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In memoriam of the work of Pietro Pratesi in the field of the Italian medicinal chemistry

It is with deep sentiment that the Italian colleagues of the pharmaceutical sciences community, both past and present, honour the memory of Professor Pietro Pratesi, emeritus professor of the Milan University and distinguished lecturer of medicinal chemistry, who died on 20 January 2002.

He will always be remembered for his contribution to the growth and development of the pharmacy sector and for the passion with which he developed organisational and didactic working activities. His work was particularly characterised by his timely and farsighted intuition, his ability to propose new ideas as well being able to realise them coherently. Adequate solutions were always found to resolve the problems, which presented themselves during his long career, in which he occupied positions of high responsibility.

Professor Pietro Pratesi was born in Florence on 27th October 1908. He studied at the University of Bologna from which he graduated in 1928 with a degree in chemistry and a diploma in pharmacy in 1929.

His training was mostly gained at the Institute of Organic Chemistry, at the Polytechnic of Munich in Bavaria, directed by Professor Hans Fischer followed by a scholarship won at the 'William The Emperor' Institute for Biochemistry directed by Professor Carl Neuberg in Berlin.

It was in this manner that he first came into contact with the German scientific world which, in that period, represented a focal point in Europe for aspiring researchers and was considered one of the most prestigious schools due to the presence of many university campuses and a strong industrial framework. It was here that he was taught the importance of research management. During this period the work carried out on pyrrole chemistry was published, which significantly contributed to the research into the chemical reactivity of this heterocyclic as well research into the structure of a few pyrrole synthetic pigments and the presence and nature of phosphates in green leaves.

On his return to Bologna, Professor Pratesi obtained a lecturing qualification in general chemistry in 1934 as well as the study of stereochemistry, which had been introduced to him by his mentor, Professor Mario Betti. He began working with the pharmacologist Donatelli on a research project between 1938 and 1940. The research was into piperidine derivatives bound with sparteine, which formed part of a study into the relationships between chemical structures and pharmacodynamic activity with the hypothesis that such bases 'are thought to be derived from natural substances due to the partial opening of the heteropolycyclic system'.

In 1940 he was elected Professor at the University of Catania as director of the medicinal chemistry and toxicology discipline. After a brief but intense period at this Sicilian location he was asked to cover the same role at the Faculty of Pharmacy of the University of Pavia in 1942.

Despite the difficulties being experienced due to the end of the war in Italy, Professor Pratesi took on this new organisational role with great enthusiasm consisting in the co-ordination and review of his collaborators' work, which he did with passion and skill and to whom he transmitted that infallible faith which had always sustained him during his lifelong career.

Being the concrete and methodical person he was, he began his organisational activity with the institution of an elementary analysis laboratory, which in that historical period represented one of the most secure analytical methods for the control of compounds for synthesis together with the acquisition of equipment for hydrogenation. During the reconstruction years in 1946 Professor Pratesi once again demonstrated his great farsightedness when he ventured into yet another new initiative. He founded the scientific journal 'II Farmaco' with Professors Ciferri, De Caro and Soldi with the aim of collating the research results of the entire pharmaceutical sector into one specialised magazine.

The magazine was rapidly distributed on a national and international level with Professor Pratesi as the co-director and then director from 1946 to 1987.

From 1946 to 1948 some of the works carried out in collaboration with Professor L. Raffa, who I would like to remember here, were published by this magazine on the theme of chemotherapy. The culmination of this work was reached in 1950 with the publication of an article in 'Science'. The article was entitled 'Some derivatives of diphenylsulfide with antispirochetal activity' in which not only the activity of the substances were

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highlighted but also included an investigation into the mechanisms behind the effects.

The discovery of important pharmacological properties such as spasmolytic, antihistaminic and bradycardic activity in *N*-arylic and aralkyl derivatives of the *N*-β-aminoethylpiperidine and the need for stronger relations to promote the development of research with the biopharmacology component of pharmaceutical sciences led Professor Pratesi to reinforce a unique initiative in the 1950s in Italy: the creation of a pharmacological laboratory at the Institute of Medicinal chemistry under the responsibility of Professor Enzo Grana, a student of Professor De Caro.

In a letter in 1955 to the International Congress for Pure and Applied Chemistry held in Zurich and published in 'Experientia', Professor Pratesi described the results achieved with the quaternarysation of the *N*-β-aminoetihylpiperidine derivatives, which took on an intense atropine-like activity. These results derive from the consideration of the fact that natural substances, which possess biological activity, are a starting point for the creation of new compounds thanks to the molecular simplification of their structure.

Convinced that relations between the chemical and bio-pharmacological components of pharmaceutical sciences could reciprocally benefit from the knowledge possessed by each respective cultural patrimony, he instituted seminars on medicinal chemistry in which many researchers from the Milanese industry participated and he also actively participated in the foundation of the Italian Society of Pharmaceutical Sciences for which he was president from 1966 to 1973.

Due to his interest for stereochemistry his research was mainly directed towards the configuration of catecholamines. He once wrote: 'In 1953 we found that optically active mandelamides can be reduced to the corresponding amines with hydride lithium–aluminium without racemisation. It was, therefore, possible to determine the configuration of β-phenyl-β-oxiethylamines using adequately substituted mandelic acids as starting products'.

This fundamental achievement led from 1958 to 1960 to the determination of the configuration of epinephrine, norepinephrine, isoproterenol and successively phenylephrine and sympathol to which the following researchers also contributed: Professors A. La Manna, V. Ghislandi, A. Campiglio and G. Pagani. It is worth noting that work on the determination of the optical configuration on *erythro*-3,4-dioxynorephedrine and on the stereospecific synthesis of the *threo*-3,4-dioxynorephedrine and other phenylalkanolamines 3^1,4^1 substitutes continued to be published even 10 years on.

During these years, Professor Pratesi began collaborating with Institutions and representatives of the principal European pharmaceutical schools such as the Department of Pharmacology, University of Oxford, a relationship, which was reinforced by inviting Professor R. Ing in 1959 to hold a series of readings on the 'relationships between the chemical structure and pharmacological activity'. Another important series of readings were held by Professor E. Ariëns, pharmacologist at the University of Nimega, author of the renowned collection of 'Molecular Pharmacology', which divulged, clarified and defined the agonist, antagonist, affinity and intrinsic activity concepts of compounds, which interact with biological systems.

From the early 1960s Professor Pratesi organised an extensive research programme with the aim of considering the problem of adrenergic and cholinergic reactivity on a molecular basis. These research activities were carried out on a chemical, physico-chemical and biopharmacological level; chemically through specifically designed compound synthesis, physico-chemically through the determination of the molecular properties of the compounds studied as well as bio-pharmacologically. The results were masterfully integrated by Professor Pratesi and included, in particular, a clever interpretation of the reactivity of the adrenergic receptors.

It is also worth remembering a few speeches he held at international congresses such as the 'International symposium on pharmaceutical chemistry', in Florence 1962 and a speech held in London at the Chelsea College on invitation of Professor A. Beckett which was consequently published in 'Advances in drug research' (Vol. II, 1965). The article provided an interpretation of the gradual changes of α-reactivity and β-reactivity and of the intensification of the latter with their relation to the structural properties of nitrogen atom substituents. A third speech worth mentioning was held at the third 'International pharmacological meeting' in 1966, San Paolo, Brazil.

In the latter, reference was made to the results of a study on a *N*-isopropylphenylethanolamines series in which the 3,4 positions of the catechol system were substituted with atoms or groups with different inductive effects and different hydrophilic–lipophilic characteristics. New light was hence shed on the problem of the passage between β-agonist and β-antagonist. Other articles included 'The approach to a chemical interpretation of the activation mechanism of adrenergic receptors', in 1971 and 'Molecular geometry and binding capacity in the series of β-adrenergic compounds', in 1975 both published in the magazine 'II Farmaco'. The latter was dedicated to interpreting the selectivity of a series of catecholamines *N*-substitutes for β-receptors in the atrium of guinea pigs with respect to those present in the tracheal muscle of calves in function of a structural parameter, which indicates the volume of nitrogen alkyl substitutes.

Professor Pratesi's research was not just limited to this area of research but also to the development of research

projects aimed at studying the steric and energetic aspects of muscarine agents, which have been cited by many authors, and a few antagonists, which are characterised by the presence of a quaternary ammonium function with the cholinergenic receptor. In the first case, the fact that it was possible to identify as a 'fit' inductor function the methyl group situated at the end of the five atoms chain of the molecule of agonistic activity was highlighted. In the case of antagonists, it was highlighted that the antimuscarinic activity is determined not only by interaction of the cationic termination but also by the hydrophobic interaction of the hydrocarbon groups linked to a system consisting of a nitrogen atom or a CH group with well established non polar residues of the active centre.

While managing these multiple research activities, Professor Pratesi could not neglect his duties with regards to guaranteeing the survival of the Faculty of Pharmacy, whose existence was questioned in 1964, with a ministerial document by proposing that the degree be substituted by a diploma and that the faculty pass under the direction of the Faculty of Medicine or Life Sciences.

Thanks to his efforts and of those of other prominent colleagues such as Professors G. Giacomello and L. Musaio, not only did they overcome this problem but they also managed to institute a new degree course, that of CTF, in a faculty which was destined to be shut down. This new course was highly successful over the years and became a focal point for both students and researchers. Recognition of his efforts in the establishment of this new degree course led to a new role: that of representing from 1966 to 1979 the Faculty of Pharmacy in the High Council for Public Education.

In the period from1965 to 1970 an initiative promoted by Professor Emilio Trabucchi, pharmacologist of the Faculty of Medicine at the University of Milan was taking shape. The initiative consisted in the institution of the Faculty of Pharmacy at the University of Milan in addition to the existing faculty at the University of Pavia, which at that time was the only faculty available for the whole of the Lombardy region. A committee composed of experts from the university, industry and the profession elaborated an executive plan in order to launch the new faculty. The High Council, where Professor Pratesi and Professor Trabucchi operated, approved the new Statute and hence the Faculty of Pharmacy at University of Milan was officially inaugurated on November 1, 1970.

Professor Pratesi was asked to join the Governing Committee as he represented one of the top professionals the country had to offer in the areas of study offered by the faculty. He was the first dean of the faculty from the academic years 1970-1971–1982-1983.

Posed with the institution of this new faculty, where everything had to be done, Professor Pratesi demonstrated that his great determination and organisational capabilities, coupled with the ability of his collaborators, amongst which I would like to mention Professor A. Soldi, were of fundamental importance to the creation of this faculty. There were many difficulties to be overcome, which included, to begin with, finding a physical location for the Medicinal chemistry Institute. It is worth noting that this Institute has since become one of the most important faculties of pharmacy for the entire country.

While managing this time-consuming activity, his flair for research pushed him to further deepen his study into the quantitative relations of a wide range of ligands of the muscarinic receptor. These ligands were specifically designed and studied in order to deduce a rational interpretation of the specific role carried out by the structural characteristics of such compounds. Professor Pratesi studied the work of C. Hansch and successively met with him on several occasions. These meetings led him to carry out an in-depth analysis of the relationship between the molecular properties and muscarinic activity with the application of the correlative analysis methodologies. Professors Silipo and Vittoria of the University of Naples also collaborated in this research project.

Despite the end of his academic career in 1983 his interest for issues relating to cholinergenic reactivity continued. He in fact inspired the research carried out on muscarines, muscarones and their analogues, which led Professors De Micheli and De Amici to synthesise the stereoisomers of these compounds and to further analyse their bio-pharmacological properties.

Whilst it is difficult to summarise his many scientific and teaching merits, especially those regarding the creation of the new school of thought, what is certain is that maybe one of the most noteworthy aspects of his career was the innovative content of his ideas and works, which in Italy, at least, can be considered of pioneering significance. The birth of medicinal chemistry, that is, the study of the relationship between molecular properties and biological activity can be attributed to Professor Pratesi and it is under his direction that the subject has penetrated many other sectors. He was the first to comprehend the importance of a close collaboration between bio-pharmacological and chemical components, intended in the widest sense, in order to obtain a process of rationalisation of the biological activity for further progress in research.

In other words, all his work can be said to be inspired by the definition of medicinal chemistry i.e. A chemistry-based discipline involving aspects of biology, medical and pharmaceutical sciences. It is concerned with invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure–activity relationships' (IUPAC 1997).

The years, which have passed, may have undermined his body but not his spirit. He was always involved in pharmaceutical activities with a moving and incredible sense of dedication.

There are no words to express the gratitude for everything he has done for us during the many years he has dedicated to this activity, for which all those who knew him are infinitely grateful.

In the emptiness left by his loss, his example to follow remains as does the wealth of his teachings, a precious gift to those who intend to use them in the knowledge that this is by far the best way to remember him.

Palermo, 20 May 2002.

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