The Biochemist

The Bulletin of The Biochemical Society **June 1989**

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La Biochimica Romana

A Tale of One City and Two Universities

BIOCHEMISTRY may be losing some of its identity as so much modern biological and medical science involves or englobes essentially biochemical techniques and concepts, and biochemists too apply themselves to broader fields. But to describe activity over these sciences in Rome alone is so far beyond us that, with apologies, we have to dismiss masses of distinguished biochemical work, and a couple of Nobel prizewinners well-known to BS members, and here define *Biochemistry* as 'science performed in Departments that think of themselves as of *Biochemistry*, but who deliberately no longer even call themselves quite that here'. By this definition, there are two University Biochemical centres in Rome, because there are two Universities, the first called 'Roma I' (pronounced 'Roma Uno') or more grandly 'La Sapienza'. This is centrally situated, within walking distance of the main Station, a convenient proximity except when the marshalling yards became targets for aerial bombardment in 1943, and the chance results of statistical scatter rendered what is now the Biochemistry library unsuitable to accommodate even the older literature, as seen in Fig. 1.

Figure 1 The Institute of Physiology, 1943. The Lebanese cedars (left) are at least 100 years old. (Photo courtesy of the authors).

Roma Antica

In saying that at the time the building housed a Physiology Department, we mean, of course, not to belittle the damage, but to bring out that, as in many places, Roman Biochemistry had a prehistory, albeit one more recent than Romulus and Remus, in a Medical Faculty Physiology Department founded in the last century. In 1930 the first chair of Chemical Physiology was founded. Its head, Professor G. Amantea, worked essentially in neurobiology. Still, to him is due the first crystallization of fetal human hemoglobin and the recognition of its crystalline form being different from the adult one.

Fig. 2 shows the Department of Biochemical Sciences as it is now (taking up most of four storeys). It is a matter of taste whether one considers our building the most, or the only elegant one in Roma I—the rest of which dates, and quite characteristically, from the 1930s. Its back windows look down on a stretch of road tramped by Praetorian Guards to and from their nearby *castro*.

Centrifugal Separation

The second University in Rome is, as might be imagined, called 'Roma II' (pronounced 'Roma Due'), and less obviously, 'Tor Vergata'. This refers to the Striped Tower built sometime before 1660, that gives a name to the frankly, nondescript surrounding locality in the SE of Rome, about 12 km from the capital and just outside the *Gran Raccordo Anulare* (GRA), the autostrada that rings Rome. The GRA also makes Roma II easy to get to—any staff member will gladly give you a lift. Roma II was founded in 1981 in response to the notorious overpopulation of students in Roma I. Its nucleus is shown in Fig. 3; architectural critics have commented on how harmoniously it blends with the environment of the GRA, on how perfectly a perceptible polyhedrality proclaims emancipation from the canons of Michelangelo. Imminent completion of other buildings including a teaching hospital is hoped for, if not in every respect looked forward to. The University can lodge visiting collaborators, who often prefer the old stuff, at the 17th century Villa Mondragone (see cover picture).

Several biochemists from Roma I went to found in Tor Vergata the Biochemistry Group of the Department of Experimental Medicine and Biochemical Sciences in the Medical Faculty, and the Department of Biology of the Science Faculty. Despite institutional and geographical separation, the biochemists of the two Universities really do form a single scientific community, with common research interests, collaborations, constant contacts and personal ties.

La Biochimica Moderna: Foundations of Independent Modern Biochemistry

If anywhere the existence and quality of a scientific community now numbering perhaps 250 can be attributed to the leadership of one man, then it can be in Rome, and that man is Professor Alessandro Rossi-Fanelli. Called to the Chair in 1949, he changed the Institute, consisting at the start of himself and a technician working under chaotic and restricted postwar conditions, into an Institute of Biological Chemistry, and nurtured its growth into the Department of 100 permanent staff and about 200 transient scientists that it is today. It could not have got off to a good start

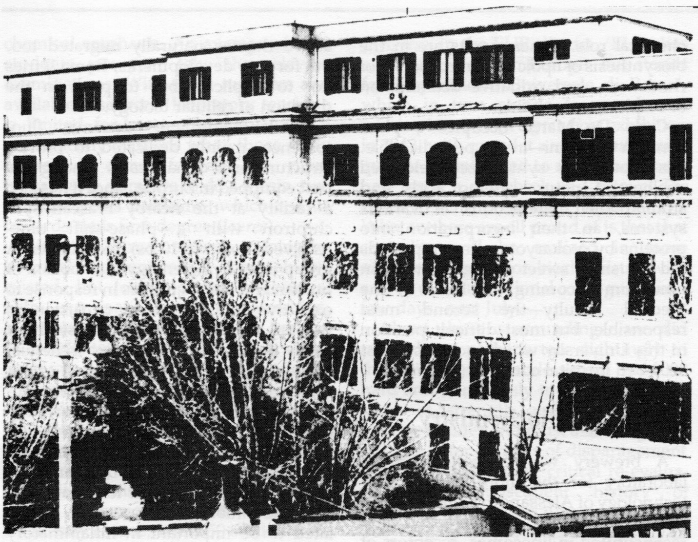


Figure 2 The Department of Biochemical Sciences, 'La Sapienza', 1989. The Lebanese cedars (left) are at least 146 years old. (Photo courtesy of the authors).

either without the key early contributions of the Rockefeller Foundation and the US Departments of Agriculture and the Navy, which it is also a pleasure to record and recognize here. The influence of Rossi-Fanelli's school extends far beyond Rome, as many of its products went to take Chairs elsewhere in Italy. As *Indispensible Man*, Rossi-Fanelli remained as Director beyond normal age limits, retiring only in 1981, but he is still much seen in the Department, and in international organizations like FEBS.

Institutional history apart, some of Rossi-Fanelli's early work has achieved the distinction of anonymity, as is the way with solutions to what we now easily forget were ever problems. We might pick out his being the first to crystallize myoglobin and his demonstration that its composition differed from that of hemoglobin; or his demonstration in the early thirties that non-hepatic tissue oxidises acetoacetate, anticipating the now standard picture that muscle, kidney and brain use for energy sources the ketone bodies provided by the liver. His interests were wide, and extended as far as important contributions in developing hyperthermia as a successful treatment of certain types of malignant tumours in limbs.

La Sapienza

On the retirement of Rossi-Fanelli the Institute was renamed the 'Department of Biochemical Sciences'. The distinction between an 'Istituto' and a 'Dipartimento' in Italian Universities may escape outsiders, but the second half of the change clearly reflects the feeling of limitation in the category *Biochemistry* of which we spoke above. The present research strengths of the Department still reflect the interests of Rossi-Fanelli. It is overwhelmingly devoted to mammalian enzymology, protein physics and chemistry—with pride of place given to enzymes and proteins that interact with oxygen, and to metabolism. DNA, for instance, gets a look in only in interaction with these, as in protein engineering, interactions of histones and HMG proteins or DNA enzymology, while other Departments of Roma I specialize in nucleic acids, cell biology, genetics, etc.

Heme- and Metallo-Proteins

The Department hosts the Centre of Molecular Biology (Head, Milina Chiancone) of the National Research Council (CNR), a setup similar to MRC centres in UK Universities, but more permeable and permanent. The output of this inextricable CNR–University collaboration is too vast and well-known to summarize. We cannot omit the occasion Jeffries Wyman came for a week in 1960 to discuss some points about Hb with Rossi-Fanelli and the late Eraldo Antonini. The points were too difficult and interesting to clear up in a week, and the visitor left in 1985. Jeffries now lives in retirement (i.e. publishes on linkage and nonlinear differential equations) in Paris. His beautiful theory of linkage, perfected in Rome in the sixties and seventies of this century and, remarkably, of his own life, is indispensable for hemoglobinologists. It will be indispensible also to other allosterists once they realize that general laws of thermodynamics apply to other species besides Hb.

Among recent work of this group, nucleated by Maurizio Brunori, has been: experimental test of the role of Mb exons, in molecular evolution, purifying and investigating a 'minimyoglobin' model of an ancestral O_2 carrier (look up in Stryer); showing the his–Fe bond as a major factor in dynamic control of ligand binding. Recent achievements in the area of bioenergetics and membrane proteins are experimental demonstrations of synchrony of e^- transfer and H^+ pumping by cyt c oxidase, and of the Marcus theory of heteronuclear e^- transfer rates for several metalloproteins, and a two-state model of energy transducing function by cyt c with transmembrane potential as 'allosteric effector' (linkage again!). A unique instrument is the microspectrophotometer that enables observation of diffusion of physiological gases into single cells: varying the parameter of Hb concentration to verify the theory of facilitated diffusion was achieved using camel erythrocytes which can be swollen without bursting. One of the many legacies of Antonini, prematurely deceased in 1983, was the chronosteric effect in interaction of protease inhibitors with their enzymes.

The group around Bruno Mondovi studies by kinetic and spectrophotometric methods the Cu-proteins, ascorbate oxidase and laccase, has demonstrated the identity of diamino oxidase with histaminase, and has identified the metal liganding groups in plasma amino oxidase and synthesized specific inhibitors with therapeutic potential.

Enzymology and Protein Sequencing

Another group, led for many years by Paolo Fasella, is well known for its contribution to the dissection of mechanistic steps and structure–function relationships in transaminases. Fasella developed strong interests in industrial biochemistry, and in 1982 left to become the European Commission's Director-General for Scientific and Technological Research in Brussels. The group has diversified its interests into characterization of chromatin proteins (Carlo Turano), DNA methylase and substrate channelling.

Arising originally from transaminase work is the laboratory for protein sequencing headed by the present Director of the Department, Francesco Bossa and his wife Donatella Barra. This

laboratory has determined sequences of numerous proteins, PLP enzymes, hemoglobins, Cu, Fe and Zn superoxide dismutases, protein inhibitors—all proteins on which other groups in Rome work from the physical or biological point of view. Of particular interest recently has been collaboration with Roman pharmacologists on structure of new bioactive peptides extracted from amphibian skin, and solving analytical problems of awkward groups in peptides, such as post-translationally modified residues, and D-amino acid residues (proved to be coded by the normal codon of the corresponding L-residue).

Sulphur and Selenium Biochemistry

The Department has a system of periodically elected directors. Doriano Cavallini was Director for three years, but he is much happier breathing the stinks of sulphur biochemistry than the atmosphere of administration, and withdrew to concentrate on his leadership of a large group that has developed from this 38-year-old interest. In recent years this group has identified a new pathway for production of taurine and hypotaurine, the enzymes involved, and new S-cyclic products of cysteine and cystamine metabolism present in urine and brain. The binding of these products to CNS membrane receptors in specific competition with neuromodulators suggests for them an important neurochemical role. Other results are in the biosynthesis of lipoic acid, mechanism of rhodanese, and oxidative deamination of sulphur amino acids.

Carlo De Marco occupies a place beneath Cavallini—in the periodic table. His group has synthesized selenated analogs of natural amino acids and studied their interactions in various systems, an their incorporation into proteins by prokaryotes. Se compounds did not smell sweet enough to restrain him from becoming the Dean of the Medical Faculty—the second most responsible, but most difficult position in this University which includes a vast 3000-bed hospital complex (*policlinico*).

Plant Biochemistry

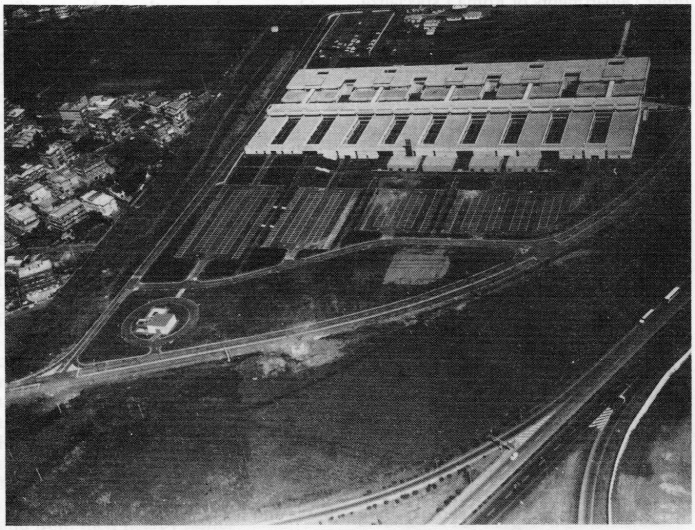
A brewery was converted into a laboratory for the more modern biotechnology of Alessandro Ballio's group. This has purified, characterized and reconstituted in liposomes, receptors of fusicoccin, a terpenoid fungal phytotoxin which mimics plant hormones and activates a membrane ATPase. (Converted Roman breweries merit an architectural star; moved to most cities they'd rate two. As to Roman beer—we do not recommend it!)

Tor Vergata

Since key biochemistry staff including Bruno Giardina, Alessandro Finazzi-Agrò, Joe Rotilio and Franca Ascoli of Roma II came from Roma I, some of the above themes naturally migrated too. But for new developments, Roma II tries not to duplicate but to push in the direction of cellular biology.

Its laboratory of dynamic fluorescence, mainly dedicated to protein structure and dynamics is among the best equipped in Europe, since it has also a facility at the nearby Frascati synchrotron with a phase-shift time-resolved (down to 10 ps) fluorometer. A group is studying energy metabolism of human and animal tissues in response to oxidative stresses using perfusion of isolated organs, especially for study of tissue damage in myocardiac ischemia. Monoclonal antibodies against toxic organic compounds and other biologically active substances are currently produced for basic biochemistry and diagnostic purposes (biosensors). Another group studies biochemistry, biosynthesis and cellular localization of protease inhibitors of mast cells, postulated to be important in inflammatory reactions. Other projects concern the biochemistry of neuroblastoma differentiation, the structure and site-directed mutagenesis of ascorbate oxidase and naturally, the comparative functional studies and relationships between domain structure and function and folding thermodynamics in hemoglobins and minimyoglobin. Joe Rotilio's group is working on the various aspects of free radical biochemistry, including oxygen cytotoxicity and superoxide dismutase. They described the structure of the active site of this enzyme prior to X-ray analysis and produced the first detailed mechansm for superoxide dismutase catalysis. At Tor Vegata this line of research takes advantage of a number of collaborative projects, borne out by the particular environment of the Faculty of Science: cloning and site-directed mutagenesis of the enzyme, in collaboration with the Laboratory of Molecular Biology, computer graphics with the Department of Mathematics and Physics, high resolution NMR with the Department of Chemistry. Of particular interest is the installment of a new ESR centre, dedicated to the detection of free radicals in cells under physiological conditions.

Figure 3 University 'Tor Vergata' of Rome II. Nothing is even ten years old. (*Photo courtesy of the authors*).



Teaching

Coming, *dalle stelle alle stalle* to students, The Roma I department straddles three Faculties and is responsible for teaching Chemistry to medical students and Biochemistry to students of science (biology and chemistry), medicine and pharmaceutical sciences. There is no specific Biochemistry degree, but students in all these sciences can select course combinations with bio-

chemical emphasis. An average of 2000 students per year take the relevant examinations. With these numbers and available resources, laboratory teaching is limited for most students. Practical work mostly happens when those really interested come forward in more manageable numbers to do a thesis, two or three years part-time, which counts towards their first degree (*laurea*).

After the laurea, research training by informal apprenticeship has always existed, but formal doctorate courses, with examinations and scholarships, only started in Italy in 1983. At present 14 students are working in a joint doctorate programme of Roma I and II.

There are also numerous postgraduate specialization courses, e.g. for medical analytical biochemistry.

In Tor Vergata 100 medical students are following the two-semester, second-year Biochemistry course and, illustrating expansion, 245, the first-year Chemistry course, while 50 students are taking Biology degrees.

FEBS Festa at Centre of World

Only one place in Rome, excepting the Coliseum, could hold two or three thousand biochemists—the *Palazzo dei Congressi* in the EUR district. 'EUR' has nothing to do with Europe, but stands for 'Esposizione Universale di Roma', which in turn stands for you-know-who's plan to hold a *grandiosa* exhibition in 1942, with round it a *monumentale* new quarter, all intended to show that Rome had made a comeback as *Centre of The World* (event postponed indefinitely). What we here are all proud of is that that centrality will be realized in more *simpatico* fashion for biochemistry with and by our international colleagues, for a few days, next July.

About those surroundings; we did refer above perhaps too slightingly to that architectural style which tried so hard and pompously to convey impressions of strength and power in its granitic facades and muscular sculpture. In truth, after decades of disparagement it is now undergoing critical re-evaluation. The subsequent history of urbanism and architecture anywhere (at Tor Vergata say) favours rediscovery of some merits in the *stile fascista*. At any rate, in this city, it now falls mellowed into place as just one in an incomparable succession of styles, Roman, Renaissance, Baroque, Umbertino, *Stile Liberty* (Art Nouveau) and others, and will be all around you at its best and most completely realized at EUR. You can continue your scientific conversations amidst the landscaping of numerous lawns, trees, lakes or, according to mood, at the Funfair (*Luna Park*) or Archaeologal, Ethnographic or other Museums (a *gelato* (ice-cream) helps homoeostasis between one street corner of a *Quartiere Monumentale* and the next in a Roman summer).

If you are not coming we are sorry, and hope you are too, but a modest extra for late registration has the same effect as throwing a cliché into the Fontana di Trevi so—another look at the programme?—*e vediamoci presto.* ■

Further details of the meeting can be found on page 51 or in *The Biochemist*, Vol. 11, No. 1, page 57.

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