

# The people's pharmacologist

→ Anna Wagstaff

**Silvio Garattini** gave up a glittering academic career to found his own set-up where research could be carried out free from commercial or political agendas. Today, the Mario Negri Institute and its founder play a vital role on the European scene, championing a 'rational approach' to drugs, and a research culture based on collaboration and transparency and led by patient need.

**S**ilvio Garattini was only 33 years old when he led an exodus from the University of Milan's Department of Pharmacology to found a fiercely independent institute for pharmacological research, named after its financial sponsor, Mario Negri. The year was 1961, and Garattini must have known he was in for a bumpy ride.

Apart from robbing the University of some of its brightest and most motivated pharmacologists, the young upstart was consciously breaking ranks with a powerful medical and academic establishment that he saw as a closed fraternity, cut off from the needs of ordinary people, heavily dominated by political patronage, and quite incapable of fostering world-class scientific research.

Garattini and his colleagues were determined that the Mario Negri Institute would be different.

From the outset the founding members decided they would publish only in English, thereby locating the institute firmly in the world of international research – and guaranteeing opprobrium from Italy's citadels of academia, who saw it as a snub not just to them but to the whole country.

But they reached outwards towards the Italian people. Breaking with a long cultural tradition that excluded the media and lay audiences, the founders

of Mario Negri defined 'dissemination of information' as one of three main areas of work, alongside research and training. Today, aged 80, Garattini still spends around 50 evenings a year addressing public forums, helping ordinary people and patient advocates understand and play a role in the processes that govern the way medical research is carried out and new treatments are made available.

They committed themselves to high levels of transparency – every piece of research undertaken would be published in its entirety. When Italy finally recognised drug patents in 1978, Mario Negri decided, in the same spirit, that it would not seek patents on anything developed within its walls.

They took a stand against the hierarchic power structures and career paths of the academic world. Researchers at Mario Negri keep no time sheets, and there is a pervading atmosphere of informality. Garattini himself dons a tie for no one. Whether he is busy with his prolific output of articles, at a formal ceremony to accept an award, making one of his frequent television appearances, or even showing the Italian President his new premises, he will be wearing his hallmark white poloneck jumper.

Above all, Mario Negri was to be independent – free from the political patronage and internal

politicking of the universities and free from the profit-making agenda of industry. To avoid becoming reliant on any single source of funding, they decided to limit the amount of any grant or contract to no more than 10% of overall income, condemning themselves to the constant pressure of finding a wide range of backers.

This was a vision so ambitious, it bordered on the audacious. And Silvio Garattini was one of the few people who could have hoped to pull it off. What was required was a mix of qualities that he happened

to possess in spades: an exceptional academic standing, unflinching self-belief, a strong and infectious motivation, and a talent for communication.

## ACADEMIC HEAVYWEIGHT

When Garattini convinced 21 of his colleagues to wave goodbye to the status and security of an academic career to embark on the Mario Negri adventure, he himself was in line to become Italy's youngest professor at the highly respected University of Milan. Having arrived at medical school





A rising star. Garattini aged 30, with Daniel Bovet, winner of the 1957 Nobel Prize for Medicine (right) and Emilio Trabucchi, head of the Department of Pharmacology at Milan University (left). This is the last known picture of Garattini in a tie

with a fully-fledged qualification in chemistry, he had soon come to the attention of the head of the Department of Pharmacology. “Every year the professor asks the students if any of them would be willing to give a lecture. I gave a lecture, I remember, on anti-histamines. I took advantage of my chemical background. I could show all sorts of structures showing which were the groups that showed activity, and the professor was relatively impressed and said, ‘Why don’t you come and work here?’”

Garattini was propelled at speed up the ranks, and within a few years was second in command and effectively running the department – his boss had been elected to Italy’s national parliament and was almost permanently tied up with political commitments. By 1961 therefore, despite his tender years, Garattini was already an academic heavyweight with a strong following.

His rise to prominence was all the more impressive because he had made it as an outsider, and this

stuff, Italian, mathematics etc. In the afternoon you had to work in the lab, and you were judged on the basis of the precision of your analysis. This was the most important degree I got in my life.”

His most important role model was his dad, who had himself been forced to make his own way in life, having lost both mother and father when he was only two years old. “He taught me to think critically, and not believe everything you see.”

As for his motivation, Garattini talks not of a life-long desire to help people or cure disease. He wants to do and facilitate excellent research aimed at providing solutions to real problems, unhampered by ulterior agendas. This drive was evident even in his first job quality checking the output of a local steel works in Bergamo. “I was in reality interested to see an analysis throughout the whole production process, but my boss said, ‘You are not being paid for that. Don’t do extra things.’” That job helped finance him through medical school.

“If we are serious about doing this research, either we go to the US or we do something different here”

## “The universities predicted no young people would come – which turned out to be completely wrong”

### RESEARCH AS A PROFESSION

But it was not until he travelled to America, in 1957, that his vision for the Mario Negri began to take shape. “I was impressed by the fact that research was a profession. In Italy, if you were at the university you did research and you published because this was a way to get promoted. If you were in industry, of course you did research the industry required.”

He came back to Italy bursting with enthusiasm. “I had a group of about fifteen to twenty people around me, and I said, ‘If we are serious about doing this research, either we go to the US or we do something different here. And the idea was to do something in our country. With a lot of naivety, I asked all the persons and groups that might be interested, ‘Why don’t you help me establish a foundation?’ Some people laughed. Some people were not interested. Some said: you are too young, you should stay at the university.”

In the end, it was an Italian industrialist who had made a fortune manufacturing affordable jewellery who gave Garattini the backing he required. Mario Negri had invested part of his fortune in small pharmaceutical companies, and came to Garattini for advice on the logistics of getting a new drug approved. They got talking, and the upshot was that Negri agreed to support the idea of a research foundation. Before anything concrete had been settled, Negri was diagnosed with liver cancer. A couple of weeks before he died, he rang Garattini, assuring him that the project they had discussed would be provided for. And sure enough, when the will was read out, 900 mn lira had been set aside to establish the Mario Negri Institute for Pharmacological Research. Garattini was named in the will as director.

The new kid on the block received a frosty reception. “We had a lot of hostility from the academic milieu. This was the first time the universities had to deal with something that was not a university, and they predicted that no young people would come to us – which turned out to be completely wrong.”

That Mario Negri survived its first decade was largely thanks largely to generous grants from abroad – the Wellcome Trust in the UK, the US National Institutes of Health, the US Army, Navy and even the US Department of Agriculture. When the institute wanted to offer degree courses, no Italian university would partner them – so young researchers at the institute now study for a PhD in pharmacology from the Open University in the UK.

### PIONEERING INNOVATIONS

The Mario Negri has grown into a world class research institute. It has published more than 10,000 articles in international scientific journals and trained more than 3,000 young scientists. Four of the 50 most frequently cited Italian scientific researchers (across all disciplines) are based there. The original group of 22 has grown to more than 900 spread between the headquarters in Milan, Garattini’s home town of Bergamo, and Abruzzi, southern Italy. Last September, Garattini and his colleagues bade a fond farewell to their old headquarters, and moved to a new building accommodating 24,000 m<sup>2</sup> of state-of-the-art laboratories. An inaugural visit by the President of the Republic indicates the pride Italy now takes in the Mario Negri.

Iain Chalmers, editor of the James Lind Library and one of the founding spirits behind the Cochrane Collaboration, argues that the influence and achievements of the Mario Negri cannot be measured only by what goes on within its own walls.

He says that the non-profit, patient-needs-driven model championed by Garattini has enabled Mario Negri to help bring about a number of important innovations in medical research. “It was the Mario Negri Institute that organised the first mega trial of a treatment, the GISSI I study, which demonstrated that streptokinase decreased mortality in patients with myocardial infarction. This study covered 90% of coronary care units in Italy – thousands and thousands of patients. They don’t get proper credit for that.”



A source of national pride. Garattini showed President Giorgio Napolitano round the state-of-the-art laboratories at Mario Negri's new headquarters last December

He also credits the Institute with fostering the development of the methodology for studying adverse effects once a drug is in use. “The Institute convened a meeting of all the international pioneers in the field. The report – *Epidemiological Evaluation of Drugs*, published in 1977 (Colombo et al.) – is a seminal book, which we celebrate in the James Lind library.”

Looking back at the development of the European medical research scene over the past decades, there are few people who have had such widespread influence as Garattini. Indeed, he remembers as little more than a minor footnote his role in founding the European Group on Cancer Chemotherapy (now the European Organisation for Research and Treatment of Cancer), in 1962, together with two great pioneers, Georges Mathé, from the Institut Gustave Roussy in Paris and Henri Tagnon, from the Institut Jules Bordet in Brussels.

“At that time very little research was being done in cancer. It was generally not considered suitable for drug therapy. So one of the reasons for establishing this group was to raise interest in industry.” As it happens, he says, industry quickly twigged that there are big profits to be made in cancer, because it is such an emotive disease. “In many cases drugs are promoted even if they are of little activity – it’s enough that a couple of newspapers say: why is it not available?”

His big concern is that many diseases fail to attract that sort of interest. A similar initiative for collaboration in the field of atherosclerosis, failed to stand the test of time. “I tried also other things, but they didn’t function. I think cancer is an essential area, but I have widespread interests. I am very interested in rare diseases and orphan drugs, because I believe this is part of equity. It is not good that people with rare diseases are left to their own devices.” Sixteen years ago Garattini helped address this unmet need by adding to the Mario Negri a centre for clinical research in rare diseases, named after its sponsors, Aldo and Cele Daccò. Located in Bergamo, it is the first such centre ever to combine education, information and research.

### PROMOTING INNOVATIVE DRUGS

The unique model of the Mario Negri has provided Garattini with an independent base to argue for ‘rational’ approaches to developing, regulating and reimbursing medicines. He has sat on countless national and international committees, and everywhere he goes he argues for certain key principles.

One of these is that it is a moral and scientific imperative that all data from all clinical trials – negative as well as positive – should be made public, and that a failure to do so results in patients being prescribed ineffective drugs. This issue recently hit

“I am very interested in rare diseases and orphan drugs, because I believe this is part of equity”

## “It would take only two words to be inserted in the legislation: new drugs must show ‘added value’”

the headlines (again) with respect to selective serotonin response inhibitors (SSRIs). Another is that new drugs should only be approved for the market if well-designed studies – preferably at least one of which is conducted by an independent trials group – show they are better than what is already available. He wants to see an end to non-inferiority trials.

One of his more high-profile public roles was thrust upon him in 1993, following a major scandal that saw many drug company officials, civil servants and even the Italian health minister jailed for corruption over drug reimbursements. Garattini was appointed to a committee to review the entire list of drugs on Italy’s national health service formulary. “Together with others, we cleaned the whole thing up. We removed all the products for which there was no scientific evidence and decreased the expenses of the state by 4000 bn lira – from 13,000 bn lira to 9000 bn lira.”

Denying patients access to obsolete medicines proved a tricky business, and doctors – with no small encouragement from the industry – put up strong resistance. Garattini responded by taking his case to the public. “I did a sort of tour of Italy to explain why there was this change, and participated in a large number of debates. It was very interesting.”

Timing, he recognises, was the key to his success. “The public was ready for a change, because they were indignant about the corruption. If it wasn’t for that, it would probably have been impossible to change. You must pick the right time to do things.”

When control over which drugs gained entry to the Italian market was ceded to the European Medicines Agency (EMA), Garattini took his arguments onto the European stage. The current set-up, he argues, favours the interests of industry over patients. “I would like to see EMA under the control of DG SANCO, where they talk about health, while today it is under the control of the DG for Enterprise and Industry, which is illogical.”

He is also strongly critical that new drugs can be approved even if they are no better, or even less

good, than what is already available. “There should be legislation that favours the approval of useful drugs, not the approval of anything that shows quality, efficacy and safety. It would take only two words to be inserted in the legislation: new drugs must show ‘added value’ – this could be greater efficacy or less toxicity or better compliance, whatever. You could make a rule to say you have to compare against the optimum treatment available.”

He has backed up his arguments with studies showing that the majority of cancer drugs approved by EMA in its first 10 years failed to show the level of evidence of efficacy required even by EMA’s own guidelines. Despite these arguments, recent changes to the regulations, which introduced the option of ‘conditional approval’, lowered the bar yet further.

Has Garattini finally met his match? He doesn’t seem to think so. Despite his advanced age, he argues that time is on his side. Sooner or later, he says, Europe’s health services will no longer be able to cope with a constant stream of new drugs that add little benefit and cost the earth. Earlier this year he helped launch a pan-European collaboration “for the rational use of medicines”. Hosted in Piper-ska, Stockholm, by the Karolinska Institute, Stockholm County Council and key personnel from Mario Negri and the Universities of Heidelberg, Liverpool and Marseilles, it was attended by healthcare professionals from nine EU countries.

“We will issue a paper, and go back to governments to argue the case. You have to continuously spread the idea. I repeat it everywhere. Little by little there will be somebody else, and then something will happen.”

Timing, as Garattini has learnt, is key. “I believe that people and organisations in general are not very rational. You need to have some special event that will shock the people and determine a change. I am waiting for the moment when the system becomes unsustainable, which will probably not take much time. That is the moment at which you say, ‘OK you have to change.’”