Marco Fraccaro, 1926–2008

Marco Fraccaro ranks among the pioneers of human cytogenetics. In 1959/60, when the first chromosome aberrations in humans were reported, he had already published on 'cytogenetic observations in mongolism', and on sex chromatin and aberrations of the sex chromosomes. He inspired Harold Klinger to found a journal in this field which was consequently titled 'Cytogenetics' and which first appeared in 1962. It became the leading journal on this topic and has remained a most relevant forum (later named 'Cytogenetic and Genome Research'). Together with Harold Klinger, Marco established the famous Basel colloquia which were held biannually between 1961 and 1975, and which originally dealt with sex chromatin and the X chromosome, later extending the scope and including, in particular, the then fashionable 'somatic cell genetics'. Marco was a member of the Paris Conference 1971 on 'Standardization in Human Cytogenetics' which forms the basis for the identification of individual chromosomes and rearrangements. In 1979 he organized a symposium in Rapallo to reflect on the discovery of trisomy 21 by Jérôme Lejeune (who was present) and the twenty years of research thereafter. And he organized another Rapallo symposium in 1984 on 'First trimester fetal diagnosis' together with G. Simoni and B. Brambati who were pioneers in this field. It was Marco who devoted himself to the task of promoting and disseminating this new method.

From these and manifold similar activities it can be seen that it was of real concern to Marco to propagate cytogenetics within an international framework.

Marco Fraccaro lived from September 26, 1926 to April 2, 2008. He was born in Pavia, Italy, where he grew up and studied. He graduated in medicine in 1950 with a thesis at the Institute of Pathological Anatomy, where he subsequently served as an assistant professor. In 1954 he took up a fellowship at the Galton Laboratory, University College, London, which at that time was directed by Prof. L.S. Penrose and was the classical place for professional training in human genetics. He became an honorary research assistant there at the Department of Eugenics, Biometry and Genetics. After two years at the Galton Laboratory he arrived in

Uppsala in 1956 to take up the position as vice-director of the Institute of Human Genetics, until March 1960. Here, he also found his wife, Inga, with whom he had three children. In 1958 he became consultant in medical genetics at Bellevue Hospital in New York. In September 1960, Marco succeeded John Edwards as a researcher at the MRC Population Genetics Research Unit at Headington, Oxford. There, he became a life member of the 'Senior Common Room' at Exeter College. In 1960, he also became 'Physician in Charge' of the Genetic Clinic of the Royal Buckinghamshire Hospital, and from 1961 until 1971, he was elected a member of the Expert Group for Human Genetics of the World Health Organization. In 1963, he became a member of the Royal Society of Medicine in London.

His wandering years ended in 1962, when Marco accepted the position as head of a research group in human cytogenetics, an 'Euratom Group', supported by the European

Community. He had various possibilities as to where in Italy to start his group, and he opted for his home town Pavia. From 1962 onwards, he had also been appointed teacher of general biology and medical genetics in the Medical Faculty of the University of Pavia, and in 1968 he became full professor on the chair of General Biology and Medical Genetics. He remained in this position until his retirement in 2001. In addition, he was the rector of a students' College, Collegio Cairoli, a position which he held since 1968. This college serves about 100 students. Becoming rector emeritus in 2002, his successor Prof. G. Leonardelli allowed him to maintain his rooms at the college for the rest of his life, and Marco took care of the college library, the growth and development of which was one of his favorite concerns. Similarly, he remained engaged in the organization of art exhibitions in the gallery rooms of the college which he had already established in 1971. His latest project which he did not live to see (the exhibition was shown from May 7 to 17, 2008) was titled: '80 artisti riflettono (su) la luce'. As a member of the 'Istituto Lombardo, Accademia di Scienze e Lettere' in Milan, he contributed regularly to the sessions, and gave his last presentation on November 29, 2007, about Camillo Golgi as a pupil at the gymnasium.

In Marco's scientific oeuvre, cytogenetics formed the larger part, but was by far not the only subject of his interests. Almost all of his scientific articles fall in the range of genetics, including occasional articles on organisms other than humans, e.g. the gorilla, reindeer, chamois, marmot and other rodents, and also some articles on *Drosophila* and *Anopheles*, reporting mainly on DNA replication studies of the sex chromosomes. When he published his first investigations in 1951/52, these included hereditary topics. There is an impressive corpus of casuistic studies, including first descriptions and the delineation of new syndromes, and also larger samples of similarly affected individuals. As the thematic emphasis of the early Basel colloquia suggests, Marco became particularly interested in the sex chromosomes, their genetic contribution and their clinical effects. In the sixties, he identified numerical and structural aberrations of the sex chromosomes, such as X and Y polysomies, mosaics, translocations, isochromosomes, deletions etc., some of them for the first time; and he characterized the disease phenotypes. With the advent of ³H-thymidine autoradiography, in 1963 he studied the replication patterns of all kinds of normal and abnormal sex chromosomes under the view that late replication indicates genetic inactivation of the respective chromosomes or segments. He also found a correlation between the DNA content of the sex chromatin and structurally abnormal X chromosomes. In meiosis he identified the Xp-Yq association of the sex chromosome bivalent.

For cytogenetics, it was the 'time of the great discoveries', and all these investigations were taken to be highly exciting. Marco was and always remained with the most current developments in the field.

The knowledge reached so far was essentially of morphological nature. With the methodological developments in the early seventies, the molecular analysis of DNA and thus

also of the sex chromosomes came into focus, and here in particular, the question of the molecular basis of sex determination and fertility were of interest. Marco contributed numerous studies to these topics. By deletion mapping, he used, apart from phenotypic evidence, specifically located DNA probes in cooperation with his associates and external colleagues, thus obtaining evidence about which chromosomal segments were involved or were not involved in male and female fertility, and in male sex determination. For these investigations, his great treasure was a large collection of clinically well-characterized patients and patient samples. Thus, he was able to study larger series of XX males, true hermaphrodites, gonadal dysgenesis cases, and even an XO male, for the presence or absence of Y-specific DNA and analyze its localization. Among the last articles with his participation in this field, the detection of the DSS gene (later named *DAX1*) which thereafter turned out to be crucially involved in testis development, was reported.

Of Marco's manifold investigations on subjects other than the sex chromosomes, I will mention here only a few. Together with colleagues from Sardinia he became interested in Werner's syndrome which turned out to have a high prevalence on this island. In 1977, together with Jan Lindsten, Marco started a European collaborative study on the 11q;22q translocation, which ended up with 43 cases from various countries, and subsequently another 20 cases could be added. Remarkably, always one and the same unbalanced karyotype was found in the offspring of translocation carriers. From 1983 onwards, Marco participated (as spiritus rector, I guess) in the introduction of the chorionic villi sampling method of prenatal diagnosis as a reliable routine procedure, as developed by G. Simoni and B. Brambati.

I will not go into further details of Marco's scientific legacy, but rather refer to some of his other activities and interests which he pursued with great enthusiasm. Apart from his scientific publications, Marco liked to write every now and then about other subjects which caught his interest. After retirement he did so more extensively. These (always rather short) writings refer e.g. to correspondence of historical interest for the Collegio or for the University of Pavia, to the art collections and to the publication activities of the Collegio. I feel that Marco followed the idea which he had expressed himself, that 'scripta manent'.

However, in the first place among his extramural engagements the Collegio Cairoli is to be mentioned. This student college was built under the empress Maria Theresia of Habsburg for the German and Hungarian students. In this marvellous baroque palace, Marco resided in two huge rooms between old precious books and works of modern art, but since he also had to run his university institute, he usually could stay in the college only in the evenings and over the weekends. As an amateur and collector of contemporary art, he organized exhibitions, mainly of living artists from Italy and also from abroad, at irregular intervals, but several times a year. Once, Marco wished to have a portrait of himself, and the artist, G.M. Barbieri, depicted him with a cigarette between his fingers. Later, after he had long stopped smoking, Marco decided to give the portrait to the

college. When, to his surprise, he noticed the cigarette (he had almost forgotten that he had been a heavy smoker), he urged the artist to paint a copy without the cigarette.

To characterize Marco further, I would still like to mention some personal experiences with him. I saw Marco for the first time when I was introduced to him at the 2nd International Congress of Human Genetics in 1961 in Rome. I then met him regularly from the 3rd Basel colloquium onwards. We came into closer contact when he invited me in 1971 to give a seminar at his institute in Pavia. I mark it as the beginning of a friendship when, at a symposium on 'Constitutive Heterochromatin in Man' at Schloß Reinhartshausen/Rhein in 1972, on a boat trip on the Rhine river to the Loreley rock, he took me aside at the railing and sang in a low but tuneful voice out of Richard Wagner's 'Rheingold' about the Rhine daughters. – At a meeting (I don't remember where and when, but no doubt on sexual development), Peter Goodfellow introduced his talk about male sex determination by projecting the colossal statue of David by Michelangelo, claiming that 'this is a human male' (to illustrate, what he was speaking about). Marco immediately got up to say: 'To be correct, this is an Italian'. At the age of about forty, I had an opportunity to acquire a double bass, and I felt inclined to shift from the violoncello to the bass. However, since I was not satisfied with the instrument, I asked Marco with his circle of prominent friends and acquaintances at Pavia, if he could not find an Italian contra-

basso for me. This projected me into the role of a wizard's apprentice: At my next visit to Pavia, Marco took me to a most abandoned place in the countryside (actually, it was a custom house of the Habsburgian period), where an instrument was deposited on a cupboard in the kitchen. It required some restoration, but I happily took it with me. At Marco's next visit to Freiburg, he descended from the train with another double bass in his arms. And when Hilger Ropers was invited by Marco to give a guest lecture in Pavia, upon his return he appeared at our home door with yet another bass under his arm – and so on, I just didn't know the incantation to stop the contrabasso invasion. – So much out of my treasury of reminiscences of episodes and experiences with Marco.

From the time he came to know me as an advanced beginner in cytogenetics, he granted me every possible patronage and opened any locked door. Unfortunately, being his junior I was not able to reciprocate all his support.

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