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Guido Pontecorvo 1907-1999

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Abstract

"Ponte", as he was known, even to his family, died in September 1999, aged 91, of complications following a fall whilst collecting mushrooms in his beloved Swiss mountains. He was the founder of the genetics of Aspergillus nidulans, and as a result of the discovery of the parasexual cycle, the originator of genetical studies in many other fungi. He made significant contributions to modern genetics in elucidating the divisibility of the gene by recombination, and in his later years in the application of parasexual techniques to mammalian cell cultures. He was also an irascible yet genial friend and adviser who attracted the great admiration of colleagues and students worldwide.

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"Ponte", as he was known, even to his family, died in September 1999, aged 91, of complications following a fall whilst collecting mushrooms in his beloved Swiss mountains. He was the founder of the genetics of *Aspergillus nidulans*, and as a result of the discovery of the parasexual cycle, the originator of genetical studies in many other fungi. He made significant contributions to modern genetics in elucidating the divisibility of the gene by recombination, and in his later years in the application of parasexual techniques to mammalian cell cultures. He was also an irascible yet genial friend and adviser who attracted the great admiration of colleagues and students worldwide.

Ponte was one of eight children of a Jewish family with concerns in textile manufacture in Pisa. His interest in biology was sparked in high school, and possibly fostered by a spell in a relative's chicken farm. However, the school curriculum was mainly classical, so that by the age of 16 Pontecorvo could read and enjoy Aristophanes in Greek, a feature which almost certainly contributed to the meticulous clarity of his English. He went on to study in the Faculty of Agriculture in Pisa, where his interest in genetics was aroused by E. Avanzi, a plant geneticist, whose assistant Pontecorvo later became. He then moved on to a cattle breeding post in Florence, where he stayed for eight years. In 1937 he visited the Institute of Animal Genetics in Edinburgh and met Alick Buchanan-Smith, who one year later offered him hospitality when dismissed from his Tuscan post as a result of Nazi-inspired racial policies. Sadly, his political problems did not end there; when Italy joined the war, he was interned for six months in Great Britain as an "enemy alien".

Pontecorvo expected to move on to an animal breeding post in Peru, but never made it, having become deeply influenced by H.J Muller, who was then working in the Institute of Animal Genetics in Edinburgh, *en route* from the USSR to the USA. Muller's interest and clear thinking on the nature of the gene prompted Ponte to abandon animal breeding and undertake a PhD under his supervision. His thesis on the mechanism of chromosome rearrangement in *Drosophila melanogaster* demonstrated a clever exploitation of biology and genetics; it was completed in 1941. On release from internment in that year, he was required to take up "war work" in Glasgow, which consisted of research on spermatogenesis and sex-ratio in the human louse (the menagerie, of course, being fed on himself). In 1945 he was appointed to Glasgow University as its first Lecturer in Genetics, and this rapidly led to formation of the Department of Genetics, which developed into a small, but very active department, headed by Pontecorvo as Professor until 1968.

Pontecorvo's work on *Drosophila* and lice had raised questions in his mind on the integrity of genes and autonomy, or otherwise, of their action, especially in relationship to the minimal units of mutation and recombination. This crystallized into the need to employ microbes to increase the "resolving power of genetic analysis" and relate the mutational, recombinational and functional manifestations of the gene, which Muller believed constituted a continuum, but others supposed could be explained by tandem "pseudoallelles". That Muller had been right was demonstrated in 1955 by R.H. Pritchard's linear intragenic linkage map of the *adE* locus in *Aspergillus* , which also demonstrated reciprocal meiotic and mitotic recombination within the gene. This was contemporaneous with Benzer's similar, but far more detailed, map of rII mutants

in bacteriophage. Typically, Ponte liked to emphasize that, in both cases, the new understanding of the fine structure of the gene was developed purely by genetic analysis, with no input from biochemistry.

Thus Pontecorvo was one of the few pioneers who had deliberately and independently advocated microbial genetics, and followed this up by developing the genetics of a new micro-organism. His choice of *A. nidulans* was not a hasty one, and was made despite scorn from colleagues who thought that its homothallism would be a practical barrier. He considered various candidates such as *Aerobacter* and *Serratia* before a parallel interest, raised by H. Raistrick, in irradiation-induced mutants for increased penicillin production, led him to the filamentous fungi. Ironically, work on penicillin, now a lively field of molecular genetics, declined in Britain as the result of the decision to transfer wartime development to the USA. Ponte's first publications on filamentous fungi dealt with heterokaryosis in *Penicillium* and *Aspergillus* species, which introduced him to the value of autonomously expressed spore-colours as genetic markers in these fungi. This was of importance when the supposed difficulties due to homothallism of *A. nidulans* were turned to advantage, and it was shown that spore colour segregation provided a ready means of identifying crossed fruiting bodies, and later, the haploid and recombinant diploid products of mitotic segregation in synthetic diploids.

The Glasgow department was notable for its research, and for a constant stream of eminent visitors, partly a testament to Pontecorvo's international standing and the warm and civilised welcome they were afforded; partly to the proximity of the fog-free Prestwick airport, often a refuelling point for intercontinental flights. Genetics attracted relatively few home-grown students, but those who did penetrate the intellectual barriers were determined and very able. By contrast, Ponte was especially proud that many students and visitors came to the department from "underdeveloped" countries all over the world, and that many returned to become research leaders. He was heard at least once to tell a new research student to work "very hard indeed, almost to the point of death--but do not die--that would be embarrassing", and often to say, in search of clarity of exposition during his daily tour around the research students, "Stop, start again, very slowly, and from the beginning.". One researcher was known to work all night in preparation for Ponte's morning interrogation, then retire to bed before he could return with new suggestions.

By 1953, the utility of *A. nidulans* as a genetic organism had been comprehensively established. One advantage of the homothallism of this species is the origin of all Glasgow laboratory strains from a single wild isolate, thus cutting out much uncontrolled variation. Another is the potential of crossing any strain with any other. A third feature that Pontecorvo could not have foreseen is the amenability of this fungus to molecular analysis, which owes much to its ease of transformation and the high frequency of homologous integration of transforming DNA, the latter possibly relating to the isogenicity of DNA from closely related strains.

Discovery of the parasexual cycle was initiated by J.A. Roper's isolation from *A. nidulans* heterokaryons, of stable diploids resulting from rare fusions of vegetative haploid nuclei. This enabled the demonstration of mitotic crossing-over which, with haploidisation, made possible genetic analysis in the absence of sex. "Parasexual cycle genetics", as Ponte called this combination of steps, provided the first route to genetic analysis in organisms like *Penicillium*

chrysogenum, *A. niger*, and *Fusarium oxysporum* whose sexual stages were or are unknown. E. Kafer and Pontecorvo also made extensive use of parasexual genetics in *A. nidulans*, where it enabled the mapping of new mutations to their chromosomes in a single step, and the simultaneous detection of chromosomal translocations.

By 1954, parasexual cycle genetics was sufficiently well developed to trigger Ponte's next major contribution: recognition that this method of genetic analysis, if applied to human or other animal cells in culture, would make possible enormous advances. Human genetics from cell cultures, on which his work started in 1959, was sufficiently important to receive initial funding from the US National Institutes of Health and the UK Medical Research Council. But it was about ten years too soon; many technical developments were needed before it would become reality. Nevertheless, Ponte's clear-minded and far-seeing advocacy, and the stream of academic visitors and students (e.g. Eugene Bell, Walter Bodmer, Renato Dulbecco, George Martin, Obaid Siddiqui) from home and abroad, helped to ensure that human genetics moved expeditiously into the laboratory, where somatic cycle genetics is practised today, even if most of those who use it are ignorant of its origin and history. Thus, important foundations of modern molecular medicine were laid in Glasgow upon Pontecorvo's Muller-derived interest in the nature of the gene. There could hardly be a better example of the unpredictable value of curiosity-driven research.

In 1968, having seen the Glasgow Genetics department established in a new building, (re-named after him at the 50th anniversary of the founding of the department) and tired of administrative chores, Ponte accepted the tempting offer to join the staff of the Imperial Cancer Research Fund's headquarters laboratories in London, directed by his friend and former Glasgow colleague Michael Stoker. Here, he influenced a new generation of young cancer researchers, and continued work on the parasexual genetics of mammalian cells, devising, among other things, the polyethylene glycol method of fusing animal cells.

As well as serving the Genetical Society of Great Britain as sometime Secretary and President, Pontecorvo was a founder member of the Institute of Biology and received many academic honours and distinctions from home and overseas institutions, including the Darwin medal of the Royal Society and the Carlsberg Foundation's Hansen prize for Microbiology. He was a Council member and Leeuwenhoek lecturer of the Royal Society, gave the Jesup and Messenger lectures at Columbia and Cornell Universities, was an Honorary member of the US and Indian National Academies of Science (amongst others), and enjoyed visiting professorships and lecture tours at many overseas institutions.

Almost invariably, Ponte's overseas academic visits were to places near alpine zones. This reflected his interest in alpine plants, which grew from early enthusiasm for the Italian alps and led to Presidency of the Scottish Rock Garden Club. With Leni, his Swiss wife, he built a small chalet in the Valais region of Switzerland and, from this base, made long-term studies of the ecology of alpine plants and compiled a major photographic archive which, alas, never found a publisher. The chalet guest-book, like that at Glasgow, is an impressive record of the biological and other friends who enjoyed the Pontecorvo's hospitality over the years. Although Leni predeceased Guido, this did not stop him from spending much of every summer and part of each winter in the chalet, often fending for himself, gardening on a 45 degree slope despite hip prostheses, and entertaining in the evenings a succession of guests and "gerisitters".

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