THE ROLE OF INDEPENDENT SCIENCE IN PSYCHOPHARMACOLOGY
SILVIO GARATTINI

Your book Psychotropic Drugs was pretty well the first modern book on Psychopharmacology and the meeting, on which it was based, must have been close to the very first psychopharmacology meeting.

The meeting was in 1957 before the first CINP meeting. I think the only thing that was before that was a small meeting at the New York Academy of Science on meprobamate in October 1956, published in the Annals of the New York Academy of Sciences in 1957. Our meeting was in May 9 - 11 1957 and we published during May 1957.

That was a fast job. There has been some debate about who was responsible for this meeting and the subsequent development of the CINP, with Dr Radouco-Thomas seeing Emilio Trabucchi as the key figure (see refs) but others I have interviewed, such as Philip Bradley see you as the prime mover. How do remember it?

Well, I was in the department of pharmacology of the University at that time and I felt that what was happening was really a new branch of pharmacology. Professor Emilio Trabucchi was the head of the department at that time and he supported the idea. You must remember that in 1956, when the idea arose and the initial organisation took place I was only 28 years old. Therefore many contacts with authoritative scientists were made directly by Professor Trabucchi, although the activities necessary for the meeting, including the list of speakers, came from me. My official profile therefore was only marginal, although the action of Professor Trabucchi was the result of my input. That this was the case is clearly shown by the fact that I was the Editor or the proceedings, with Dr Vittorio Ghetti, representing CIBA, one of the major sponsors of the meeting.

We had support from the Ciba company among others - but Ciba was the most interested because they had reserpine. At the time of meeting reserpine was of course available and there was the knowledge that reserpine had a mixture of sedative and hypotensive effects, which one could perhaps separate and get something that could be more specific for the vascular system and something more specific for the brain.

Then there was also chlorpromazine and the first very positive results in psychotic patients and there was the first tranquilliser, meprobamate, for which the term tranquilliser was established. It was Dr Frank Berger, working in Wallace Laboratories, the discoverer of meprobamate, who utilised the term tranquillisation because it wasn't really a type of sedation in the classic sense and proposed that this was related to effects on the central nervous system but also to some relaxant activity on the skeletal musculature. There was another drug, hydroxyzine, which was also a centrally acting drug but with less clear effects compared to the others. Then we had the monoamine oxidase inhibitors and later on the tricyclic antidepressant compounds.

We at the Institute were very interested in serotonin, which at that time was known mostly because of its presence in the platelets of certain animal species and in the gastrointestinal tract. In the brain there were very small concentrations and many people believed that these traces - you'll find this, for instance, in one of the articles of Erspamer, who was one of the discoverers of serotonin - were really only something that remained from the presence of blood

in the brain. The amounts were so small that nobody believed that serotonin had a function. It was only later that the neurochemical mediation induced by serotonin became apparent.

We were interested to investigate this issue at that time with methods which were rudimentary in a way, hoping to establish how drugs could change the level of serotonin in the brain and I remember around this time we had got a spectrofluorimeter which gave us the methodology to measure serotonin in a more specific and quantitative way than with the spectrophotometer. At the meeting we reported the effect of electric shock on levels of brain serotonin. I did this with Dr Luigi Valzelli. He was a very close colleague of mine and he was in the Mario Negri Insitute from the beginning until he passed away. He had done a lot of work during the years on serotonin, and in particular on aggressive behaviour.

The meeting was actually a mixture of experimental and clinical data and we mixed up, as much as possible, the two things. I remember there was enthusiasm because there was something new - an enthusiasm I experienced some years before working on isoniazid, the antitubercular drug which changed the treatment of tuberculosis, from which iproniazid was derived and the monoamine oxidase inhibitors.

It was also during that meeting that we had received from Dr Rothlin from Switzerland, the idea that it would be useful to have a branch of pharmacology called psychopharmacology and the basis was laid for establishing the Collegium International Neuropsychopharmacologium (the CINP). The idea first came up during this meeting, after which it was of course implemented, and from then they have had regular meetings of the CINP. I was involved with the organisation of the first meeting of the CINP in 1958 because Professor Trabucchi was involved and therefore I was drafted in to help him with various duties. Dr Radouco-Thomas was another key person.

What do you recall from the 1957 meeting. Are there any talks or any people in particular whose work interested you that you recall clearly now.

Well there were several people who were quite outstanding in the field. You can get some feel by looking at who was at the 1957 meeting. On the question of metabolism of neuro-transmitters, there was Dr Blaschko who gave a very good paper on the enzymes metabolising monoamines. Dr Hoffer, he was the one, who believed that adrenochrome was exerting effects on the central nervous system to cause psychosis.

There was the group of Dr Himwich and Dr Emilio Costa. Dr Costa was a young man at that time. We had been colleagues at the Institute of Pharmacology because he came from the Cagliari Institute of Pharmacology, where he worked with a pupil of Professor Trabucchi, by the name of William Ferrari and he spent some time in Milan with us as well. Then he went to the United States and worked with Himwich on amino acids in the central nervous system and later as you know he became a member of Dr Brodie's staff before going on to his own career.

Could you give me your thoughts on what role Brodie has played in the field because he was also the editor of Neuropharmacology wasn't he and he's had a very big influence.

Yes. This came a little bit later but certainly Neuropharmacology was a very important journal as was Psychopharmacologia, another journal devoted to psychotropic drugs. Neuropharmacology, in fact, was born in St Tropez, during a meeting between Dr Brodie, Dr

Costa and myself. Dr Costa contributed a lot in basic fields for the understanding of brain function. Actually in 1959, I visited him at the Galesbury State Hospital, where he was working with Dr Himwich and we did some work together. It was immediately after Dr Kuhn had discovered the antidepressant effect of imipramine. There was a lot of skepticism about the reality of this discovery because imipramine was so close to chlorpromazine in terms of chemical structure that nobody really believed it in the beginning. But it generated a lot of activity in trying to establish some way to show antidepressant activity.

I was working with reserpine and I got an idea which was refined by Dr Costa. Since reserpine was an agent considered to have depressant activity, we thought that an antidepressant agent might inhibit its action. In fact, we established and we published that imipramine and its metabolite, desipramine are inhibitors of some effects of reserpine, including sedation, hypothermia, ptosis and diarrhoea. We published a paper in 1960 on this in Experientia (refs). Unfortunately Experientia is not a Journal that is read by pharmacologists, so that paper although it was the first one to show the effect of imipramine as an antidepressant agent in a test, was never quoted by anybody. They quoted subsequent papers.

You will remember at that time there was a lot of work on reserpine and there was also a lot of work on the mechanism of action of antidepressants - it was about that time it was discovered that these agents blocked the uptake of noradrenaline in the brain and affected noradrenaline transmission. This was Dr Axelrod's work.

In terms of the people who were involved - Costa, Himwich, Axelrod, Brodie - who for you were the key people ?

I think the most influential man for me was Brodie. I don't want to diminish the fundamental contributions of Julius Axelrod and Sidney Udenfriend but Dr Brodie had more of a pharmacological attitude. As you know he was the man who established the basis for pharmacokinetics, drug metabolism and the importance of measuring blood levels and so on. He represented a great impetus because Costa worked with him and really became known working with him. Dr Pletscher, who was responsible for monoamine oxidase inhibitor work, spent a lot of time with him. Arvid Carlsson, who was extremely important for his work in the area of catecholamines worked with him. Dr Bowman developed the spectrofluorimeter in his labs. So there was really a large number of people that have exerted a lot of influence in psychopharmacology that originated or at least made contributions in psychopharmacology while working in his labs. Obviously many key investigators in psychopharmacology passed through the labs of Dr Axelrod, Dr Glowinsky for example, and Dr Udenfriend also.

What type of a person was Brodie?

He was a very interesting character. I had the privilege to spend a lot of time with him on various occasions in Bethesda or Milan - because he came from time to time to visit us particularly when I established the Mario Negri Institute in 1963. Steve was was a man that was always working. One couldn't find him doing nothing; he was always working, thinking and enquiring. He had the capacity to discuss problems with people putting the right questions, insisting on getting answers, insisting on getting opinions. He was really what I you might call, I don't know if there is an English word for it, *a maieutic*, which is a Greek word to say he could extract ideas from people by asking questions. He was quite good in this respect.

I remember that he used to work a lot during the night. With him it was difficult to go to bed before 2 or 3 o'clock in the morning. There were all these sessions he was asking questions and he alternated discussions with correction of papers. I learned from him a lot about the logic of writing scientific papers. He was never completely happy with a scientific paper. He was always thinking about the possibility to improve it. For me it was really a very important schooling and I remember him always with great affection and gratitude. I think that he has really helped a lot in the development of psychopharmacology.

Who else was important...?

Well Denber. He was working on a system to categorise psychotic reactions to the various drugs available at that time. Rothlin was the man who really helped made LSD available and undertook a lot of studies on the action of LSD.

What kind of a person was Rothlin. There has been some ambiguity about his role in the establishment of the CINP. Philip Bradley remembers him as being a key figure canvassing support for the idea, while Hans Hippius remembers him as being initially against the idea of a CINP but later emerging surprisingly as its first President.

Rothlin was a very good scientist, a very methodical person. He was a nice person although he had very clear ideas about what he wanted to obtain. We in Milan organised the 1957 meeting with the idea that a subsequent international association was desirable. I put a pressure on Professor Trabucchi to lead this organisation but he did not want to become President because of his poor knowledge of English at that time. Clearly many people had the same idea but I think without the 1957 meeting, in all probability the birth of CINP would have been postponed.

Did Hofmann play much part in any of this or did he just accidentally find LSD and then fade out.

Well without him there would have been no LSD but he was more on the chemical side. The man who developed knowledge on LSD from a biological point of view was Rothlin. Weiskrantz was important for studies on reserpine. Stata Norton was also important in the beginning because she was the one that tried to establish the action of various psychotropic actions on behaviour because at that time behaviour in pharmacology was certainly not very developed.

Observations of behaviour were already happening but all the tests this time were still simple tests. Obviously there were already people involved in behaviour but these were not known to pharmacologists. Neal Miller was one. Dr Leonard from the Roche Institute was involved very much in the effects of drugs on behaviour. Looking retrospectively I think we got a very good selection of names. I'm surprised. At that time I was a young investigator and although I asked advice from many people, to be able to put together a programme of this kind surprises me.

Erik Jacobsen was another one. He was studying benactazine but he didn't have much luck. And there was Dr Gatti from the Istituto Superiore di Sanita in Rome. He didn't get enough credit at this time. He was working with Bovet at the time and he really did some fine work on

behaviour and in fact he was using conditioning tests in rats at that time. Actually some of these tests would be useful even now seeing that looking at the effect of neuroleptics on operant behaviour is now a relatively modern way to look at drugs.

Now of some historical interest on the programme, we had Thuillier, a psycho-pharmacologist who played a role in the early days of the CINP. Nakajima who is now Director of WHO was working with him then. He was a pharmacologist and I think at that time, he had a fellowship in France with Dr Thuillier to work on what they called the turning mice. They were giving dinitropropyl and they were testing what the various drugs were doing on this turning behaviour. At that time there was very little known but I don't know if we have any better screening tests today. They reported at our meeting an extensive series of drugs that they studied on these systems.

Moruzzi and Bovet were present. They gave basic papers on electrophysiology and the function of the reticular formation. Dr Bovet and Dr Longo were interested in the effect of psychotropic drugs on electrophysiology. Philip Bradley was there and he was already using microelectrodes to study effects of drugs on the reticular formation. Another neurophysiologist was Monnier. And Killam was also an important person because of course he started the techniques of self-stimulation in the brain and studying the effects of drugs on self-stimulation.

Gastaut was at the meeting but he was actually more interested in the effects of neuroleptics on behaviour and then there was Unna. From a cholinergic point of view there was Feldberg from the MRC. He was mostly interested in behaviour with particular reference to the control of body temperature, which was affected by some of these psychotropic drugs. Dr Bein gave one of the direct papers on psychopharmacology, in which he discussed in great detail all the actions of reserpine. Dr Plummer was also important. He was also from Ciba but from the American branch. He did a lot of studies on the behavioural effect of reserpine and then a lot of studies on a large number of derivatives and these studies led to more chemically simplified compounds, such as tetrabenazine. Roche were working on derivatives of this while Ciba was working on analogues of reserpine.

Arvid Carlsson, who was the first to establish that reserpine was affecting catecholamines, was there. I remember at that time the puzzle as to why there should be an increase of catecholamines without changing the synthesis of catecholamines. This created the basis for the concepts of release, reuptake and storage. Arvid was very important in this respect. He was able to put together biochemical findings with physiological techniques. He is still in fact very active in the field.

We also had Courvoisier, who was the person who discovered chlorpromazine and the person who did all the early work on structure-activity relationships in the area of the phenothiazines. She was working at Rhone-Poulenc.

There's some dispute among the French as to who was the most important person clinically in the discovery of chlorpromazine - was it Henri Laborit or Jean Delay

Yes I think they had different roles. Laborit was using it mostly to produce deep hypothermia to make possible certain surgical operations but I believe Deniker was really the person who established the antipsychotic effect.

Erspamer was there and gave a talk on the relationship between the gastrointestinal enteramine (which was his name for serotonin) and cerebral serotonin. Shore and Brodie reported on the depletion of brain serotonin by reserpine, which they followed up by looking at its effect on noradrenaline. There were a great deal of interesting discussions as to why animals treated with reserpine took so much time to recover from depletion of monoamines. It was quite unusual for drugs to have such a long biochemical effect. There was not a complete correspondence with the pharmacological effect and this gave rise to the concept of "hit and run" drugs, which do something and then the drug is no longer present but the effect is there.

We had Tripod there; he tried to characterise agents on the the basis of their effects on the chemical transmitters that were then available. He was working on the action of the various drugs on acetylcholine, adrenaline, histamine and trying to make up patterns for the various categories of drugs. We know now how difficult this is considering that what we see may be the effect of a result of an action on multiple subtypes of receptors.

Looking through the programme you see here we have Alfred Pletscher, who gave the first observations of the antagonism between iproniazid and reserpine. This was a marked antagonism which was quite different from the one that is observed between imipramine and reserpine. At this meeting he reported on some of the biochemical effects of this interaction looking at the levels of serotonin that were antagonised by the action of iproniazid.

Clinically then there was Delay and Deniker. There were a number of psychiatrists commenting on the use of hydroxyzine and there was Frank Ayd.

You don't hear much about meprobamate these days but it seems as though at the time there was almost as much interest in it as there was in chlorpromazine.

Yes meprobamate actually was a drug that enjoyed quite a good market and it could have been done even better if in the States it hadn't been marketed by a relatively small company, Wallace, which actually became quite large because of the sales of meprobamate. Dr Berger was the man who had an essential role in developing and sustaining the knowledge of meprobamate. But then with the advent of the benzodiazepines, there was a decrease in its market. I don't know if it was good or bad because certainly we didn't have any knowledge at least at that time of any dependence to meprobamate.

Why do you think things took off as quickly as they did? Chlorpromazine was really only produced clinically in 1954 and by 57, 3 years later you have such a meeting. It's pretty remarkable isn't it.

Yes I think that this happens at the begining of a new field. Things are ripe so when something starts there is a flourishing. I think we have had the same type of experience with the cytokines. The various interleukins came about in a relatively short time. And now I guess it will take some time before they will discover other cytokines. It seems to be a pattern, at least in pharmacology, that you have a burst and then improvements and then a sort of plateau, where you try to understand the mechanisms of action. But actually if you look at the situation, in practical terms the progress was not so fantastic. We already had a tranquillizer, meprobamate - now we have benzodiazepines, many of them but they are all more or less the same. In terms of antipsychotics the only thing that was new was haloperidol and all its derivatives. Haloperidol, well it's different from chlorpromazine, maybe its an improvement

over chlorpromazine because it's more specific. We had the monoamine oxidase inhibitors and in 1959 we have the first tricyclic antidepressant. There has been no important progress after 1959. Some differences in the mechanisms of action but equivalence in potency. Maybe smaller differences in side effects which have not really been exploited in clinical practice. Clozapine may represent a progress in the treatment of the psychoses but that's all.

So why then did so much happen during 10 years and nothing very much since despite huge research enterprises ?

Perhaps one of the reasons is that we depend for new drugs very much on the industry and the industry rather than wanting to find out more about various areas, aims at finding a better drug than the previous ones but always keeping a large spectrum of activity. Now this can't be. We have already got something for anxiety, for depression, for psychosis. The only thing which is new is the effect on compulsive behaviours. Whether or not the SSRIs are superior or not is open to discussion but its a new area where something can be done. In this situation its basically difficult to have new things - unless you start to think that within anxiety you have different components and you try to find out agents that are useful for that particular component. But this doesn't really appeal to the industry because probably the market is too small and they don't want to have a large investment just to get a part of the market. But in reality at least retrospectively most of the companies that have developed one of the hundred antidepressants available didn't have a big piece of the market anyway. So they tried to have a large market but in essence most of them got a relatively small market, so there was no real advantage.

Now all the potential research available is addressed to the area of cognitive function but for the moment there is very little happening. But that's probably the next area. There will be something available in the future which means being able to do something for senile dementia. It looks like we may not be far away from that particular development.

The Mario Negri Institute where you work is now extremely famous. Why did you want to go independent when you did?

Actually the reason for which I sought to develop an independent institution was my first visit to the United States in 1957. I had two big impressions. One was the fact that at that time in the United States research was considered a professional activity. In Italy, in the University, research was considered a way to make a career in the University it was not considered a value in itself. It was instrumental to do something. The second thing that I was impressed by was the variety of institutions. There were universities. There were private and public universities. There were the big company research laboratories and there were these foundations.

I was interested in the concept of a foundation because it had, at least in my simple way to look at it, at that time, the advantage that foundations were not submitted to the bureaucratic laws that govern the public institutions including the universities. A second advantage was that you don't have to make profit. You can devote yourself to the public interest so that in the way I understood the situation it could be a sort of simple statement of private initiative in the service of the public interest that appealed to me very much.

So in 1957, actually after this symposium, I visited the main institutions in the United States for a period of 3 months. Coming back I got my group together. I said well if we are serious about

doing research, we have an alternative either we all go over to work in the United States where there was a request for us as scientists at the time or we try to do something different if we want to stay in Italy. In the end the idea was why don't we try to establish something different in Italy.

Who was Mario Negri?

Mario Negri was a self-made man, an industrialist in the field of jewellery, who came to me because he invested some money in a company called Farmacosmici, which represented Burroughs Wellcome in Italy. He and his director, Dr N. Damiani wanted some advice about new drugs.

I had a chance to talk to him about this on a number of occasions and after a while he was persuaded to establish a foundation. He wanted to when he was alive but unfortunately he got cancer of the liver. About 2 weeks before he died he called me in the clinic and told me to make sure I did what we had discussed. He died in April 1960 and when the Will was opened there were all the indications to establish the Institute with all the general policy that we had worked out together. In the Will, he named me as the Director of the Institute. At that time, what he left was a fair amount of money.

We started on the legal and financial aspects. We first got recognition by the US Government and then from the Italian one and at the end of 1961, we started to build the Institute and on 1 February 1963 the whole group of 22 people moved into this new building with a lot of anxiety but also with an interest to start the new adventure.

The Institute should have 3 aims - the first was to perform research, not so much in trying to discover new drugs but in understanding the mechanism of action of drugs thinking that if you understand how a drug is acting you are in a good position to have a better use of the drug. The second thing was to train young people to do research. This is now something very common but in 1963 the idea of having trained people in Italy to do research as a profession was something relatively new. The third thing was to disseminate information that was collected from the research phase. By dissemination of information we mean not only in scientific journals but also to inform in various ways physicians about the results of research and even the public. Again in 1963, this was rather revolutionary, when at least in Italy for an academician to talk to the public was considered something that was likely to lead to a loss of a prestige.

In the beginning we had a lot of interest because this was the first example of a foundation in Italy that was doing research. We had quite a lot of hostility from academia. I left the University with the whole group and since I was very close to get the Chair this was considered by the academicians as a sort of insult. So we had a hard time for the period.

We established a few simple rules for our practice - the first one was not to spend the money that was not available. The second one was to establish as much as possible a situation where there was auto-discipline so in the Institute we never had a union but equally we never checked the time of anybody. This is based on the idea that everybody has to do as much as possible. The third rule was not to accept grants or contracts for more than 10% of our total budget. This was to keep independence of judgement. The fourth rule was not to take out any patent - again in order to be free. So the Institute doesn't take out any patent even if we have

something to patent, the results are either given to the ones with whom we have collaborated or they are published. So, these were the simple rules that we put at the beginning of ...

Simple yes but very far reaching in their effects.

Well I think one of the problems we had because of the experience we had in the University was that we wanted to be free from political, industrial, academical influence and be able to say at any time our opinion about things which...

You think the Universities aren't free?

They are not entirely free because they depend very much on the ministry of education or the ministry of health for their support and if you depend entirely from a single entity it is not easy to criticise what the supporting entity is doing. But if you get just a fraction of your total income from any one source, then it's easier because you can afford to lose something if it is necessary to speak out about certain things.

So the first 6 or 7 years were really difficult in Italy but fortunately we had a lot connections at the international level and this is what really was very helpful to us. At the beginning we had grants from The Wellcome Trust to buy equipment. We had quite a lot of support from the National Institute of Health at Bethesda and also from some American foundations, such as the Gustavus and Louise Pfeiffer Foundation in New York. And after that the Institute was gradually accepted by academia here and supported also by the Italian sources. In the beginning almost 50% of our budget came from abroad and now it's much less.

The training of young people is an important goal for us. We now have about 850 people divided between the Institute in Milan, the Institute in the South of Italy, one in Bergamo and the other one that is being completed. We have tried to separate the field of interest of various groups. In Milan it is mostly cancer, psychotropic drugs and some aspects of cardiovascular pharmacology. In the South, it is mostly thrombosis, coagulation and neuroendocrine problems. In Bergamo, it is mostly renal diseases.

With time we have integrated our activity. We started purely on an experimental basis in the laboratory and then little by little we moved into the clinical area. The first one was to add clinical collaboration to protocols and then to arrange multicentric studies that were directed by the Institute of which the best known are the GISSI studies. These were studies on myocardial infarction. They were large size studies. We had 3 studies. The first one was a demonstration of the efficacy of streptokinase after heart attacks; we had a 12000 patients. The second one was a combination of streptokinase and aspirin in comparison with tPA; there were 20,000 patients in that. The third, which has just finished was the combination of ACE inhibitor with nitrates..

This was really worldwide wasn't it?

Oh yes, as I say in order to collect 20,000 patients we needed 200 centres in all of Italy, 200 coronary units and about 600 cardiologists - it was a very big organisation, only possible because of the collaboration of the Associazione Nazionale Medici Cardiologi Ospedalieri but now it's established as a network and the mortality of myocardial infarction has been almost halved in these 10 years of studies.

So, we integrated the laboratory with clinical work with epidemiology and then Bergamo was established because we wanted more direct access to patients. In Bergamo, we have joint appointments at the Institute and in the Department of Nephrology at the Hospital so that we can have a movement from the lab to the clinic to the lab. The Negri South is our institute to help young people in the South of Italy to enter biomedical research.

The last location of the Institute is at Villa Camozzi. This is a place where we want to establish a unique clinical research centre which will be devoted to rare diseases - why rare diseases? Because patients with rare diseases are doubly unlucky; they have a disease and nobody can help because there is no competence, no financial support, no knowledge. This will be a big place actually with 350 rooms and a beautiful park. There'll be 3 main activities there. One is to function as a centre of information for rare diseases where everybody can come and present their case and network with specialists. We'll keep an update of information about their disease and also an indication of the best Italian or foreign places where they can get assistance - if they want we will help them to establish a connection. This is work that is done free.

Then we will have a day hospital with 10 beds and there will be by the end of September 30 beds for chronic patients with all the necessary diagnostic facilities - a small hospital. The idea here is not to get the patients as they want to come in but to organise research on patients where they will be for one week. One week we will collect patients with a given rare disease and this we hope will trigger a number of specialists from all over the world to come because they will have such an opportunity. We will give hospitality in the same building and for one week there will be intensive work with a given group of patients with a particular diagnostic label - collecting biological samples, establishing therapeutic protocols etc. And then there will be another disease. Of course we will have our own projects in our own field of interest but the place will be available to foreign groups to use the facilities in order to study certain problems that they are interested in. Most of the work to remodel this building has been done with private money and by the end of September, as I said, it will be running.

What about the questions of not being prepared to spend money that wasn't available and the autodisciplinary issues?

Yes well, the first one means that we have been always working with our own money. In other words we never borrowed any money even for a very short period of time and this was vital because in the history of every Institute you find years in which it is easier to get support and years in which it is less easy to get support and then years of difficulty such as the one that we are having in Italy today. If you have your own resources you can survive. If you don't have them you are in trouble because you start to need to get loans and you have to pay interest.

Auto-discipline is the idea that you don't make too many controls that are meaningless. People can be there at a given time and if they don't do things they don't. The idea is that if you give freedom then of course people become more responsible. In previous periods of Italian history in which the unions had been extremely powerful in all the organisations, we never had any union inside the Institute and we never had strikes or whatever because people felt that the future of the Institute depended very much on them and not just other people. This I think was a very important part of the Institute.

You've been extremely careful about maintaining your independance - has it paid off?

Oh yes. I think so. Of course, independence means so many times that you have less resources. It means that you have more difficulties because you don't have any padrino that is taking care of your needs but in a period of scandals in Italy, it was very important that we didn't have anything to do with the politicians. So this has paid off because the public gets a clear understanding of these problems and I think that the Institute has been looked at by the public as an independant and reliable organisation, a scientific organisation that was close to people. This was shown up also by the support that we have received. Donations represent right now every year over 20% of our total budget - from private people, from banks or other organisations.

I think that there has been some important periods. One certainly was in 1972 when I was part of the committee to select the drugs for what was at that time our National Health Service. There were pressures to put in drugs, you know there was a lot of industrial pressure and so on, I resigned and I explained why I resigned. I think the public understood the fact that I wasn't willing, actually not me but the Institute wasn't willing to support things that were against scientific knowledge. Another important moment was in 1976 when we had the Seveso disaster, where the Roche factory blew up.

At that time through television and the media, the Institute said clearly what they thought about things, while industrial and political interests were trying to cover up or to minimise the importance of these events. We did a lot of work at this time. This happened on the 10 July and more or less half of the Institute announced that they would not take a summer vacation in order to work on this problem and I think that the public understood that to have a scientific institution is not just to have people who are working on their problems but to have people that care about what affects society.

The Institute was also well known because we took a public position against the presence of useless drugs in the Italian market. This was also unusual because in a way we have always been working very closely with industrial research and we think it is absolutely necessary and useful to collaborate with industry but I have always thought that we should not confuse the roles that co-operation with research is one thing but this doesn't mean that you are forced to help industry in public relations. This was also very difficult but I think we managed to keep the 2 things quite separate.

I have been involved many times in public discussions about problems of the use of useless drugs. Recently for the first time, I should say under the pressure of the public, I have been asked to take part in a committee for approval of new drugs, but this is happening for the first time after 40 years of work in pharmacology.

From a neuropharmacological point of view, what have been the achievements of scientists within the Institute. Samanin, Mennini these are names I am familiar with

Dr L Valzelli has been involved very much in work related to aggressive behaviour. Dr E Mussini has been very active on benzodiazepine kinetics and metabolism and actually we have been the first to show that many of the drugs that were put on the market as new drugs in fact were metabolites of other drugs such as temazepam or oxazepam or desmethyldiazepam. We have done a lot of work in that area. Dr R Samanin has been very active in antidepressant agents as well and has made a lot of contributions to the mechanism of action

of anorectic drugs and to the role of serotonin in drug activity. He has done pioneer work to show that serotonin was important for the control of food intake.

The group of Dr Mennini has been quite active in the area of receptors. Dr Consolo is well known for her work on acetylcholine and all the various drugs that effect the cholinergic system. I think she is one of the few that has developed methods to measure acetylcholine with a microdialysis technique which allows you to determine what is the extracellular level of acetylcholine. More recently Dr G L Forloni and Dr M Salmona have been working on those peptides that are neurotoxic and part of the amyloid structure; one of the papers was recently published in Nature. Dr S Caccia has contributed to the relationship between brain levels of drugs and their metabolites and pharmacological activity.

Then we have the clinical part where Dr A Spagnoli is mostly interested in Alzheimer's disease at the clinical level and he has done multicentric studies. Dr E Beghi is working on epilepsy. Dr B Saraceno is in psychiatry and he is mostly interested in epidemiology of mental diseases and the quality of the mental health service - psychotropic drug utilisation by hospitals as well as by practitioners. So these are some of the things that we have been doing. I think we have probably close to 1000 papers published in neuropharmacology and related fields.

The Mario Negri South has more recently contributed to outlining the mechanism of second messengers, the mechanism of secretion of chemical mediators, both of these areas are covered by Dr A Luini and Dr D Corda who have both worked for a long time with Dr Axelrod at NIH. They came back when we established Negri South. Work on molecular biology is led by Dr A De Blasi. Dr G De Gaetano, the director, Dr M B Donati, Dr C Cerletti and Dr A Poggi have contributed to knowledge of drugs acting on platelets, which may be considered a model for nerve terminals.

You've had 30 years to look at the interaction between neuropsychopharmacology and culture generally. Obviously the whole field has influenced popular culture when you get articles in the popular press and on TV and radio about prozac for instance. Do you want to comment on how the field has influenced culture or how the larger culture has influenced the field ?

Sure. Well you go through phases and there was a phase in which everything was wonderful - wonder drugs or magic bullets that were able to change psychiatry. This was part true particularly for the psychotic patients because it was possible to dismantle somewhat the psychiatric hospital due to the fact that we have these drugs available. And then there was obviously the phase where criticism occured and after all you had a lot of non-responders and you had a lot of problems caused by the drugs, side effects and so on. Now I think we are in a phase, where the drugs have established a pattern for determining whether a treatment is with or without efficacy. We have recently raised the problem of the legitimacy of psychotherapy and the various forms of psychotherapy, how it's justified and how they can justify whatever they do - as you know there are now up to 250 different methods of psychotherapy.

I had as a result of this a debate with a group of psychotherapists, where they invited me to express my view and where I strongly suggested that they are professionals and they have to justify what they do. Up till now there were only a few studies available and very little was done in Italy. Of course it is much more difficult to prove the efficacy of psychotherapy than prove the efficacy of drugs but this is not a reason not to try. As a result of that I think there has been

a lot of people, particularly young people, who want to collaborate on research in Italy to try to evaluate psychotherapy. This is certainly not an easy job.

The other way around our culture influences psychiatry or the use of drugs. That in my opinion is less obvious. At least if you look at the Italian scene, we don't have the problems that were typical of Halcion story or the Prozac story. There were newspapers who reported some of the discussion but there has never been a real dramatisation of the situation, so I don't really see much influence from the culture.

I could be wrong on this but it seems to me looking at what's happened over the last 30 - 40 years, not all Europeans have actually contributed equally to psychopharmacology. France was very crucially involved in the start. For some reason perhaps Italians have always been involved the whole way from the start. Is there any reason why psychopharmacology has taken root in Italy

Probably the reason is that Italy participated since the beginning and I think this is always important in any new field. For instance we are having difficulties in molecular biology because it came at a later time and we didn't participate in the development. In the area of psychotropic drugs, we were there perhaps by chance but we were there since the beginning. There have been some good groups - Dr Gessa in Cagliari, Dr Bovet, Dr Moruzzi, the department of pharmacology in Milan, Dr Racagni, Dr Cuomo, Dr Clementi, Dr Costa and others. There has been not only a presence from Italy in the beginning but also there has been a lot of cross-fertilisation with foreign groups.

One can argue that there is a certain cultural imperialism about psychopharmacology. It supports a very US/UK view of what the mental illnesses are - that has become prevalent in DSM III? How does that go down in Italy?

Well I think that Italy has been very weak in psychiatry. There was little science, a lot of talks, a lot of comments, a lot of theories but psychiatry has never been as strong and therefore either they follow psychoanalysis or they have to follow whatever has developed in the Anglo Saxon countries - there is no other way. There is not enough strength to develop something autonomous.

Can I pick up a point you raised earlier which is the question of drug specificity. It seems that for 10 - 20 years after the 1950s we went down the route of trying to get more specific drugs and that seemed to be a good thing to do but in the last 5 - 10 years there's been something of a crisis of confidence. It seems almost as though the purer the drug the less effective it's going to be.

Well for the moment this is the impression but there is no scientific basis to say that but I think that we should distinguish 2 areas in psychopharmacology. There's an area that I would say is the area of knowledge, where we have a lot of interest in having extremely specific agents because it is by having a specific agent that you can pinpoint the importance of a given chemical mediator or a given receptor or a given enzyme in general brain functioning.

But this has to be distinguished in a way from the practical applications and perhaps the strategy to develop new psychotropic drugs is not necessarily the same as that which improves your knowledge. So, there must be some distinction, although it is not known where you have

to draw the line. Certainly you shouldn't use the first approach as the best approach in order to fulfill the second aim.

Well then is the idea of trying to develop a rational psychopharmacology something of a myth?

It is a myth for all science in a way because the complexity of a living organism is such that if the aim is to cure something it is difficult to proceed only on a very rational basis. I think we will probably come back to the idea that you need models of given psychiatric disorders, which you have to try to correct and then work out what has happened. Obviously its an osmotic process because on the other hand you develop agents, which affect given chemical mediators or whatever and if you achieve this you try to see if they are doing something in the models of mental diseases. But while there is at present a lot of interest in establishing tools for research, there is an imbalance in terms of looking at models and investing in models.

What do you mean by investing in models

I mean anything that you develop in order to mimic the whole or an aspect of a given disease. Such as, for instance, you can see that schizophrenia is a disease with many symptoms, you have positive and negative symptoms and you should be able to develop models on which to test if you can modify any of these symptoms. It is obviously very difficult to modify these symptoms reliably in real life but if you have the model, in which it is simple to modify these symptoms by proper drugs, you can then go to man and see if the extrapolation is possible. This is neglected at the moment.

Certainly for schizophrenia but there are a lot of animal models of depression.

There are animal models for depression. Yes there are many but of course each one covers only a small aspect of depression. One should try to modify them by drugs but I think one should try to modify it by a primary approach because obviously if you test these models with only drugs that have given effects on chemical mediators you pre-establish what you are going to test. And that will not give you a new type of drug. In other words I think that you should apply new tests if you want to find new drugs. If you are using old tests for a known mechanism you are going to reproduce the same drugs.

Why is the industry so conservative then?

Well the industry in this area is probably not convinced that you can make a lot of progress. Therefore they try to get a slice of the market. I think that the concept of Me-Too drugs depends always on the fact that you don't believe that we can develop something new. In Alzheimer's, where there is nothing, the industry is investing with determination. There is also another aspect, which is that there is a great discrepancy in the sophistication with which we look at the mechanism of action of the various antidepressant agents and establish whatever can differentiate one drug from the other and then when we arrive at the clinical level, there is extreme uniformity in testing them, as though you would not be interested to see differences (see refs).

We use the same 2 or 3 rating scales and force all drugs to conform with them...?

Yes the type of protocol that is used is used not to show difference but to show equivalence Industry makes a bet. They say if they can get an antidepressant agent through the FDA they may have a chance to have a big slice of the market. And since they know how to do this in terms of development, it is an easy way to go. Industry establishes pre-clinical differences for different drugs that it doesn't use in its clinical trials but it does use to exploit the market. Marketing is not based on the fact that my drug is superior to the other. It is based on the fact that my drug is affecting dopamine more than serotonin or more than noradrenaline with respect to another drug.

Coming back to the question of purity, on the question of testing for the toxicology of new drugs, I've heard you say that we cannot always rely on cell lines, that sometimes we have to go back to the whole animal. Do you want to comment on that because it's very politically correct these days to praise the virtues of cell lines?..

Yes I've just come from a meeting in Baltimore which was the world meeting on alternative techniques and there was a session called Point/Counterpoint where a man from OECD was defending the alternative method and I was supposed to defend the animal methodology. I presented practical cases to show that a certain effect could not possibly be seen in tissue culture. The organism is so complex that the idea that we can mimic this complexity in a tube, it's really absolutely irrational. The approach taken by many of these groups that are interested in alternative tests is that essentially they are saying that since the mouse or the dog or the monkey is not man, therefore it may be misleading to extrapolate to man. I take the same approach and say if you go down to a level which is even further away and hope that by simplifying things you can solve a very complex problem, you are unlikely to succeed. Politically it pays because again there is money available to study alternative testing. There is little money to do animal research because it is not popular anymore.

This again is something that our Institute has been very strong in Italy in trying to tell people why we need to use the animals. I have had a lot of debates in public and on television to indicate that this is what we have to do if you want to make sure that you have better drugs, chemicals that are not damaging man, you have to rely on animals. Thats the best thing that you can do now and the fact that in the future you may have alternative techniques, doesn't mean that you have to put obstacles in the way of the present line of research. Philosophically I'm convinced that it will never be possible to do without animal work in toxicology because I would like to know how a cell could tell you about convulsion, tremors, anorexia, cachexia, hypothermia. These are things that cannot possibly be seen in any cell, whatever you do, whatever type of methodology you may have available. But it is very unpopular to say this.

Well now can I ask you why 40 years into the psychopharmacological era, the more rational we become about how we develop drugs, the more irrational people on the street have become. They prefer to go out an buy health foods thinking that they are safer even though the compounds in health foods haven't been tested and sometimes even are old drugs that have been rejected by orthodox medicine as unsafe. Why is this happening?

Well, first of all there have been all these Green movements and they have popularised a concept that seems logical - that nature is good and what man does is bad and so we should follow nature. I always try to say that this is tragic; it is stupid to think that nature is good and man is bad because nature may be good or may be bad. Viruses and bacteria are not all that

good. Most of the poisons are present in nature. The rational way to look at the problem is not to generalise about nature or man but to look at the various compounds one by one and try to evaluate them one by one and one may discover in some cases that nature is good and in other cases it is bad. In the same way man as part of nature sometimes he makes good things and sometimes bad things and you have to evaluate each one on its own. This applies to everything. The idea that herbs or health extracts are good because they are made by nature is stupid. It is irrational; it is a kind of sub-culture.

Why are we so influenced by this kind of thinking?

Well because the environment is becoming an important issue, Having lost a lot of meaning in our life, religious and moral then you must have some value and the environment appears to be something good for many people. Not for all. The Greens are still after all a very small minority, a very vocal minority, who may seem to be more than in reality they are but because it is fashionable nobody opposes these views because if you oppose you become unpopular. But I think that the role of science and the role of scientific institutes is sometime to be unpopular because we are interested in what appears to be the truth and it's our duty not to follow fashion but to follow what we think is rational. Unfortunately I should say that the scientific community is not outstanding in this respect and most people prefer the quiet life rather than to expose themselves and to discuss these issues.

It's easier to get on a TV chat show as well if you're going to take the popular point of view.

Sure. If you defend the animals you are immediately popular and a good man. If you say look if you want to have safe drugs I don't know of any better way at the moment than to use animals and then you become somebody that is cynical or questionable.

As we have lost cultural, moral and religious values in recent years, have the larger pharmaceutical companies become centres of culture in their own right?

Yes this I see as dangerous for science because now there is relatively little freedom in science. If you look at most of the meetings, they have sponsorship and nobody sponsors anything unless at the end it gets some interest. Most of the journals that physicians are receiving are paid for by advertising; this creates a sort of distorted information that is very difficult to compensate by free information, independent information. I always say that in Italy the industry is spending about 3,000 billion lire every year to advertise their products in various forms and probably we are spending a few millions to have independent information. This is very bad.

In the long run it is not in the interest of the industry because the industry in order to improve must be stimulated. The industry must have a relatively difficult life in order to become productive. If you give it an easy life, obviously you are not going to make a big improvement. So in the end it is also in the interest of the industry to develop criticism, to increase the level of critics. But it doesn't at the moment I think. And this at the end influences all our knowledge and also the evaluation of efficacy. It is not by chance that we don't have any comparative studies among drugs. Because it is not in the interest of the industry. The state apparently doesn't seem to be interested in these problems and at the end what is done is only what ..

When you say the state is not interested is it that they don't want to lose their pharmaceutical companies.

I don't think so. I think it's a lack of culture. There is no culture, at least in the Italian National Health Service. They should be interested because if they take drugs and they establish that there is no difference or that one is better than the other there is a lot of consequence in terms of what they would do and also how much they will spend so they should be interested but at the moment there is not this type of culture.

When I raised the question about the industry being a centre of culture, I was thinking actually about something slightly different which is they will sell antidepressant drugs to treat people who are depressed, they will sell antipsychotic drugs to people who are psychotic, but at the moment they've got a great number of drugs that will enhance sexual performance for men and women, drugs that will delay orgasms for men who have a premature ejaculation problem and bring it forward for women but they don't market these. The smart drugs are another example. Companies are happy to get involved with drugs to treat Alzheimers but social engineering..

Makes them very wary. Well they may fear public disapproval. It's the same reason for which Roussel doesn't want certain countries to use their abortive drug - in countries where there are strong religious groups that would object and say to their members don't buy drugs from that company. They may feel that it would be counterproductive.

Pursuing the issue of culture. The range of psychopharmacological cultures around Europe is interesting. You get antidepressant that are best selling antidepressants in France, like maprotiline, which don't sell in the UK and then prothiaden is the best selling antidepressant here but nowhere else in Europe...

I made an analysis of the 50 most sold drugs by value for the four biggest European countries, Italy, France, Germany and England and it's amazing to find out that there are only 7 drugs in common to the 4 countries (see ref). The differences are amazing. In Italy there are 3 preparations containing interferon, which is not present in the 50 most sold drugs, in any other country. In Germany it's ginseng which brings to the rational use of drugs an alternative medicine - that is really crazy. The success of homeopathic medicine is having in Italy is unexplainable. People buy nothing. Homeopathy contains nothing. And how nothing can do something it's really astonishing. But apparently people are interested.

Despite the improvement in scientific culture there is still a lot of interest in magic. Perhaps it's a reaction against science. People are afraid of science and they take refuge in magic. It's very strange in a way because people take advantage of all the scientific developments but they are afraid and that's probably because the growth of science has not been accompanied by a growth of the scientific culture in the public. You can see that the schools are not teaching elementary things belonging to science. If you talk with normal people about basic problems such as what is a risk, what is a probability, what is a risk factor people don't know. They have, for instance, a perception of a risk which is many times inversely proportional to the real risk.

Well in a sense, clinical trials and all that have highlighted that there is a small risk of things happening that we wouldn't have known about if we hadn't done the trials, but the trouble is once people become aware of any risk, panic sets in.

Yes and for other aspects when they take the car they have a much bigger risk but that risk has become part of culture. Other risks have not. And that's where the school should have a lot of influence but they don't teach these things at school.

Can those kind of things actually be taught?

Yes I think so. If you start with children to tell them what the meaning of probability and of risk is and if you give them examples of effects for instance if you smoke you have a much higher risk than anything else you can do, that should be illuminating and something that will then remain in a culture but if you are teaching them ...

In a sense we are talking about trying to teach people to do things that are very unnatural aren't we. The calculation of risk uptil the late part of the 20th century are things you do spontaneously. You don't work out with a pen and a piece of paper. Now we are saying we are in an era where we can put weights on all of these risks. It's very..

Yes but what I find is that people may have a relatively good perception of the acute risk but they don't have a perception of the chronic risk because they don't see the relation between cause and effect. It is so far away the effect that they don't ever see it. For instance, if you talk with people about the risk that could be intrinsic when we eat a given food a given vegetable and so on, their reaction is well people learn what is good and what is bad. Yes they have learned but nobody knows if a given vegetable contains a carcinogenic agent and after years of eating it you may get a cancer. This is out of the imagination of people to think in this way. Again its a question of teaching.

When the adverse effects of drugs reach public consciousness through the media and newpaper reports, they do so as "acute" risks in a sense...

And they don't have the knowledge to distinguish one case per one hundred from one case per one hundred thousand. They don't see the difference; they see them as all the same. And the public doesn't appreciate the fact that you cannot find out the toxic effects of drugs before they go to market. You can find out the very evident and very frequent effects but not problems that occur one in ten thousand and when you withdraw a drug from the market they are extremely surprised. They don't think that this is a good outcome because you have been able to localise a toxic effect. They think that this should be possible in the beginning. But it is not possible and it's necessary to explain these things to people.

I've heard this put quite well recently in terms of for some reason now we seem to feel that we are born with a warranty in a way that we didn't really feel 30 years ago. When people began taking the first psychotropic agents 30 years ago they felt life was a thing in which there were risks and if things went wrong tough luck. Now we've got this feeling if things go wrong there's someone to blame, a pharmaceutical company or some researcher somewhere and we want to be able to sue them

Yes this is partly what we have taught people. Because for a long time the pharmaceutical industry and whatever was connected with it denied any possible toxic effect of drugs which were depicted as magic bullets and then if you give something that is wrong you pay for that. Now we are paying for the extreme degree of confidence that we tried to instill into people

about drug efficacy and safety. We haven't mentioned toxic effects and we haven't told them that a drug is after all what comes out from the ratio of benefit to risk and that benefits have to be there in order to justify the risk. The culture has always been safety first which is wrong in terms of drugs. It is simply meaningless; there is no benefit if there is no risk. And we are paying for some of the distortion in things that we have been inserting into the public whether in a conscious or unconscious way I don't know but that's what we have told them and now they react because we have told the wrong things.

I should like to explain. I have recently been involved in a sort of scandal because of a report showing that in Italy there were killer drugs in circulation. I had a role in looking at this data and then in explaining to the television and to the people what was the problem. What I said was that you shouldn't be surprised that there are toxic drugs - all drugs are toxic. What is important is the use that you put the drug to and I gave the example that if you take a drug which is an anti-cancer agent which everybody knows is extremely toxic and if you give it to a patient who has cancer you expect that the benefits are much more than the risk and even if you have a risk of a second cancer nobody cares because it means that you can survive for 15 years or so in order to get the second cancer. But suppose you give the drug to a patient for whom the wrong diagnosis has been made. He has no cancer. It will be devastating because you have no benefit since he has no cancer. He has all the risks. See how the ratio of benefit to risk is something that applies to given indications. It shows that toxicity is not a problem if you have enough benefits.

But this way of reasoning is not the way in which the effects of drugs are presented. Industry wants to show safe compounds. They wrongly think that whatever will raise attention on toxicity will decrease sales and they are against it. In the long run it pays to tell people how things are in reality because if you don't it will boomerang.

REFERENCES

Garattini S, Ghetti V (1957). Psychotropic Drugs. Elsevier, Amsterdam.

Costa E, Garattini S, Valzelli L (1960). Interactions between reserpine, chlorpromazine and imipramine. Experientia 15, 461- 463.

Garattini S, Garattini L (1993). Pharmaceutical prescriptions in four European countries. Lancet 342, 1191-1192.

Garattini S (1996). Experimental and clinical activity of antidepressant drugs. in Psychotropic Drug Development. Social, economic and pharmacological aspects ed Healy D, Doogan D P, Chapman & Hall, London pp 1-12.

See Hippius H (1994) Meeting Wolfgang de Boor & Radouco-Thomas C (1994) Meeting Emilio Trabucchi in Towards CINP, eds Ban T A, Hippius H, J M Productions, Brentwood, Tennessee, pp 37-41 & pp 42-44.

Radouco-Thomas C (1994) Proposal for Founding of the CINP. in Towards CINP, eds Ban T, Hippius H, J M Productions, Brentwood, Tennessee, pp 47-50.