G. Semenza and R. Jaenicke (Eds.)
Selected Topics in the History of Biochemistry: Personal Recollections VI
(Comprehensive Biochemistry Vol. 41) © 2000 Elsevier Science B.V.

Chapter 13

A biochemist by chance: Alessandro Rossi Fanelli, builder of the Roman school of biological chemistry

GINO AMICONI

'Alessandro Rossi Fanelli' Department of Biochemical Sciences, University of Rome 'La Sapienza', Piazzale Aldo Moro 5, 00185 Rome, Italy

At the end of September 1981, Alessandro Rossi Fanelli was honoured at the National Academy (l'Accademia Nazionale dei Lincei) in the context of a scientific symposium organized by some of his pupils. The stated and obvious aim was to re-unite as many as possible of his old and young Italian pupils (Fig. 1) and many foreign scientists of international renown who in previous years had had more or less continuous contacts with the Rome University's Institute of Biological Chemistry (at that time there was only one university in Rome) to honour the founder of the so-called 'Roman school of biochemistry', who had reached the age of retirement. In Italy, as is well known, university professors retire gradually and in general never entirely give up their organizational, scientific and teaching responsibilities. At the age of 70 they are retired from the teaching body, but can remain as heads of departments, institutes or specialist training schools. At the age of 75 they are retired, in the sense that they are officially pensioned off, but for the most part they continue to attend the department or institute where they have spent the last part of their academic life. They often

Fig. 1. Alessandro Rossi Fanelli (front centre) with some of his closest collaborators on the occasion of the celebrations in his honour at the Accademia Nazionale dei Lincei in 1981. Proceeding from the bottom to the top row and from left to right: in the front row, Maurizio Brunori, Lilia Calabrese, Franca Ascoli Marchetti, Alessandro Rossi Fanelli, Dagmar Siliprandi, Emilia Chiancone, Anna Giartosio; in the second row, Giuseppe Rotilio, Carlo De Marco, Donatella Barra, Doriano Cavallini, Francesca Riva, Eraldo Antonini; in the third row, Noris Siliprandi, Silvestro Duprè, Roberto Strom, Carlo Cannella, Paolo Cerletti, Bruno Mondovì; in the fourth row, Roberto Scandurra, Giorgio Federici, Bruno Giardina, Alessandro Finazzi-Agrò, Carlo Turano, Carlo Crifò, Francesco Bossa.

do so as individuals, but every so often they may also have some official title. Shortly after they retire, in fact, the title of Professor Emeritus or Honorary Professor may be conferred on them, on the grounds of their reputation, by the President of the Republic on proposal by their faculty. It was in 1981 that Alessandro Rossi Fanelli ended all official activity in Rome University – though he was predictably named Professor Emeritus in 1984 and continued to attend the institute of which he had long

been director – and the symposium was therefore of the greatest importance to him because it was on that occasion that the concluding summary of the whole of his academic life was presented.

It was William E. Blumberg [1], a brilliant scientist from Bell Laboratories, who at the time was collaborating with Bruno Mondovì, who presented a summary of Rossi Fanelli's scientific career with ingeniousness using statistical tools a little more elementary than those adopted by Eugene Garfield for his *Citation Index*. Bill Blumberg focused on Rossi Fanelli's work from 1946, that is to say from when he started to publish as Professor of Biological Chemistry at Pavia University until his retirement in 1981 from the La Sapienza University of Rome. In those 25 years, Rossi Fanelli's scientific output followed a course typical of that of many great men of science (according to Bill Blumberg): an initial stage (1946–1954) with a progressive increase in the number of publications, followed by a period of almost constant high output (1955–1966) and then a gradual decline (1967–1981) in the number of scientific publications as he devoted more time and more energy to other activities (science policy, search for financing, administration and, why not, also to sailing, a passion that continued for the whole of Rossi Fanelli's life).

The continuous theoretical curve that describes the bell-shaped trend in scientific output nevertheless ignores some details, as three clear peaks in the number of Rossi Fanelli's publications appear around 1955, 1960 and 1965. These unexpected blossomings markedly exceed the mean predicted by the theoretical curve that passes through the numerical data. The first peak is due principally to research on thiamine and myoglobin, the second chiefly to papers on the oxygenation of haemoglobin, and the third in part due to study of the physicochemical and functional properties of the haemoglobin sub-units. Myoglobin and haemoglobin therefore take up the lion's share of publications by Alessandro Rossi Fanelli and his collaborators. There is therefore nothing to be wondered at in

the remarks with which Morris Reichlin [2] concludes his review of the book on haemoproteins by Eraldo Antonini and Maurizio Brunori: 'This book is a weighty testimony to the enormous experimental contribution of the Rome group to our understanding of hemoglobin and myoglobin. If the reader is not careful he may even come to the conclusion that hemoglobin is after all an Italian molecule.'

If, on the other hand, one looks at his scientific output as a whole, one notes a gradual increase in the size and complexity of the biochemical systems tackled by Rossi Fanelli, who started his research career studying small molecules (amino acids and vitamins), progressing to globins and multi-sub-unit proteins, and finally to very complex polymers. The present research strengths of the Department of Biochemical Sciences (the direct successor of the old Institute of Biological Chemistry) mostly reflect the interests of Rossi Fanelli, being overwhelmingly focussed on mammalian enzymes, protein physics and chemistry (with pride of place given to enzymes and proteins that interact with oxygen) and to metabolism. Study of the nucleic acids is restricted to their relevance in relation to proteins, as in protein engineering and interaction with histones. No lipids, now as then, and no glucides, now as then.

As regards the more substantive institutional aspects – that is to say the space available, and the permanent and other personnel – the celebrations provided a striking demonstration of their enormous growth from very small beginnings, thanks to Rossi Fanelli's tenacious efforts. From very few rooms and a single technician doing the most varied jobs, the department had grown to occupy most of the four floors of the building that housed the first institute and to over a hundred teaching and non-teaching personnel.

Biochemist by chance

Alessandro Rossi Fanelli was born in Naples on 4 January

1906 to a family from Puglia that had a legal tradition. His ancestors included advocates and magistrates, but no doctors. In spite of that Alessandro chose to study medicine. As graduation drew near, he encountered a field to which he was particularly attracted, neurology, and he started to attend the Clinical Neurology Department with interest and assiduity. Determined to pursue a university career in the field of neurology, he felt it a duty to master the conceptual and material tools necessary for serious medical research. A university instructor is no such thing unless he also does scientific research in his own field of interest. What could be better than the conceptual and material instruments of biological chemistry (or physiological chemistry as it was then called) to conduct leading edge research in medicine? He discussed it with his Professor of Neurology and, having obtained his consent, became a student intern at the Institute of Physiological Chemistry at the University of Naples, headed by Gaetano Quagliariello. It is likely that Alessandro Rossi Fanelli was also fascinated by the fame that the Naples School of Biochemistry then enjoyed. It should be remembered [3] that Naples University was assigned the first chair of physiological chemistry in Italy, occupied by Antonio Pasquale Malerba from 1898. It was also at Naples that the great Filippo Bottazzi [4–6] worked at the beginning of the century: a physiologist in name and biochemist in fact, he gained international fame for his brilliant research work and was invited to join the editorial committee of *Biochemische Zeitschrift*. It was Bottazzi who occupied the Chair of Physiological Chemistry [3] on the death of Malerba, before his pupil Gaetano Quagliariello took over in 1926. Alessandro graduated in 1929, presenting an experimental degree dissertation in biochemistry. In those days a brilliant young man full of initiative could have a swift and brilliant university career and so, following graduation, Alessandro Rossi Fanelli believed he should be given a staff position as Assistant in Neurology. In fact he believed that on the grounds of his own merits, the

quality and quantity of the work he had done and, why not, of a sort of chronological right as the most senior student intern, he was the person who should have been given that post. His professor thought otherwise and gave the post of Assistant in Neurology that was available to the son of a friend and colleague. Alessandro felt that his rights had been infringed, his dignity offended and the affection he felt for that professor destroyed. Without making any complaint or demanding explanations from the neurologist, Alessandro Rossi Fanelli turned to Quagliariello, asking to be accepted in his institute, and from that moment on was never seen again in the Department of Neurology. Some months later he encountered the professor again on a bus, and the latter asked him in ironical tones, what ever had happened to him. When he recounted this episode, Alessandro Rossi Fanelli concluded bitterly, 'At that moment I realised that he had never liked me.' For him, as a man of the south, human and work relationships were then, as for the rest of his life they remained, based not only on esteem, but on sincere affection. An event like that just recounted, apparently commonplace and even insignificant for today's sceptical mentality, profoundly marked the soul of young Rossi Fanelli, who not only used to recount the episode from time to time in chatting with young pupils, but made it his emblem for the rest of his life, in the sense that to progress in their careers, his pupils were always to be judged on the basis of their scientific merits. This fundamental criterion of meritocratic justice gave life and energy to the Roman school of biochemistry that he founded after World War II.

The years of apprenticeship

Alessandro Rossi Fanelli's career in the Institute of Physiological Chemistry at the University of Naples was very rapid. In 1930 he was awarded a scholarship by the Rockefeller Foundation. In 1931 he was appointed Assistant. In 1932 he sat a competitive examination to win the post of Assistant in

Physiological Chemistry. In the meantime Gaetano Quagliariello had given him a room in the centre of the corridor in front of the main entrance to the institute. 'Though it was the biggest room in the building', recalled [7] his first Neapolitan collaborator, Alfredo Ruffo, who was to become Professor of Biochemistry first at the University of Perugia and then at the University of Naples, 'at certain times of day it was inaccessible because of the throng of collaborators and students ... On one bench there were two Van Slykes, on another the Pulfrich photometer for colorimetric microanalysis (famous at that period), at the centre of the room two Warburgs, always in noisy movement. And also pumps, burners and bellows as in a glassblowers workshop. His exceptional manual ability often drove him to construct some small pieces of equipment to solve some problem of the moment.' Rossi Fanelli's manual ability and inventiveness must have been truly uncommon, since another of his collaborators wrote as follows [8]: 'I remember with admiration his great ability – manual, too – in setting up various rather complicated apparatus with 'bits and pieces' gleaned here and there, and his undisguised satisfaction when the work was completed. His innate respect and almost, one might say, loving care for all apparatus is a direct outcome of those arduous years.'

In the years from 1933 to 1935 Alessandro Rossi Fanelli went to work in foreign laboratories; first at Freiburg under Professors Thannhauser and Bohnenkamp on the composition of nucleoproteins, and then in Prague under the guidance of Professor Waldschmidt-Leitz on the activation of enzymes. These were very formative periods for the young Rossi Fanelli from both the point of view of idea stimulation and that of manual and conceptual techniques, as any one who has gained fruitful experience in well-organized foreign laboratories can well imagine.

Back in Naples, he continued his biochemical research and took the exams of the chemistry course, obtaining that degree in 1937. Alessandro Rossi Fanelli in fact held that medical

training was basic to understanding the nature and importance of the various biomedical problems that he was facing in his scientific research, but that on its own it did not provide sufficient methodological training for tackling all biochemical problems efficiently.

This period of apprenticeship, which we can call Neapolitan, ended in 1942 when Alessandro Rossi Fanelli was winner of the first university competitive examination to be given the name of biological chemistry (until then the subject had been called physiological chemistry in Italy) and in November of that year he was called to the Faculty of Mathematical, Physical and Natural Sciences in the University of Pavia.

Among the scientific results of this Neapolitan period one can include the demonstration that non-hepatic tissues are able to oxidize acetoacetate, anticipating the now accepted idea that muscle, brain and kidney use the ketone bodies provided by the liver as fuel. Of no less importance was the demonstration that part of the α-ketoglutarate produced from citrate (in the process that was controversial at the time and only described as the tricarboxylic acid cycle by Hans Krebs some years later) can be transformed into glutamate. Thus, a hint was given of the transamination process and of the interconversion of monosaccharides into amino acids. These and other equally important results were for the most part published in Italian in Italian scientific journals, with a few in German journals. At the time communication with the English-speaking scientific world was not easy and for that reason the results were denied the resonance that, with hindsight, they deserved. That notwithstanding, Alessandro Rossi Fanelli's name was cited in the *Annual Review of Biochemistry* (Vol. 2, 1933; Vol. 5, 1936; Vol. 6, 1937) as well as in *Ergebnisse der Enzymforschung*, *Handbuch der Enzymologie*, *Die Methoden der Fermentforschung* and *Handbuch der Katalyse*.

Sentimental education

Alessandro Rossi Fanelli always retained a vivid recollection of his scientific youth, as of the profound friendship with his colleagues of that time. He had a quite special respect and affection for his master Gaetano Quagliariello, from whom he learned the passionate dedication necessary for creation of a department and his deeply-felt dedication to academic values. On this subject one of his first pupils, Noris Siliprandi, who went on to the chair at Padua University, made the following important observation [9]: 'I believe that this devotion to his master coupled with his innate gifts contributed greatly to making him an authoritative founder of a school. In fact the history of science proves that the scientific elite and the schools that have imposed their leadership have been formed in communities that knew how to honour their masters and at the same time valorise the talents of their students.'

Seeds of glory on a field well-tilled by illustrious predecessors

In the late 1930s and early 1940s Alessandro Rossi Fanelli started a line of research in Naples, the development of which would constitute one of his greatest scientific glories and was the first cause of the fame that his name gained in the English-speaking scientific world: the study of haemoproteins and in particular of myoglobins.

Haemoproteins were a subject that had already been tackled by many laboratories in Italy, including that of Naples, since the end of the previous century. Studies on haemoglobin began in Italy in 1882 with the appearance of an article on the multiple presence of haemoglobins in the blood written by Giovanni Gallerani of the University of Camerino, the same scientist who later did so much to popularize spectrophotometry in Italy with an invaluable booklet written in 1903. In the years that followed (between 1909 and 1923) E. D'Agostino

of Naples measured the spectrum change of ferric haemoglobin during the transition from an alkaline to an acid environment (a phenomenon he traced to the oxygenated haemoglobin) while the Neapolitan Filippo Bottazzi devoted his attention to the conductivity of haemoglobin solutions that had undergone dialysis for long periods of time.

One can also point to the landmark work published in 1910 by Joseph Barcroft on the shape of the curve for the equilibrium of haemoglobin with oxygen, since his co-author was the Italian Mario Camis, a physiologist from the University of Parma who had gone to England to work at Cambridge. After returning to Italy, Camis continued his research on haemoglobin. In an attempt to provide an experimental foundation for the theory of the state of aggregation of haemoglobin, he studied the changes produced by lactate on the surface tension of haemoglobin solutions. In 1921 he discovered that, at constant temperature, the molecular surface energy (the surface tension multiplied by the molecular surface area) fell with the rise in lactate concentration. Camis interpreted these findings in terms of a molecular aggregation of haemoglobin. During the same year, Rossi Fanelli's master, Gaetano Quagliariello, repeated Camis' experiments in the presence of various salts and acids, but arrived at the conclusion that there was no connection between decrease in surface tension and molecular aggregation. Giulio Pupilli, one of Camis' students, entered the debate as well, performing a series of highly accurate refractometric measurements in 1923. In an approach worthy of Solomon, he worked along two separate lines, one supporting Camis' thesis and the other based on Quagliariello's assertion.

One need merely mention Giuseppe Amantea of Rome who, back in 1923, used a method of his own to observe that the crystals of haemoglobin obtained from the blood of new-born children differed from those produced from the blood of adults.

While on the subject of haemoproteins, it is impossible to ignore the contribution of Rodolfo Margaria, who spent a

long period of time in England during the early 1930s on a grant from the Rockefeller Foundation studying the physiological effects of carbon dioxide with Joseph Barcroft and Francis J.W. Roughton. Among other results he obtained a large amount of experimental data pointing to a possible effect exercised by carbon dioxide on haemoglobin through direct combination with the protein, above and beyond the indirect effect stemming from its acidic properties. Though extremely interesting, these results were not suited to an accurate quantitative treatment. Margaria later went to Boston (United States) to work at Harvard University under A.A. Green, with whom he published an important paper demonstrating quantitatively that the presence of carbon dioxide shifted the curve for the equilibrium of haemoglobin with oxygen to the right, regardless of pH.

It was in Naples in the late 1930s and early 1940s that Alessandro Rossi Fanelli entered this research field already well-tilled by Italian scientists, including, as we have seen, many Neapolitans. It cannot be denied that Italian research on haemoproteins from the start of the century was of great interest and also in the vanguard, although the impression remains that it lacked a guiding line that could have provided a unified overall vision of the whole question of structure and function interrelationships. Rossi Fanelli himself apparently acted like his predecessors, that is to say he did not continue along a route that had already been opened up but tackled an entirely new topic, though it turned out to be a well-chosen one, triggering an explosion of scientific results aimed at explaining the functional behaviour of haemoglobin at the atomic level. He produced the first experimental evidence demonstrating that haemoglobin and myoglobin both had the same prosthetic group, meaning that the physicochemical and functional differences between the two molecules had to be traced to differences in the globins.

In the chair at Pavia

In November 1942 Rossi Fanelli started the Pavia part of his university life. The chair he occupied was a newly-created one and so – in that time of war – the new professor was not only not assigned a laboratory but not even any equipment suitable for either research or teaching purposes. For this reason he returned to Naples at the end of the academic year to spend the summer with his family and with the intention of carrying out research in his old laboratory. War and politics intervened: the Anglo-American landings in Sicily in mid-July 1943, the dismissal and arrest of Mussolini, the Cassibele armistice and Italian co-belligerence with the Allies at the beginning of September, almost immediately followed by Mussolini's release by German special forces, and finally the transfer of the seat of the fascist government to northern Italy in October (the formation of the so-called Salò Republic) while the south of the peninsula was occupied by Allied troops. The division of Italy into two prevented Alessandro Rossi Fanelli from returning to Pavia at the beginning of November as planned. At that time, and until the end of the war, connections between the north and south of Italy were difficult or impossible. In fact the railway wagon onto which Rossi Fanelli had loaded all his furniture in August to send it to Pavia had still not arrived by the end of October. For a while all trace of it was lost and it was only several months later that he managed by chance to find it and recover the entire load of furniture, miraculously undamaged. In this risky and chaotic situation Alessandro Rossi Fanelli applied to the University of Naples to work there. His application was accepted and for the following two academic years he was temporary lecturer in Applied Biochemistry and then in Food Science at the Naples Faculty of Pharmacy.

As soon as possible, that is to say when the war had ended and in June 1945, Alessandro Rossi Fanelli returned to Pavia, where he was accommodated in a building that housed the

Institutes of Physiology and of Hygiene, two disciplines traditionally linked to physiological chemistry, at least in Italy [3]. Thanks to the generosity of colleagues in these fields, he managed to form the first nucleus of what was to become the University of Pavia's Institute of Biological Chemistry. He was given seven rooms linked by a spacious corridor, a room for practical exercises by students, a lecture hall and a small store. September of the same year saw the arrival of the first collaborators and with them he started on experimental work using the little equipment available. Their names were Noris Siliprandi and Giulio Perri, who became Assistants at Pavia and then followed him to Rome 4 years later when he was called to the Chair of Biological Chemistry.

He resumed scientific research. Having heard of the possibility of reproducing insulin-deficient diabetes in laboratory animals by means of administration of alloxan, an easily prepared substance, Alessandro Rossi Fanelli applied himself first to the metabolic study of alloxan-induced diabetes and the mechanism by which this substance damages the pancreatic cells specifically. Although undertaken with very limited means, this research nevertheless produced very good fruit.

However, his unappeased desire to continue his research on the myoglobins, started in his last period in Naples, led him to the study of human myoglobin. He was constantly in contact with the various hospitals of Milan and Pavia to ask for limbs amputated following traumas or obstructive vascular disease. And it was Alessandro Rossi Fanelli himself who went to the San Matteo Hospital in Pavia with his wife to get a whole amputated leg, from which he obtained the first crystals of human myoglobin. He used to recall with a smile the anxiety that gripped him that cold Pavia night when, at the wheel of his Fiat Topolino, he saw a policeman on the road leading to his institute and crazy phrases started to whirl though his mind as potential justification for the presence of that leg in his car.

The method he used to prepare the crystals was the same

one he had developed in Naples for horse myoglobin. After homogenizing the muscle in the presence of a phosphate buffer at pH 7, the creamy paste was filtered and pressed through pieces of his old underwear (a great joke to his pupils) and the opaque red liquid obtained was treated with ammonium sulphate. Rossi Fanelli had discovered that the difference in solubility of myoglobin and haemoglobin in ammonium sulphate solution made removal of haemoglobin by preliminary perfusion of the tissues superfluous. This simple method was successful, and the red crystals of human myoglobin, so long awaited, were deposited on the bottom of the Petri dishes. The myoglobin crystals, obtained and systematically obtained again, were subjected to all the examinations possible at that time and place and allowed Rossi Fanelli to give the first description of the chemical composition of human myoglobin. His results, published in *Science* in 1948 [10] were also the subject of a paper [11] to the Barcroft Memorial Conference held in 1948 in Cambridge and attended by the leading scientists working on haemoproteins and many future Nobel Prize winners.

The time was now ripe. From Pavia University – that of Lazzaro Spallanzani, Alessandro Volta and Camillo Golgi – Rossi Fanelli was called to the Faculty of Medicine of Rome University to fill the Chair of Biological Chemistry. Rossi Fanelli felt the ancient fascination of Pavia, even the subtle intimate pleasure of its fogs and its long winter silences. He who came from Naples, the city of '*o sole*' and '*o mare*', began also to love the Pavia spring that always comes so late. 'For the first time', he confided to Noris Siliprandi [9] one sunny day in April 1947, 'I am appreciating the spring, its sudden, unexpected flash of brightness.'

In Rome, starting again from zero

In Rome, Alessandro Rossi Fanelli had in effect to start again from nothing. The space assigned to the Institute of Biological

Chemistry – directed until his arrival by Giovanni Amantea – comprised a few rooms surrounded by wide and useless terraces on the top floor of the building that housed Pharmacology and still houses Human Physiology. Furthermore, the wing that now houses the offices had been repaired rather approximately following the destruction it suffered in the 1943 bombing raid on Rome (Fig. 2). Then, the equipment was quite useless for serious biochemical research, having been intended for neurophysiological work. As for the personnel, there was only one executive technician assigned to the institute and no assistant, young or old, who could do scientific research. From these very poor beginnings, imposed in part by the general situation in the post-war years, Alessandro Rossi Fanelli created what by the time of his death (the evening of 24 November 1990) was the La Sapienza University of Rome's Department of Biochemical Sciences and currently bears his

Fig. 2. This is how the building that housed the Institutes of Human Physiology and Pharmacology appeared after the 1943 bombing. The Institute of Biological Chemistry, entrusted to Rossi Fanelli in 1949, was on the top floor and included the part that seems, in the photo, to have been destroyed.

name: 24 full professors, 15 associate professors, 12 university research scientists, 10 research scientists from the CNR (National Research Council), 15 doctoral students, a variable number of scholarship holders and unpaid assistants as well as various technicians and a variable number (20–30) of foreign scientists who spent longer or shorter periods in its laboratories each year, and very advanced instruments for fast kinetics (many pieces of equipment with time windows in the milliseconds, microseconds and nanoseconds), for crystallography, for biomolecule analysis (based on integration of mass spectrometer and classical biochemical methodologies), for calorimetry and for site-specific mutagenesis.

As one might imagine, the programme for development of biological chemistry in Rome that Alessandro Rossi Fanelli pursued – once he had realized the real situation of the institute that had been entrusted to him – followed the three classical lines: the search for personnel, for equipment and for more space, all of which were obviously based on obtaining substantial financing. The task of construction began immediately with the calling to Rome of the two assistants who had collaborated with him at Pavia, to whom there were almost immediately added some medical students still under 20 years old, among them Paolo Fasella and Paolo Cerletti. Still in 1949 there arrived Doriano Cavallini, back from a long period at a respected biochemical laboratory in New York, that headed by future Nobel Prize winner Du Vigneaud of Cornell University. Cavallini was assistant in a subject that perhaps exists as such only in Italy, General Pathology, which studies elementary disease phenomena common to many diseases observed from the point of view of their causes and modes of operation, including at the molecular level. The one in Rome was a good school of General Pathology which, thanks to the scientific and organizing ability of its head, Guido Vernoni, had gained international reputation. For this reason, and also because it was rightly considered as a subject of great value for the training of doctors, many students applied to be

accepted as student interns in the Institute of General Pathology to prepare their degree dissertations. Three of these, Eraldo Antonini, Carlo de Marco and Bruno Mondovì, moved to the Institute of Biological Chemistry immediately after Cavallini moved there, thus completing the original core of research scientists that was to prove decisive for the qualitative development and scientific solidity of the Roman school of biochemistry. This flight from General Pathology to Biological Chemistry did not take place by chance. Vernoni himself recommended it to his assistant and to his very young students as he was about to retire. In Italy, until the 1960s it was the brutal custom for the new professor to send away all the old professor's assistants and students and bring in his own collaborators.

With much effort, in 1950 and 1951 Rossi Fanelli managed to get hold of some scientific equipment paid for under the European Recovery Program (ERP), better known as the Marshall Plan, from the name of the then American Secretary of State who spelled out the aims of economic assistance to the western European countries that had been more or less destroyed during World War II. Among the specific objectives spelled out in the ERP was modernization of equipment, and in 1950 this allowed Rossi Fanelli to obtain one of the first spectrophotometers to reach Rome, a black Beckman DU, and then a refrigerated centrifuge and a huge and space-consuming Tiselius apparatus for electrophoresis, soon replaced by a much handier Perkin Elmer.

But a still more substantial step forward in the acquisition of scientific equipment was made thanks to a providential contribution from the Rockefeller Foundation. Dr. Gerard R. Pomerat was then a member of that Foundation with the task of reporting on promising scientific research groups in Europe that were worth supporting financially. Pomerat's arrival was pre-announced, and thanks to some acquaintances Doriano Cavallini had made during his time in New York [12], Rossi Fanelli came to know the day and hour of his landing in Rome.

A small delegation was organized to go to Ciampino airport in Rome and welcome the illustrious guest, who was pleasantly surprised by the kind thought. Pomerat was given a meticulous presentation of research projects and needs in terms of equipment and reagents, and in December 1953 Rossi Fanelli obtained a contribution of $7500 to be spent in the following 2 years 'for equipment, minor apparatus, consumable supplies and chemicals and *possibly* for the salaries of research assistants or technical aids' [13]. This was a very important result, not only for the sum, a considerable one for the time, but especially because of the significance attached to recognition of Rome University's Institute of Biological Chemistry by such a prestigious international institution.

As can easily be imagined, difficulties were the order of the day. There was very little, too little, money available for scholarships and there were many young people attracted by research on biomedical systems at the molecular level. It was therefore necessary in the general interest, that is to say in the interests of Italian biochemistry as well as of the Rome Institute of Biological Chemistry, to hold onto the best people as long as possible. Mindful of the hardships he himself had suffered during his years of apprenticeship and during the war, Rossi Fanelli therefore proposed to divide each of the few scholarships available into two. In other words, the winner of the scholarship had to give half the sum received at the end of each month to one of those who had got nothing. This solution, at which some people might turn up their noses today, did not scandalize any of those attending the institute at that time. They all accepted this proposal from the director calmly: indeed they considered it proper and fair, because they had the greatest confidence in him. Those concerned were young medical graduates and young women with degrees in biological sciences or pharmacy (in those days there were almost no female students of medicine in Italy) and therefore people who could have earned large amounts of money if they had practised the professions for which they had qualified. But they

were fascinated by biochemical research and by Rossi Fanelli's loveable personality, to the point where they spent an average of 10 h a day in the laboratory for very little money. Nor can it be presumed that those young people stayed because they were counting on an easy university career, given the limited foreseeable development for biological chemistry. It is worth recalling that in those days biological chemistry was an optional subject in the Faculty of Medicine and it was only in 1954 that it became a compulsory subject in Italian medical schools. Even then the decision was not made for educational reasons or because of the position established by the Italian Biochemical Society, the new society was founded in Rome in 1951 mainly on the initiative of Gaetano Quagliariello and Alessandro Rossi Fanelli. Rather, the ministerial decision was made in response to outside pressure. The United States had threatened not to grant legal recognition to Italian medical degrees because two areas held to be of fundamental importance, biochemistry and microbiology, were not included in the curriculum.

After the solid foundation, the grand construction

In the meantime, financing from Italian government agencies was slowly improving, though still insufficient for an organization that was becoming ever larger and more active. However, the opportunity that made increased funding possible appeared in 1955 with the creation of the 'Enterprise in Enzymology', later converted into the CNR's Centre of Molecular Biology, which was integrated into the institute and which still today is very active and efficient; this Centre was headed first by Alessandro Rossi Fanelli and then by Eraldo Antonini. Right from the first year there was conspicuous financing available to purchase new scientific equipment, for its maintenance and for consumables (reagents and the like). The greatest benefit, however, came from the availability of very well paid contract positions. Then there was the financing

received from the United States Department of Agriculture for research on cottonseed and from the United States Navy for research on transport of oxygen and conservation of blood in vitro, financing that in turn made it possible to give contracts, scholarships and lump sum grants and that opened the road to research for many young graduates.

In the meantime, many of Rossi Fanelli's first collaborators had developed and acquired much research experience (some of them had become assistants), so that they managed to obtain financing and equipment for their own specific requirements from public or private sector bodies through their own personal abilities.

Things having reached that point, Rossi Fanelli felt impelled to undertake another highly meritorious task, that of asking universities outside the Rome area to hold competitive examinations for professorships in which his most deserving pupils could take part, as they gradually reached the point where they could apply for such positions with hope of success. This political wisdom made it possible to create links and close working relationships with other universities, including those of L'Aquila, Cagliari, Camerino, Catania, Chieti, Messina, Udine and Viterbo, and to export to them the vivacity and scientific maturity acquired in Rome. In the meantime biochemical teaching and studies were being established in other faculties in Rome, with the formation, in addition to the Faculty of Medicine's Institute of Biological Chemistry, of other institutes such as those of Chemistry in the same faculty, of Biological Chemistry and of Applied Biochemistry in the Faculty of Pharmacy, and finally the Biological Chemistry and Chemical Structure Group in the Faculty of Mathematical, Physical and Natural Sciences, all hosted and working in the Faculty of Medicine's Institute of Biological Chemistry, which from then on was organized in the form of a department.

On the problem of premises, through meticulous detailed work Rossi Fanelli first managed to use the big terraces,

converting them into laboratories, a library and studies and then, thanks to the transfer of Pharmacology elsewhere, divided the space released with Human Physiology, immediately converting his share into laboratories. Eraldo Antonini got the ground floor, where he organized his research along with his two best collaborators, Maurizio Brunori and Emilia Chiancone, and where he established the Institute of Chemistry (for the Faculty of Medicine) of which he became director. Doriano Cavallini was assigned the task of fitting out the basement, which was made habitable with a great effort and became the seat of the first Institute of Biochemistry in the Faculty of Pharmacy, over which Rossi Fanelli presided for a long time. It was then possible to raise the height of the building (Fig. 3) after a long and difficult struggle with the Rome city authorities to obtain the building permit. Most of the new floor was subsequently occupied by Carlo De Marco and his group.

Fig. 3. The Department of Biochemical Sciences as it appeared in the late 1980s. Comparing this picture with the previous one (Fig. 2), one can easily distinguish the additional height Rossi Fanelli wanted and obtained.

The last operation for enlargement of the premises came after the La Sapienza University of Rome acquired the buildings that had once produced Wührer beer; a large part of these premises were assigned to the group of lecturers who taught biological chemistry at the Faculty of Science, allowing a partial if little-noticed decongestion of the main site.

The creation of the second university known as 'Tor Vergata' with the two faculties of medicine and science allowed a further expansion of the Rossi Fanelli group's Roman area, this time outside the first university known as 'La Sapienza'. Paolo Fasella, Alessandro Finazzi-Agrò, Giuseppe Rotilio and many others migrated there, creating their own research groups, though maintaining continuous collaboration with their friends and colleagues in the 'mother house', collaboration that included frequent joint meetings to decide on problems of common interest.

Before most of these new premises were acquired, the social climate in Italy had deteriorated and the political situation had become complex and difficult to handle. Both aspects favoured the student's revolt of 1968. This attitude of revolt against society and the academic world soon developed a terrorist character that led to formation of the 'Red Brigades' and after years of violence culminated in the assassination of former Prime Minister Aldo Moro in 1978. University professors daily found themselves faced with occupation of the buildings that housed their various institutes and with the destructive violence of an extremist fringe of the students. This general climate was the reason for the cancellation of the International Biochemistry Conference (IUB Meeting) that was due to be held in Rome in 1970 under the presidency of Alessandro Rossi Fanelli and was then organized hurriedly on short notice in Switzerland.

The travails of the Italian universities obviously also perturbed Rossi Fanelli, but never to the point of deterring him from his daily activities. His shrewd ability to accept change was put to the test in those circumstances. He started

to assemble all the staff in the library from time to time in order to keep his finger on the pulse of the situation and fixed weekly meetings with the full professors for discussion of academic problems and future projects (previously such meetings had been held quite irregularly, only when necessary). This was a great innovation in the running of the institute leading to a form of collegial management. Because of their apparently sectarian character, Rossi Fanelli jokingly referred to these meetings as meetings of the 'Beati Paoli'. And the Roman biochemists are still known by this name to many Italian and even foreign colleagues. The origin goes back to the television production of a long, dramatic story, divided into various episodes, entitled *The Baroness of Carini*. The story was based on a real historical event on 4 December 1503 in Carini Castle, Sicily, where the baron Vincenzo La Grua Talamanca killed his wife Laura, believing her guilty of an intimate relationship with a knight of an opposing faction. In each episode of the television serial the large audience could watch a meeting of notables, including baron Carini, a meeting held secretly underground. These were meetings of the Beati Paoli, members of a secret society that held the real power in the whole area (as distinct from the merely apparent authority of the official politicians) and which when necessary re-established true justice. The society of the Beati Paoli was therefore a sort of 'good Mafia'. Tickled by the affair – since at the time the press were calling university professors 'barons' and 'Mafiosi' – Rossi Fanelli jokingly re-baptized the full professors of biochemistry attached to his institute and those who swarmed in the Rome area (there are currently four universities in Rome) with the name of the 'Beati Paoli'.

Official recognition

Around Rossi Fanelli there had thus been created one of the best equipped centres of scientific activity with one of the highest reputations in Europe and it exerted a great attraction for

many scientists from the most assorted countries. It is therefore not surprising that, as time went on, offers to Rossi Fanelli of important positions in management of universities and non-university institutes multiplied, as did offers of honorary titles and national and international awards. A significant recognition of this scientific growth, which reached its plateau in the 1960s and 1970s, and that had unquestionable repercussions on the progress of Italian biochemistry, is to be found in the inaugural statement at the FEBS Meeting in London in 1964. The President, Arne Tiselius, in reviewing the status of biochemistry in member countries, defined Italy as a 'scientific miracle'. In fact, its rapid arrival at a scientific standard comparable with that of the countries in which biochemistry had been born many years before does merit this description, and Rossi Fanelli was certainly one – if not the main – creator of this 'miracle'.

The flow of honours, which continued to the end of his life, comprised a vast constellation of attestations of esteem of which some can be respectfully listed: Member of the Accademia Nazionale dei Lincei (of which he was also secretary), of the Accademia Nazionale delle Scienze (called of the XL) and of the Accademia Lancisiana, President of the Italian Society of Biochemistry, honorary member of the American Society of Biological Chemistry, awarded the gold medal as 'Benemerito' of education, culture and art, and then the Feltrinelli Prize, not to mention appointments in the Italian National Research Council's Medical and Biological Sciences Committee, the Higher Health Council, the International Union of Pure and Applied Biochemistry and so on.

Teaching: without enthusiasm, but seriously

In addition to undertaking scientific research, the university teaching body naturally has to give part of its working time to teaching; some professors do so with great dedication, others parsimoniously.

The medical student who attended lectures on clinical subjects at Rome University in the 1950s and 1960s would notice with astonishment that in each lecture hall the first two rows of seats were occupied by people in white coats. These were the various assistants of the full professor who was giving the lecture. Nothing similar was ever seen at lectures given by Alessandro Rossi Fanelli. He was in the habit of telling his assistants to do experiments rather than attend his lectures. That was not because his lectures were not worth listening to but because, on a scale of priorities, in his mind research was clearly more important than teaching, which nevertheless always had to be done well – not only for the benefit of his students, but also and particularly for the rigorous training of the scientific mentality, which requires method, organization of the discourse and focus on essentials in the description and interpretation of phenomena, in addition, obviously, to a profound understanding of the subjects concerned. This was an opinion he shared with St. Francis of Sales, who said, 'I listen and forget, I read and remember, I teach and I understand.' It was precisely because of this way of thinking that every academic year each of Rossi Fanelli's assistants, except for the most junior, had to give a series of lectures on a specific biochemical topic, while the youngest were assigned responsibility for practical exercises. The rigour in teaching that Rossi Fanelli imposed found deserved recognition in March 1961 in an article in the *Messaggero* (a national daily, printed in Rome) that severely criticized the insufficiency of practical aspects in Rome University's Faculty of Medicine – with one exception, that of the course in Biological Chemistry in which, notwithstanding economic constraints and scarcity of personnel, action was taken to provide teaching adequate for the times and for the needs of the students. Thus, wrote the author of the article who, like all reporters of daily news, included a certain number of inaccuracies, such as confusion between assistants (paid by the university) and contract personnel (at that time paid by the

Rockefeller Foundation): 'A serious attempt to give the student an experimental idea of medicine is made in the second year by Rossi Fanelli, holder of the Chair of Biological Chemistry, much loved by the students and director of one of the best-equipped institutes. The possibility to equip the institute derived from the fact that Professor Rossi Fanelli managed to obtain foreign contracts from the Rockefeller foundation, which also provides him with funds to pay assistants. Rossi Fanelli thus has a full fourteen assistants who divide the six hundred odd students into classes of sixty for theoretical work and of 30 for practicals. But the fourteen assistants are not enough. At least double that number are needed.'

Rossi Fanelli always carefully administered this fund of the affectionate esteem which the students had for him. So much so that when he had to give lessons on topics he considered boring, he often preferred to pass them on to his assistants, who might get a phone call at seven in the morning asking them to substitute for 'the professor' in a lecture at eight.

The situation in the university in the 1960s was that described by the Messaggero reporter. In the subsequent decade, teaching at the university was put to a severe test following a law passed by the Italian parliament in 1969, liberalizing access to university study, permitting admission to any degree course (which had been restricted to holders of leaving certificates from certain types of school) to school leavers from any type of secondary school, thus abolishing any type of connection between the education received at school and the continuation of studies in the university. But, independently of their quality, it was the sheer number of the students that turned the structure of the university upside down. In 1972 over 4000 students matriculated in the Roman Faculty of Medicine alone. At that time the Rome biochemistry group was responsible for teaching chemistry to medical students and biochemistry to students of science (biology and chemistry), pharmacy and medicine (in Italy, and therefore in Rome,

there was not and still is not a degree course in biochemistry, though students can select combinations of courses with a special emphasis on biochemistry). There is therefore nothing to wonder at if over 5000 students asked for examinations with the Rome biochemists during the 1970s. Italian folly, that only the good will of individuals managed to counterbalance to some degree, meant that the same lecture was repeated twice or thrice at different times of the day in order to allow course students to attend in at least tolerable discomfort. With those numbers, and with the human resources available, laboratory teaching was obviously reduced to a minimum for the vast majority of students. But in that situation Rossi Fanelli called for calm and did the maximum possible. Everyone was roped in during those years: full professors, assistants, contract scientists, young people paid a lump sum or not at all (these last under the legal umbrella of 'cultivator of the subject'). This overcrowding was a further dampener on any surviving enthusiasm for teaching, with the result that all the enthusiasm was directed instead into research.

Two lines of research among the many

There were many lines of research carried forward by the biochemical group of the Roman school [14]. Alessandro Rossi Fanelli took part in some personally; in others he was a tireless animator. For every one of his pupils he managed to find the post most appropriate to their abilities and commitment in the various lines of research, and to all he offered the assistance of a scientific organization that was first class (and not only in terms of equipment). Among the many research lines, it would be good to briefly recall two, just as examples: one on myoglobins and haemoglobins that made him famous in his field, and the other on treatment of malignant tumours by controlled hyperthermia that made his name known to the general public in much of Europe (and perhaps also in the United States).

In Rome, Rossi Fanelli continued the research on myoglobins that he had begun in Naples and continued in Pavia, especially the study of their oxygenation properties, using a very simple but powerful instrument put together along with Eraldo Antonini. Immediately afterwards there came the discovery of the transheme reaction, that is to say of the ability of some myoglobins and haemoglobins to exchange their respective hemes under physiological conditions, and the development of a method for preparation of globin in its native state from human haemoglobin [15]. The publication in which these last results were presented was much cited in the scientific literature in subsequent years, to the point that in 1985 Eugene Garfield invited Rossi Fanelli to write what he considered to be the probable reasons for that success. Among the various hypotheses advanced by Rossi Fanelli one can recall that in which he states [16] that the publication had become a *Classic Citation* as it had opened 'a new era in the investigation of the structure–function relationships in hemoglobin because it allowed probing of the role of the chemical nature of the prosthetic groups in controlling the phenomena of heme–heme interactions and the Bohr effect, which has become a prototype of molecular control in functioning macromolecules'. This idea of haemoglobin as a model to illustrate some fundamental aspects of protein behaviour was subsequently put to the test in its smallest details and with enormous success. And together with myoglobin [17] haemoglobin continues to be a prototype to describe new frontiers for research on proteins, like the time course of the tertiary and quaternary allosteric changes in the nanosecond time range and at the atomic level.

At this point one cannot omit to mention that Jeffries Wyman arrived in Rome in spring 1960 'captivated by Eraldo Antonini's engaging personality' [18]. He stayed there for a week to talk about haemoglobin's unsolved problems; but the topics were not only interesting, they were also very difficult and obviously could not be clarified in a mere 7 days. The visit

that Wyman had intended to repeat the following year grew longer, expanding to over 25 years, constantly nourished by the warm welcome from Rossi Fanelli and by Eraldo Antonini's enthusiasm[1]. Relations between Rossi Fanelli and Wyman, always excellent, were maintained in French, because one knew little English and the other no Italian. Wyman had a fine room at Regina Elena Institute where Antonini spent most of his time. The group of Rossi Fanelli, Antonini, Wyman and Caputo was joined immediately by Maurizio Brunori and soon afterwards by other more or less young collaborators including Emilia Chiancone. In the meantime Max Perutz had resolved the three-dimensional structure of horse ferric haemoglobin, opening new horizons for research on this molecule. In those years the major task of the Rome group (as the handful of research scientists working at the Institute of Biological Chemistry and the Regina Elena Institute was called in international circles) was to find physical properties and chemical probes that would reveal differences between the structure of ligand-bound haemoglobin and that of deoxyhaemoglobin. In particular, the group carried out extensive studies of the Bohr effect, teramer–dimer dissociation and the reactivity of haemoglobin towards dyes and other specific chemicals. A remarkable finding was that the rate of digestion of haemoglobin by carboxypeptidases, which remove the C-terminal residues from the α and β chains, is fast for oxyhaemoglobin but much slower for deoxyhaemoglobin. This indicated that differences in accessibility exist. The products of the digestion had profoundly altered functional properties (generally low or no co-operativity and high oxygen affinity) which showed that the C-terminal residues play an essential role in haemoglobin function [19]. Experimental work subsequently concentrated on characterization of the structural and functional properties of haemoglobin sub-units, isolated with the

[1] The scientific lives of J. Wyman and J.T. Edsall have been recounted by the latter in vol. 36 of this series.

method developed by Enrico Bucci and Clara Fronticelli, and on the physiological effects of 2,3-biphosphoglyerate. In that period Eraldo Antonini held that the induced fit model of Koshland, Némethy and Filmer was more appropriate than the Monod, Wyman and Changeux model to describe the behaviour of haemoglobin, an opinion based on some experimental evidence obtained in Rome (e.g. the very good linear correlation between CO binding to deoxyhaemoglobin and the release of Bohr protons, and the linearity in the reactivity of thiols at β93 which monitors the quaternary conformational changes). The years that followed saw spectacular progress in haemoglobin research, partly fuelled by the hot debate between the supporters of the induced fit model and those of the concerted model [19]. The impact of the Rome group at that time is witnessed by the stream of young and established visitors who came to work and discuss science at the Institute of Biological Chemistry and the Regina Elena Institute over the years: J.F. Taylor, J.T. Edsall, C. Tanford, W. , J. Libby, J. Kendrew, M. Kotani, Q.H. Gibson, G. Gilbert, M.F. Perutz, K. Imai and many others. The sabbatical spent in Rome by Rufus Lumry led to the organization of a number of discussion meetings within a limited group of people with a format which was and still is rarely used [20]. The topics of interest, all starting from haemoglobin but with the broad picture of protein chemistry in mind, were discussed extensively without strict time limits and no formal presentations, largely with the help of a blackboard. Seven of these meetings took place over the years and became known as the 'La Cura Conference' from the little town near Viterbo where the first meeting took place in a castle kindly offered for the purpose by Bruno Mondovì's family. In 1983 Eraldo Antonini died at only 53 years of age. This was a terrible blow that left the whole scientific community in Rome deeply shaken. Rossi Fanelli, who loved him like a son, wrote a dignified and gratifying obituary [21]. Wyman was deeply affected and the tragic event was the prelude to the end of his Roman period.

In 1963 Alessandro Rossi Fanelli and Bruno Mondovì organized a work group composed of biochemists, oncologists and anaesthetists to study the selective sensitivity of neoplastic cells to heat. Initially, research was carried out on the heat sensitivity of various tumour tissues cultivated in vitro and optimal conditions for the action of heat were determined. Starting from these results, close collaboration with the clinicians of the Regina Elena Institute (Section for the Study and Treatment of Tumours) was launched, as also with the Americans of Wisconsin University who perfected a new technique called 'extracorporeal regional hyperthermic circulation'. This meant heating the blood that irrigated the tumour for 2–3 h to 42°C (at first only in laboratory animals and then also in man). In this way an almost total necrosis of the cancerous tissue was achieved, followed by an almost complete disappearance of the disease process. The treatment in man was used on many cases of tumours of the limbs (such as melanomas, osteosarcomas and sarcomas of the soft tissues) with excellent results, by far superior to those obtained with conventional treatments. Hyperthermic treatment of tumours is widely adopted today in Italy and abroad. The first significant results on man were published in the journal *Cancer* in 1967 [22]. All the Italian newspapers and many weeklies immediately reported the news, which was gradually disseminated to many other countries in Europe. To take an example, one can cite *La Tribune de Genève* of 24 October 1967 which carried a front page headline 'Important victory over cancer' and devoted the whole of its page 15 to the subject, while the German weekly *Quick* devoted the cover of its issue for 11 October in the same year to it. Obviously this fame did not displease Alessandro Rossi Fanelli, and he was certainly cheered still more when, some years later, he read in the Madrid newspaper *ABC* that, thanks to his research on cancer, his name was on the short list for the Nobel Prize for Medicine in 1975. The presentation piece, written by the reporter for his readers,

described him thus: 'Holder of the Chair of Biological Chemistry at Rome University; a great candidate (for the Nobel Prize) who enjoys well-deserved world-wide prestige; his field of research is cancer, and he has demonstrated the undoubted influence of temperature on the development of certain malignant tumours.' However, he did not obtain the Nobel Prize for Medicine, which that year went to another Italian, Renato Dulbecco (together with H. Temin and D. Baltimore). Also in 1975, Eugenio Montale won the Nobel Prize for Literature.

Not only scientists but also managers

It is said that carp grow best in artificial ponds in which there is a central rock that emerges from the water. A point of reference around which to swim is good for the health of the individual and the growth of any population, not only in the case of fish. To his successfully grown pupils, Rossi Fanelli was a rock of reference until his death.

As they matured, many of his collaborators not only became extremely able in carrying out excellent research and in organizing and managing it in the best way, they also showed themselves capable of managing people and institutions, supporting universities, chairing faculties and directing departments and organizations of various kinds. It would be easy to give examples, but this could take up much time and space, so here are just a few of the most significant. After a brilliant career in scientific research at the international level, Paolo Fasella devoted himself to science policy and for 14 years was Director General of DG XII at Brussels where he was one of the principal architects and promoters of the EU RTD Framework Programme of Community policy on research and development that became the principal platform for efforts towards scientific and technological co-operation in Europe. Maurizio Brunori has been President of the International Union of Pure and Applied Biophysics. Many pupils, at

different times, have been chosen as rectors of universities or chairmen of faculties: Carlo De Marco, rector at Cagliari first and then chairman at Rome 'La Sapienza'; Alessandro Finazzi-Agrò, first chairman and then rector at Rome 'Tor Vergata'; Roberto Strom, rector of the Free University of L'Aquila; Bruno Mondovì and Francesco Bossa, chairmen at Rome 'La Sapienza'. Outside the academic environment it may be sufficient to mention Giuseppe Rotilio, appointed President of the National Institute of Nutrition, and Emilia Chiancone, designated Director of the CNR Center of Molecular Biology.

After that list it is not hard to imagine that among the Beati Paoli there were always men of great talent. Their independent characters and determination to get ahead were certainly potential forces for disintegration of the community of Rome biochemists, but precisely because of their rivalry and mutual emulation, governed by Rossi Fanelli's sensible and paternalistic (one must say this without shame and with deep respect) hand, it was the foundation of their harmony. He was well aware that seen from the earth the movements of other planets seem confused and irregular and that therefore one has to imagine oneself in the sun to be able to evaluate the ordering of the whole system correctly, and he knew equally well that something similar happens in a community – like that of the Beati Paoli – in which each of the members judges the whole in which he lives much more erroneously than the person who has to manage it. For this reason Rossi Fanelli always, and especially in his last years, felt his responsibility as a point of reference ('the sun') to dampen the distorted view of the individual and promote harmony between all his pupils and in particular among the Beati Paoli. This moderating role was always recognized and appreciated, so much so that an anonymous Beato Paolo wrote this 'verse' in his honour in the 1980s.

When the problem gets complicated/Without a solution/
Sometimes one turns/For a wise mediation/To one who for half a century/Was teacher to all/He lends himself nobly/
Patient and concerned/He listens willingly/Advises affectionately/Trying to calm/Their ephemeral disputes.

Human quality and surroundings

Running away to sea was the traditional English way of emancipation from paternal authority; it was a heroic initiation. However, this was not the case for young Alessandro, who went to sea only for the pleasure of doing so. Left fatherless at the age of 14, he had in fact never any desires for revenge concealed in the meanders of his psyche. He certainly had a competitive spirit, but he never showed it openly in clashes with other people or in other visible forms. One could divine it from his impulse to enter the lists. In fact, during his youth in Naples, during his university studies and thereafter, he used to enter competitions with the small sailing boat he owned, called Kon Tiki, for the colours of the oldest yacht club in Naples. There 'Sasà' (as his friends called him) was known and appreciated more for his ability as a sailor and for the respectability of his family than for his qualities as a scientist.

Perhaps, without his knowing it, his inclination to defend his convictions energetically accompanied a mentality that it is the custom today to describe as 'win-win-win'. In truth one could more accurately call it a mentality with Napoleonic streaks. It is said that Napoleon greatly preferred officers who were simply lucky to those well read in military strategy and tactics. The emperor, one knows, wanted only to win battles and wars. On many occasions Rossi Fanelli demonstrated a similar way of assessing and appreciating people, as when he was about to start on the first collaboration with the Regina Elena Institute, in which many properties of haemoglobin were studied in depth. In introducing Eraldo Antonini to the head of that Institute he used these words, 'He is a very intelligent person, cultured, with great manual

ability, but what counts most in this young man is his almost brazen luck. Exactly that, he is truly lucky. Every time he finds himself with two alternatives in interpretation or experimentation of apparently equal value, he invariably selects the right one.'

It was Rossi Fanelli's great merit that he knew how to choose his pupils. But a still greater merit was that once the choice was made he held the reins loosely in many spheres, but especially with regard to the research topics that most interested them [23]. He then simply compared the promises made against the results subsequently obtained, and acted in consequence. The people with whom he surrounded himself to conduct research had to be creative and therefore could not be constrained by petty regulation. Indeed, if no great damage resulted, Rossi Fanelli also accepted conduct a bit out of the ordinary. He once assembled lecturers and technicians in the library. Pressed by the librarian about the continual disappearance of books, he could not avoid taking action. In Italy in the 1960s, many state employees, such as the librarian, worked only in the mornings and therefore in the afternoon the library was open to the scientists but with no supervision. The librarian asked that it be closed in his absence. All those doing research rebelled at this proposal, with arguments of varied validity. At the end of the meeting, to the pleased surprise of those present, Rossi Fanelli said: 'I understand you very well. In my time I acted in the same way. When I left Naples to go to Pavia, in going through the house I had to leave I found a great number of books from the library that I put into three big cartons and returned. Love for research is also love for books, especially for books important for the research one is doing. So I prefer that the books continue to disappear rather than to close the library.' And the library stayed open.

This way of his of addressing certain behaviours that could be considered reprehensible was not the fruit of an irresponsible attitude but came from a profound knowledge of the

human soul. The eyes see what they are used to seeing, but often the most valid people are obscured by actions of their own that arouse doubts in others. Rossi Fanelli's Neapolitan astuteness presented this truth, in which he firmly believed, through a story he told from the Kingdom of the Two Sicilies (which had Naples as its capital). 'The king', said Rossi Fanelli, 'stopped at a road block in the dead of night. Recognising him, the guard commander ordered his soldiers to present arms. They, sleepy, dishevelled, in shabby uniforms, stood to attention. Observing them by the light of the torches, the king was first thoughtful and almost depressed; then, turning to the commander, he asked, 'And so these are our men?' 'No, your majesty', replied the commander, 'these are the idiots. The men are asleep in their own homes." The men that Rossi Fanelli, too, needed were those who had obtained a certain inner freedom and were therefore ready to pursue their research with alternative theories as opposed to one single point of view. He well knew that research does not always follow the highway but ventures through the lanes and sometimes – especially if it is innovative – must leave every beaten path behind. If he had known it, he would certainly have shared the view of Paul K. Feyerabend [24] that science needs a variety of criteria and that scientists work best without any authority, including that of 'rational reason'. Rossi Fanelli, therefore, always suggested seeking unexpected effects, inviting his researchers to find 'flying asses' rather than 'walking asses', reversing a popular saying. Among the various ways of attaining that end there was also that of aiming determinedly at the most extreme experimental conditions. One example of this way of proceeding was the isolation of a new protein, baptized acalin, from cottonseed. To a sample of clear total extract from these seeds, Eraldo Antonini added a large quantity of soda, but nothing happened. Into another sample he poured great quantities of hydrochloric acid, without obtaining any evident macroscopic change. Finally, while wandering the corridors of the

institute with his mind taken up by this problem, Antonini came across a bath containing a mixture at − 20°C into which, as one inspired, he immersed the flask with the clear extract, which immediately became cloudy due to the formation of a white precipitate. This was pure acalin, which separated from all the rest by the effect of very low temperature alone.

Once experimental results had been obtained, they had to be published, and for that they had to be dressed in their best, that is, organized into a strictly inductive or deductive logical system, as appropriate for the case. In other words, the scientific paper had to be written. The bright impression given by Rossi Fanelli's writings was the fruit of an often tormented relationship with the blank sheet of paper destined to receive the message [9]. The worry that the written expression could in some way distort the result or its correct interpretation tormented him at times more than it should have done. But he did not mind about that, because he knew that those in the habit of writing unfortunately do it even without ideas, like the doctor at death's door who felt for the pulse of the armchair on which he was sitting.

Rossi Fanelli was always known for his typically Neapolitan cordiality and wittiness. He had a particular ability to entertain in gentlemanly fashion without betraying even the slightest sign of impatience with the string of visitors who knocked at the door of the institute he headed. His affability never decreased, not even for those most boring; in truth, with people of that kind he did most of the talking, thus avoiding getting bored.

A thing that astonished some people was that Rossi Fanelli considered it advantageous and even astute to concern himself with his pupils (and sometimes those not even his own) just to ensure proper recognition of their value. Generosity apart, in his view altruism was good business, convinced as he was that in our world it is advantageous to act with a sense of justice towards others, mindful as he always was of

the injustice he suffered in his youth when he was not appointed Assistant in Neurology. He did not expect gratitude for his actions. The balance sheet of human actions, the debits and the credits, he once told the President of the Accademia Nazionale dei Lincei [25], covers much more than the relationship between two individuals. It is more as if we all had an account with the bank into which to pay our own generosity. If the recipient of the generosity is not grateful, that does not matter, because the debit is covered by the bank, without receipts for acknowledgement. This munificence in evaluation of human affairs was his habit and his style, and played a part in the majority of his decisions. He considered generous behaviour almost as a duty for successful people like himself, as he recognized that in all success there is a large dose of good luck.

Acknowledgements

The author is grateful to Francesco Bossa, Maurizio Brunori, Doriano Cavallini, Emilia Chiancone, Carlo De Marco, Alessandro Finazzi-Agrò, Bruno Mondovì and Filippo Rossi Fanelli for the information, recollections and photographs with which they have generously provided him.

REFERENCES

[1] Blumberg, W.E. (1982) Structure and Function Relationships in Biochemical System (Bossa, F., Chiancone, E., Finazzi Agrò, A. and Strom, R., eds.). Adv. Exp. Med. Biol. 148, 7–19.
[2] Reichlin, M. (1972) Science 178, 296.
[3] Amiconi, G. (1989) Rendiconti dell'Accademia Nazionale delle Scienze detta dei XL XIII, 3–30.
[4] Libonati, M. (1997) Rendiconti dell'Accademia delle Scienze fisiche e naturali di Napoli LXIV, 57–69.
[5] Ghiretti, F. (1984) Rendiconti ed Atti dell'Accademia delle Scienze mediche e chirurgiche di Napoli CXXXVII, 328–355.

[6] Ghiretti, F. (1984) Biochim. Ital. 1, 39–46.
[7] Ruffo, A. (1991) *Commemorazione di Alessandro Rossi Fanelli*, January 23rd, 1991, Aula Magna dell'Università degli Studi di Roma 'La Sapienza', pp. 17–19.
[8] Siliprandi, N. (1982) Structure and Function Relationships in Biochemical System (Bossa, F., Chiancone, E., Finazzi Agrò, A. and Strom, R., eds.). Adv. Exp. Med. Biol. 148, 1–6.
[9] Siliprandi, N. (1993) Rendiconti dell'Accademia Nazionale dei Lincei, serie IX, Vol. III, 21–31.
[10] Rossi Fanelli, A. (1984) Science 108, 15–16.
[11] Rossi Fanelli, A. (1949) *Haemoglobin* (Roughton, F.J.W. and Kendrew, J.C., eds.), pp. 115–120. London, Butterworths.
[12] Cavallini, D. (1991) *Commemorazione di Alessandro Rossi Fanelli*, January 23rd, 1991, Aula Magna dell'Università degli Studi di Roma 'La Sapienza', pp. 11–15.
[13] Pomerat, G.R. (1953) Letter to Prof. Alessandro Rossi Fanelli sent from Bologna, Italy, on 18th November 1953.
[14] Whitehead, E. and Beati Paoli (1989) The Biochemist 11, 6–9.
[15] Rossi Fanelli, A., Antonini, E. and Caputo, A. (1958) Biochim. Biophys. Acta 30, 608–615.
[16] Rossi Fanelli, A. (1985) Current Contents 22, 19.
[17] Srajer, V., Teng, T., Ursby, T., Pradervand, C., Ren, Z., Adachi, S., Schilkamp, W., Bourgeois, D., Wulff, M. and Moffat, K. (1996) Science 274, 1726–1729.
[18] Edsall, J.T. (1986) *Comprehensive Biochemistry: Personal Recollections*, Vol. 36. (Semenza, G., ed.), pp. 99–190. Amsterdam, Elsevier.
[19] Brunori, M. (1999) Trends Biochem. Sci. 24, 158–161.
[20] Brunori, M. (1996) Rendiconti dell'Accademia Nazionale dei Lincei, Suppl., serie IX, Vol. VII, 53–57.
[21] Rossi Fanelli, A. (1983) Riv. Biol. 76, 375–378.
[22] Cavaliere, R., Ciocatto, E., Giovannella, B., Heidelberger, C., Johnson, R., Margottini, M., Mondovì, B., Moricca, G. and Rossi Fanelli, A. (1967) Cancer 20, 1351–1381.
[23] De Marco, C. (1992) Atti dell'Accademia Lancisiana di Roma XXXVI, 45–48.
[24] Feyerabend, P. (1982) *Come essere un buon empirista*. Rome, Borla.
[25] Salvini, G. (1991) *Commemorazione di Alessandro Rossi Fanelli*, January 23rd, 1991, Aula Magna dell'Università degli Studi di Roma 'La Sapienza', pp. 7–8.