedo: Bringing two worlds together

→ Interview by Anna Wagstaff

At the tender age of 29, Dr Pinedo found himself in charge of a group of cancer patients who were being left to die, and he set out to find a way to treat them. What followed was a remarkable story of one man and his lab, whose pioneering work brought new hope to a generation of patients and helped set the standards for translational research.

Your involvement with cancer started at a time when medical oncology was not even recognised as a specialist area of medicine and all the action was taking place in the US. What prompted your interest?

BOB PINEDO It all started when, fresh out of medical school, I arrived in Utrecht to take the post of Chief Registrar in Internal Medicine. I was struck by the fact that some cancer patients were left lying on the ward, neglected and lacking treatment. They were simply dying. I was 29 at the time. I had completed my training in internal medicine in Leiden, and had just defended my thesis on hypertension. When I arrived in Utrecht, hypertension was well taken care of but cancer patients were completely neglected, so I decided to forget about hypertension, and concentrate on cancer.

What did you do?

BOB PINEDO One of the first things I did was to create a division of Medical Oncology – the first in the country and one of the first in Europe.

Then I signed up for some of the general oncology courses run by the UICC [International Union Against Cancer]. In those days, Gianni Bonadonna had just started his adriamycin trials in Milan, and I introduced the drug to treat breast cancer patients in Holland. My colleagues were all highly critical. They said: “This is a terrible drug; you will give your patients heart failure.” So I put my patients on a heart monitor. It seems ridiculous now, but at the time it was needed to stem the criticism and enable me to continue treatment with the drug.

By 1974, I knew I needed more training and decided to go to the US. So at the World Cancer Congress in Florence that year, I searched out Paul Carbone – who was very influential within the National Cancer Institute [NCI] – and asked if I could come over. He agreed, but when I arrived at the NCI, I was told he had just left, and true enough, his luggage was standing in the corridor. So there I was, a young man, who had come to train but had no sponsor. The staff, however, were very nice and told me: “You can do whatever you want – go ahead.” So I did.

I was intrigued by methotrexate at the time, so I went to see Bruce Chabner, chief of the Pharmacology section, who was particularly known at that time for his work on this new drug. I explained that I wanted to study the pharmacology of methotrexate in mice, and he said “OK”. Along the same corridor I found a basic pharmacologist, Dr Zaharko, who agreed to let me do the research in his lab. He told me about a company that had started making infusion systems that could administer drugs under the skin of mice, and suggested I write a protocol. I proceeded to do it and it won his approval. Then I had to do the pharmacology. So I went back to Chabner’s lab and asked the assistant technician there to show me how to measure mouse methotrexate levels. I began the research and it proved a big success. But I also needed to study the effects on bone marrow stem cells, so I set out to find a lab where they had bone marrow stem cells I could use to culture my mouse marrow. I found Dr Joan Bull,

who had previously been working with Carbone, and she said: “Fine, go ahead.” This was what was so nice there. Though the person who had brought me to the NCI had left, everyone was eager to give me a chance. Eighteen months later I had already five papers published in *Cancer Research* and other leading US journals on the effects of methotrexate on the bone marrow of mice. That, for me, was the real scientific start.

How did you use the knowledge you gained at the NCI to improve the treatment of your patients back in Utrecht?

BOB PINEDO Apart from my contribution towards researching methotrexate, I learned at the NCI about how the skills of a basic scientist could be combined with my training as a clinician to better understand what effect a particular dosage of a particular drug and metabolism has on a particular patient. I was determined to set up a

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With Bruce Chabner.
“Pinedo and Chabner” became known to generations of oncology students through the *Cancer Chemotherapy* annuals they edited for many years. The two of them became lifelong friends during Pinedo’s days at the NCI, where Chabner was Chief of Pharmacology



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lab when I returned to Utrecht, and combining the worlds of scientist and clinician has been my approach to patient care ever since.

Shortly before I left the US, in 1976, Chabner told me of an experimental pharmacologist named Al Leyva who had just applied for a job at the NCI. So I called him and said: "Al, can you help me? I am a clinician and I want to set up a lab." He agreed to help, and a few weeks later we set up the lab at the hospital in Utrecht, and started doing pharmacology in patients, beginning with high-dose methotrexate for osteosarcomas. We created quite a stir and came in for a lot of criticism.

Was there no regulation limiting your freedom to experiment in this way?

BOB PINEDO No. One could just go ahead. For instance, we didn't have the money to pay for the methotrexate we needed, so I asked Al to purify it from the patient's urine, because almost 90% of this expensive drug is excreted in the urine. So we purified it and gave it back to the patient. This worked fine. I still see one of those early patients. After that, we started trying out platinum on testicular cancer. I knew that Larry Einhorn, whom I had met in the States, had achieved terrific results with platinum, but the drug had never been used in Europe. So when a colleague of mine developed testicular cancer we agreed I should pick up some platinum on my next trip to the US, which I did and brought it back in my pocket.

Then I began receiving phone calls from oncologists in our Cancer Institute: "Are you crazy to use platinum? You will make these patients horribly sick." It was true. My patient was very sick. He was the first patient in the Netherlands – probably the first in Europe – to be given platinum, and we were still learning how to use the drug properly. But he survived, and his metastasis disappeared. And he still visits me every year. Two years later, my critics started using the

drug themselves. This is how I had to do things, because if I'd done it in another way, it would have taken years.

After that first patient, we drew up a protocol for a proper trial of platinum in testicular cancer, and then went out to many hospitals and presented our first ten cases. We explained that we wanted to learn how to use the drug, and people were impressed and started referring patients to us. A few years later, I and Dr Stoter (who was a member of my staff, and is now professor in the Rotterdam Cancer Institute), published an important paper in the *Lancet* showing very good results. We then moved on to using a platinum regimen in ovarian cancer, and again we conducted a large study in Holland, known as the Dutch Ovarian Cancer Group. This was within a couple of years of returning from the NCI, and there were still only four of us doing this work.

You achieved all this by the age of 35 with very little money and no co-operation from those around you. How do you account for the fact that today we see such slow progress from million-dollar research efforts and huge multi-centre collaborations that were unimaginable in your early days?

BOB PINEDO It's not the money that determines the result, it's the method. Let us not forget that while the big research money and major trials are concentrated in the US, most cancer drugs come from Europe, because European chemists are good. Adriamycin came from Italy, carboplatin from the UK, VP16 from Switzerland, oxaliplatin from France, cyclophosphamide from Germany, and now CPT 11 for colon cancer, also from France. The US has the system and the money. They are good at taking a European drug and doing big trials.

When it comes to translational research, the number of participating centres should be limited.



With Frits Duparc, Director of the Mauritshuis art museum in the Hague, at an oncology Masterclass in Tenerife last year. Duparc was one of three patients Pinedo invited to talk to the young doctors on the course about how patients feel about discussing their disease

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Take adriamycin. It was developed here in Europe by Gianni Bonadonna at his own institute. He said: I don't want to involve the EORTC [European Organisation for Research and Treatment of Cancer], I have enough patients in my institute. And it was a hit.

Translational research makes use of the tissues and blood of your patients to understand the biology in the patient, the pharmacology, and pharmacodynamics. This involves not only measuring the drugs, but measuring the effects of the drugs on organs. It is meticulous work and the most important thing is to achieve complete standardisation of the processing of the tissue and close observation of the patient. This is much harder to achieve when several centres are involved.

In my view, the European Community is making a mistake in always seeking collabo-

ration between many groups – eight or twelve centres in four or five countries. That is good for trials, and it may be good for basic scientists, but for translational research, 4x2 is better than 1x8. So please, European Community, accept small groups. We can each do an excellent job in our area, and have standard tissue processing.

Translational research is strongly promoted by large sections of the cancer world today, but how much is it actually taught to trainee clinicians and basic scientists?

BOB PINEDO When I joined the Free University, Amsterdam, in 1979, as Professor of Medical Oncology and Head of the newly created Department of Medical Oncology, I made it my priority to teach my students the philosophy of

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translational research and the importance of bringing the worlds of scientists and clinicians together. Unfortunately, this is not generally the case elsewhere. We held regular clinical research seminars attended by basic scientists, where the presentation was oriented towards patients, not science. And we held basic science seminars attended by clinicians, which were oriented towards basic science. Basic scientists were encouraged to come with clinical proposals, make suggestions, and ask the clinicians all sorts of stupid questions. And clinicians were encouraged to feel free to ask the basic scientists stupid questions of their own. This broke the ice.

I also insisted that the clinicians pursue a lab project, and that the basic scientists spend one week in the clinic, on the unit, with the nurses, residents and interns. Can you imagine a chemist or a biologist involved in a phase I trial sitting and listening to clinicians explaining the proposition to patients, talking through the patients' concerns and maybe hearing patients explain why they don't want to participate?

Initially I met with a lot of resistance. It's strange for a biologist to sit and drink coffee with nurses and listen to them discussing the problems of this or that patient. But just sitting in that coffee room for half an hour and listening to what the nurses are saying is crucial. At the simplest level, it helps them understand why the piece of tissue they need to examine arrives at 5.30 in the evening, and not at 8.00 in the morning, because the surgeons who have to take that biopsy for the protocol for the translational research won't do it in their routine programme. They will do it at the end of their programme, at around 3.00 or 4.00 in the afternoon. That is why you may have to stay an hour or two longer in the lab to process the tissue. And if you have been in that environment for a week, you understand this, and you feel more motivated because you see the two worlds coming together.

I also think it's very important for medical oncologists to know internal medicine and understand the pharmacology of the drugs they prescribe. The problems of our patients affect all organ systems – we have to deal with cardiac toxicity, renal toxicity and so on. Many of our patients will have comorbid conditions and will need other drugs as well, and the functions of their organs are often abnormal. Medical oncologists need to ask the question: “What is happening with the painkiller I prescribed if the liver is not functioning well?” If we don't think about the pharmacology of drugs we can cause a lot of harm to our patients. This is not taught enough in medical schools.

Breaking down barriers between the world of the patient and the world of the clinician is something that is also very important to you.

BOB PINEDO I can tell my patients everything and they can tell me everything. A newly-diagnosed may tell me she wants to postpone the start of her treatment. So we sit down and talk frankly about the risks of waiting, say, until after her holiday.

All drugs are very important, but half of the work is how you approach your patient, and I'm convinced that an empathic approach helps them live longer. I have a patient with a tumour on her liver, who enjoys biking. Every time I palpate that big protruding liver, I know she will be watching the expression on my face. I can either grimace, and utter – “Oh God!” – or I can ask her: “How far have you biked today?” And we will talk about the good things in her life. This is the secret of homeopaths. They make use of the shortage of doctors, and take time with their patients – time that we don't have. The patients are happy and I believe live longer as a result. This particular patient has been biking around with a huge liver for four years, after having been told she would die in three months.

How do you teach this approach to your students?

BOB PINEDO By doing rounds. On teaching rounds, the students follow you around and they see how you talk with your patients and how you touch your patients. Touching your patients is not taught in medical schools, but most patients like to be touched if you are talking to them. Not necessarily Spanish-style, when you kiss your patients on both cheeks – though I do have Spanish patients, and I am happy to greet them in this way. I also have many patients from Curacao, which is where I come from, and when I see them on my rounds I will say two or three words in Papiamentu. None of my students understand, but the patients are delighted. You need to find a connection.

I also teach Masterclass courses for the European School of Oncology, where I have the chance to talk to medical oncologists from all over Europe, including many countries where there is very little tradition of openness with patients. I recently invited three of my patients to accompany me on one of these courses so the doctors at the Masterclass could see how I talk to them, and how they talk to me. I wanted to let them speak – to say how they feel about discussing their cancer, what they feel about phase I trials, or what they feel about anything. They did a wonderful job. They could see some of the doctors were afraid to ask questions, so one of my patients said: “Listen, I want you to ask me anything that comes to mind. I can talk about it, I know I am going to die.”

Many of the doctors were shocked and didn't know how to respond. If we keep doing this, particularly at international courses, I believe we will get the message across.

Where do you see progress in the fight against cancer being made?

BOB PINEDO I think targeted agents will be very important, and a much better multidisciplinary



The human touch

approach. We need to start talking more about surviving with cancer and not only stressing the cure. Many people are failing to recognise how much longer our patients are living now than they did 25 years ago. Instead of three months, they live eight years. I am convinced that cancer will become a chronic disease, as long as we have enough doctors and enough time for our own patients. We need to start getting people accustomed to this.

Some of my patients are reluctant to go to work because people tell them they “stink of chemotherapy” – this can be a terrible blow to a person who is fighting cancer. Businesses must learn to accept the fact that they have four or five cancer patients in their office, and the whole social system should be more accommodating to patients living with cancer. We should stop talking just in terms of a cure rate, because the time is coming when these targeting agents, even if they don't eliminate cancer, will keep it under control and society will have to make the necessary adjustments.

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