

Dear Diary,

July 1982 After 6 years, I graduate in medicine, just about, as my supervisor goes missing the morning of the viva (thesis: “Effect of Dermorphin on human gastric secretion”). I have to chase him through the hospital as he has obviously lost any interest in me.

This is the final signal that surgery is not for me. Back to my first love: pathology.

November 1982. Passed the State examination: I can now practice! To celebrate I join the post graduate school of pathology where I will spend my next four years as a junior doctor. Please note, in the rest of the world junior doctors are employed and paid rather good salaries. Not in Italy! I had to pay tuition fees instead (via “Bank of Mum and Dad” of course...).

1982-1983. My first year as a junior doctor. As I rather like biology I divide my time between the Pathology Department, where I start my professional training (I avoid detailed descriptions that may upset the audience), and the Department of Immunology at the Italian National Institute for Health for research training. My research work is more civilized; I investigate how one sub population of our lymphocytes changes when artificially activated in a laboratory Petri dish, rather than in the human body. This may sound useless but it is not: it can provide information on the biology of the cell that we can subsequently use in verifying how these cells function in patients.

1983 My professional training keeps going. Alongside the rotation through different subjects of pathology, I also join the small team performing diagnoses of blood diseases, i.e. working on the lymphatic organs and their tumours. This is something I will now do every day of my life, having never stopped since!

One day during this time something interesting happens. The head of the Immunology Department calls me (looks like I am the only young doctor around with no particular duties) and asks me to investigate the recent literature about something strange. He had a rather alarmed call from an association representing patients with haemophilia, a congenital blood disorder requiring continuous treatment with products derived from blood. Apparently, there is worrying news

The natives were friendly so we stayed the night

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of a bizarre infection linked to blood transfusion. One or two hours are enough to find all that has been published so far as it is not a lot. Well, my research plans are changing.

Patients with this infection not only die, killed by microorganisms that are usually harmless, but also develop very large lymph nodes. I start jumping from one hospital to another racketeering post mortem samples while also starting to collect lymph node biopsies from live patients as they arrive in Pathology so as to learn a bit more and to have new reagents to be used in the laboratory. I travel to Paris and head straight for the Pasteur Institute. I do not feel I need to book any appointment in advance and so I start to wander in the corridor, asking people to tell me where the laboratory of Professor Montagnier is, the French lead investigator working on this subject. Eventually I ask for directions from a young lady a bit older than me, who is hanging around in a corridor: she turns out to be Françoise Barre Sinoussi, and she has isolated the virus. My mission is a success! I get plenty of advice and some reagents. All this leads to my graduation thesis (and the odd publication), describing the changes that this virus induces in human organs and which cells it infects. At one conference I get also some advice from Jonathan Salk. It is also my chance to thank him for providing my generation with the first ever polio vaccine.

July 1986 My dissertation “Systemic Lymphadenopathy (LAS) and Acquired Immunodeficiency Syndrome (AIDS). Immunohistology and pathogenetic correlations” is ready! I qualify as a pathologist.

Nov. 1986-Oct. 1987: The Fatherland now remembers that I exist. So, it's one year in the Army. Compared to medical training it is very relaxing, and offers me an opportunity to have one year of experience in general practice.

October 1987. Served my time in the army. No real job opportunities around, although I tried the few things available but no luck.

December 1987. Having successfully applied for scholarship funding for 2 years of research abroad, I am off to Oxford. My supervisors will be two of the founding fathers of the pathology of blood tumours and of a technique called immunohistochemistry (see explanatory note 2). This novel technique is rapidly revolutionizing how the diagnosis of cancer is made throughout the world. My project will be to integrate immunohistochemistry, by then well established, with the newly emerging molecular tests based on the examination of patient DNA.

December 1987. Sometime between Christmas and New Year's Eve. The Fatherland suddenly remembers me once again. Via the Deputy Head of the Dept. of Pathology of my Alma Mater, I get a telephone invitation to apply for the post of Researcher that has been “set aside” for me. It is just unfortunate that the deadline for the application, which requires weeks of laborious bureaucratic procedures, falls on the 31st of December, a few days after the invite is made. Well, maybe Father Christmas has come too late this year! But not to worry, they have somebody else ready to get the job.

Explanatory Note 1: Immunohistochemistry.

When we get an infection, some of our blood cells, called lymphocytes, produce large proteins, called antibodies. These antibodies are “tailor made” according to the type of infection, to specifically target and destroy a bug. For example, if we have flu, we will produce antibodies which can recognize, and link to, the particular flu virus infecting humans that winter. However, they would fail to recognize, for example, the virus causing hepatitis. As antibodies can recognize viruses, they can also specifically recognize cells and their components. For example, you can have an antibody which recognizes and links to a muscle cell while another will recognize a cell from your skin. It has been discovered that, by injecting a target, like a virus, into a laboratory mouse, it is possible to produce,

in special conditions, an unlimited supply of a specific antibody. When a patient has a suspicious lesion for a cancer, a sample of the lesion is taken by surgeons. They send it to the pathologists who, after proper processing, cut thin slices of the lesion and looks at it through a microscope. This already allows them to make a first diagnosis, but to have a more precise indication of which type of cancer the patient has, some sections are incubated with different antibodies. This is an example: under the microscope it can be seen that there is a tumour made up of big, variable cells growing diffusely and which do not look like any normal organ. Then you incubate different slides with different antibodies - one that recognizes the muscle, another which recognizes the cells covering your gut, or one that recognizes the lymphocytes. Only one of them will link to the tumour's cells, say, for example, the one against the lymphocytes. From this you know you are dealing with a tumour from blood cells. This specificity allows doctors to use a treatment that accurately targets that particular tumour.

December 1989. The Fatherland is deeply disappointed with me. Instead of coming back to work for free and wait for salvation, I choose to remain in Oxford where I have been offered a proper job as a Post-Doctoral Researcher (or, as it is commonly called, a post-doc). It is the first step in an academic career, after a doctorate or a medical degree, and it allows me to carry on my work on lymphomas (one group of blood cancers) and their underlying DNA alterations. This type of position is usually held for 5 or 6 years.

April 1990. Just in case, I register with the General Medical Council: this will allow me to practice medicine in UK in the future. You never know.

Sometime 1993 (remember this is a retrospective diary - I cannot be precise). Coup de grace! After a long string of failed job applications in the Fatherland, one succeeds and I am offered a job. At the same time, at my first attempt, I also get another job in the UK. But I choose the Fatherland. Only one caveat: my wife is also a doctor (same Fatherland), working in Oxford, but surely with her qualifications there will be no problems back home!

March 1994. I am back, south of the Alps. I am immediately told that, al-



legedly, the Megabank behind the hospital where I am going to work has some financial problems and a bit of a cut to my salary would help. I start to use the colourful swearing language I learned in the UK. Anything else? Not really, apart from my new head of department explaining to me that he could be my young "Uncle" but I need also a more mature "Dad": a pleasant family orientated environment. He also offers me a piece of advice: perhaps I want to start to look for a new job (and get away from his sight).

Sometime later in 1994, early in 1995. Work however goes well. After more than 6 years of full-time research, I am back doing clinical duties. On the academic side, a most interesting thing happens, which will mark the rest of my career. A friend who is a thoracic surgeon, specialized in lung cancer, has organized a large retrospective study on hundreds of patients. He wants to validate all the markers published so far for

lung cancer which are claimed to predict the outcome of this disease. I have friends back in Oxford working in a field that is rapidly expanding: it is the study of the formation of new vessels inside tumours, or as it is called for brevity, Angiogenesis.

Explanatory Note 2: Angiogenesis in tumours.

Angiogenesis, i.e. the formation of new vessels, is something that must happen to allow a tumour to grow, according to Judah Folkman (a professor of surgery from Harvard). He thinks he has conclusively demonstrated that this is the case: no formation of new vessels, no tumours. Therefore, he reasoned, if you block the formation of new vessels, you block the tumour. He thinks that, by blocking this formation of new vessels, any cancer can be treated. In a 1998 interview with the New York Times, James Watson, Nobel Laureate for discovering the structure of

DNA, enthusiastically stated that “Judah (Folkman) is going to cure cancer in two years”. As a result, the number of new vessels in a tumour comes to be regarded as the most accurate prognostic marker possible in any tumour, and targeting the vessels with drugs to be the most likely universal cure for cancer (I’m not joking - oncology went a bit off the hook in those years). It sounds naïve, and it is. But not to worry, Yours Truly will sort it out.

Sometime later in 1994, early in 1995.

I advise my friend to include the quantification of new vessels (angiogenesis) as a potential prognostic marker in his study of lung cancer. He thinks this is a good idea provided I do the evaluation of the vessels, and so he sends me a few hundred lung cancer samples. Sadly, the number of vessels in a tumour turns out not to be, in our study, the great prognostic marker it was thought to be. On the contrary, some of the tumours appear to completely ignore Folkman’s hypothesis. They keep growing, they are aggressive, and they do not have any newly formed vessels at all: they just exploit the normal vessels already present in the organ they come from (the lung in this particular case). This observation completely undermines the beautiful hypothesis of angiogenesis, that is now sweeping the world of oncology. It suggests that tumours behave according to a yet unknown biology! As the great nineteenth century British scientist Thomas Huxley said, this is “The great tragedy of science - the slaying of a beautiful hypothesis by an ugly fact.”

At the same time... Good news! After a long and frustrating search, my wife is offered a very good and interesting job: to help set up and run a new Diabetes Centre in one of the University hospitals in Milan. Everything is agreed, including working hours, salary and start date.

A little later ...Bad news! The Fatherland has not changed. My wife’s job has suddenly disappeared into very, very thin air. Apparently, the Professor of Endocrinology has tried to set up this Centre without the blessing of the local Godfather of Diabetes, who outranks him. The project is therefore dead. One of the worst stereotypes of the Fatherland (a nation run by godfathers and similar) is confirmed. Not that she did not try to talk with the Godfather, but shortly before the day of the meeting he was (rather embar-

rassingly) arrested... (a bit of embezzlement here, a touch of fraud there). She then starts to do some of the work she did in England for her Oxford boss from home. He re-employs her immediately for long distance work (e-mails have appeared by now).

Spring 1995. Well the graft has failed! I let my English friends and colleagues know that I am ready to go back. I become a Member of The Royal College of Pathologists, the qualification necessary to practice pathology in the UK. As my British supervisor once told me, it is a title that comes straight from the Queen!

Summer 1995. I receive two offers from London over the phone. I am spoilt for choice between two great places to work.

March 1996. I start my new job as Senior Lecturer and Consultant (broadly equivalent to Associate Professor) at University College London. The head of department is an old friend of my Oxford supervisors and, with them, one of the leading world pathologists on blood cancers.

1996-2000. Despite my position being an academic one, there is a big clinical workload. Still, I start to raise grants and to investigate the tumours that defy the scientific literature by growing without making new vessels. Papers keep being published!

May 2000. My old supervisors have managed to raise the money for a new position and so I am offered a more research-oriented job in Oxford. I am moving back there!

The work in Oxford is initially an equal mixture of research and clinical work. Over the years, this balance will be frequently altered by the growing clinical workload. As it is quite specialized, it is also difficult to recruit new colleagues and therefore, when necessary, it is the research side that suffers. Still, although in a rather bumpy way, the work on cancer and blood vessels goes very well as two new fields of cancer biology emerge.

The first is the study of the biology of non-angiogenic tumours: some cancers are purely non angiogenic but others contain both angiogenic and non-angiogenic areas and can switch both ways between the two modes. The angiogenic or non-angiogenic behaviour of the neoplastic cells is therefore not necessarily determined by the genes of the cancer and seems, so far, correlated to the repro-

gramming of the cell activity. The second field that has opened up is the study of how cells co-opt, i.e. exploit, the pre-existing normal vessels of the human body. This is turning out to be an active process involving the action of specific cellular functions. Co-option, so far investigated only as a means of exploiting pre-existing vessels, is likely to be relevant also for the interaction between cancer cells and newly formed vessels. Understanding this new type of cancer growth promises the hope of new ways of treating it.

August 2008. The University of Oxford promotes me to Professor of Tumour Pathology

October 2014 In all cancer biology textbooks there is a chapter called Angiogenesis. As discussed before, it will tell you that tumours can only grow if they can create new vessels. Blocking the formation of these vessels is believed to be the way forward to cure cancer. Well, as we showed that this is not always the case and other situations can occur, it is time to update the textbooks! Oxford University Press offers me the possibility to edit, with two old friends and colleagues, a new cancer textbook to rectify this misconception. Within this book there will not be a chapter called Angiogenesis any more, but one called Cancer and Blood vessels that will integrate all the new biology discovered so far.

May 2019. The Oxford Textbook of Cancer Biology is published

May 2020. Most of the patients with cancer have disappeared from the hospital’s daily workload. Something is going very wrong because of the coronavirus infection. In medicine it is very dangerous to have a fashionable disease; it leads you to forget that all the others are still there. Especially the one that the physician and author Siddhartha Mukherjee called “The Emperor of all Maladies”...

NOTA

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