Obituary

Guido Pontecorvo (1907–1999): a pioneer in fungal genetics

Alan ROPER

44 Stumperlowe Crescent Road, Sheffield S10 3PR, UK.
E-mail: a.roper@sheffield.ac.uk

Received 26 March 2000; accepted 12 April 2000.

Guido Pontecorvo, 'Ponte' to all who knew him, was born in Pisa, Italy, on 29 November 1907. His death on 25 September 1999, in his beloved Swiss mountains, marks the loss of a scientist whose breadth and vision had major impacts on genetical thought and experimentation.

After a classical education at Pisa lycee, he studied agricultural sciences at Pisa University (1924–1928) and later took postgraduate courses, including a diploma in silkworm breeding, in Milan and Pisa. His first research was in Florence, at the Agricultural Advisory Service for Tuscany; he worked on the beautiful Chiano breed of cattle for which he retained a strong affection. The breadth acquired in this and later periods was of lasting value. It had a lively impact on undergraduate courses in Glasgow, and for members of his first research team, all concentrating on microbial genetics, Ponte drew on a wealth of relevant references from his background, and applied ready corrective measures if he suspected a blinkered outlook.

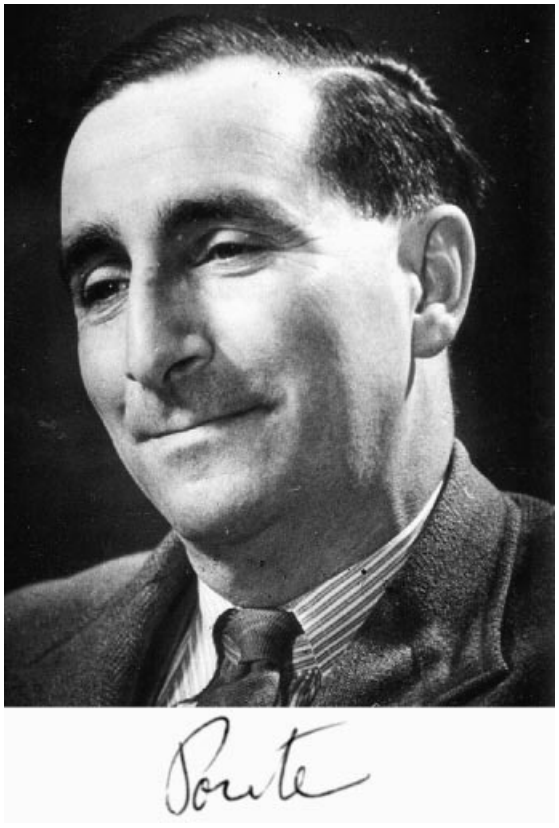

Fig. 1. Guido Pontecorvo (1907–1999).

Ponte left Italy in 1938, sensing the anti-Semitic developments that lay ahead. He had planned to move to a post in cattle breeding in South America but, fortunately for British genetics, he stopped off in Edinburgh; there he met Hermann Muller (later to be a Nobel Laureate) and decided to read for a PhD under Muller's supervision. Research of that period shows the emergence of one of several themes that would dominate future work. The study of radiation-induced chromosome loss in *Drosophila* was ingenious (Pontecorvo 1941, 1943a, 1943b). It was rooted firmly in the approach of classical genetics, the sharp segregation of heritable phenotypic differences, with the distinguishing feature that the 'segregating units' were manipulated to fit the problem. Later this outlook was to prove fruitful in the exploration of novel and unexpected recombination processes in fungi.

In 1941 Ponte moved to Glasgow where, in 1945, he was appointed to his first tenured academic post. He was promoted to Reader in 1952 and appointed to the newly created Chair of Genetics in 1955. The early years of this period were not easy, as the climate was unfavourable for the development of genetics. As Ponte recalled in his Weigle Memorial Lecture (Pontecorvo 1985), in 1945 the then Dean of Medicine '… could not think of one thing in genetics that might be of use to medicine …' At first Ponte's group was housed in two small rooms in the Materia Medica building, and some equipment, such as water baths, had to be found from the discarded apparatus of more affluent departments. Later the department moved to slightly more space in the old Anderson College of Medicine, a college famous principally for having

https://doi.org/10.1017/S095375620000335X Published online by Cambridge University Press

trained Dr David Livingstone. Despite the material problems, there was an intellectual vigour generated by Ponte and by the flow of distinguished visitors whom he attracted; the visitors' book from that period reads like a 'Who's Who' of American and European genetics.

Initially Ponte was exploring the potential for genetical research of bacteria (Devi, Pontecorvo & Higginbottom 1947, 1951) and of some conidial filamentous fungi (Pontecorvo & Gemmell 1944a, 1944b). One aim was to develop systems of genetic analysis for these species and, in the case of industrially important microrganisms, to exploit genetic methods for their improvement. The far-sighted paper on heterokaryosis (Pontecorvo 1946) emphasised this approach: '…the view that there cannot be a 'genetics' of agamic species thus seems outdated. Classical genetics has taught us concepts and techniques which have some application in the study of any system of heredity and variation involving particulate units…provided these units have two essential properties of the gene: mutation, and reproduction in the mutated form;…heterokaryotic systems call for a novel type of genetics based on segregation and recombination other than meiosis and karyogamy'. In extending the thinking to bacteria Ponte wrote '…if particles can be exchanged between bacteria, the whole picture should be similar to that of heterokaryotic systems…' Ponte had been convinced that bacteria must have a system for genetic exchange, and it is an interesting coincidence that the 1946 paper was presented at the symposium in which Lederberg reported the first results on recombination in *Escherichia coli* (Lederberg & Tatum 1946).

Ponte eventually chose the homothallic ascomycete, *Emericella nidulans* (anamorph *Aspergillus nidulans*), as his 'ideal' species. Uninucleate conidia, with autonomous colour mutants, colonial growth, and simple nutritional requirements were among its attractions (Gossop, Yuill & Yuill 1940). Henrard (1934) had concluded that homothallism was a total barrier to genetic analysis; if cleistothecial ascomata of hybrid origin were formed, they would be indistinguishable from the 'selfed' ascomata. Ponte's solution lay in the use of balanced heterokaryons, already pioneered by others in *Neurospora* (Dodge 1942; Beadle & Coonradt 1944). The *Aspergillus* heterokaryons had components differing in conidial colour, which facilitated the detection of heterokaryotic growth, and balanced growth was maintained by complementary nutritional requirements. Recombinants were selected on appropriate media, by methods similar to those used in bacterial recombination, and the proportions of 'selfed' and 'hybrid' cleistothecia were irrelevant. The first steps in formal genetic analysis were undertaken by a very small team: Ponte, Ted Forbes and, part-time, Olive Adam (Pontecorvo 1949; Pontecorvo, Forbes & Adam 1949).

The formal genetics of *Aspergillus nidulans* was by no means the principal purpose of the overall research programme, but it was an essential preliminary. Ponte's fundamental aims lay in the '…problems of intracellular spatial organisation of metabolic activities' (Pontecorvo 1950, 1952a, 1952b) and in the further question whether '…the distribution of genes, between [chromosomes] and along the chromosome is haphazard in relation to their functions' (1950). Heterokaryons, with their potential for flexible nuclear ratios and later, strains with heterozygous diploid nuclei, offered a unique approach to the study of the spatial distribution and function of genes.

A planned assault on the matter of spatial distribution of genes and their function arose after discussions between Ponte and the microbial biochemist, Henry McIlwain, who was studying the metabolism of vitamin-like substances. McIlwain (1946) had speculated that, in bacteria, each step in a sequence of reactions involving vitamin-like substances might be mediated by only a few, perhaps only one, molecule of enzyme per cell. Ponte's hypothesis, exciting and entirely plausible in the then state of knowledge, was that for effective function the enzymes in such a sequence might need to be organised as an 'assembly line' and that this would be reflected in the close linkage of the genes concerned.[1] The first test of this was made on three independently isolated biotin-requiring mutants and the mutations were found to be very closely linked (Roper 1950); the results were interpreted, incorrectly, as linkage between three genes with different biochemical specificities. In fact, this was an early demonstration of recombination between different mutant sites within one gene, something that was contrary in 1950 to the concept of the gene as the ultimate unit of genetics. Fine structure analysis, as it came to be called, was extended in *Aspergillus* by Pritchard (1955) and in *Drosophila* by MacKendrick & Pontecorvo (1952). The picture that emerged, taken to its peak in phage by Benzer (1955), was ready for, and compatible with, the structure of DNA proposed by Watson and Crick. Ponte had played a key role in this probing of the gene, and later publications offered speculations, clarifications and postscripts to this era (Pontecorvo 1956a, 1958; Pontecorvo & Roper 1956). Ponte's 1956 paper brought much-needed order to the concepts and terminology of allelism and complex loci; and in the essay on heterosis (Pontecorvo 1955), he foresaw the development of studies in intragenic complementation and suppression.

The first major review of *Aspergillus* genetics (Pontecorvo *et al*. 1953) became a handbook for the growing community of *Aspergillus* geneticists. The review presented the early results of genetic analysis by mitotic recombination of strains with diploid nuclei, and so offered a model to those aspiring to develop the genetics of other, non-overtly sexual microbial species.

Balanced heterokaryons between haploid components differing in conidial colour and nutritional requirements, produced rare conidia with prototrophic, heterozygous, diploid nuclei (Roper 1952). During vegetative growth these diploids produced recombinants detected by the uncovering of recessive conidial colour mutations. Interpretation of the genetic events responsible for mitotic recombination was painstaking slow. It would have been impossible without parallel standard meiotic analysis and equally impossible without Ponte's knowledge of *Drosophila* genetics. Most of the infrequent diploid recombinants arose by mitotic crossing

[1] Ponte visited McIlwain's home in Sheffield in 1946. I was then a postgraduate supervised by McIlwain and I was fortunate enough to be present at the lively discussions and, in 1948, to join Ponte's small team in Glasgow.

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over (Pontecorvo & Käfer 1956, 1958), a process until then known only in *Drosophila* (Stern 1936) where it had been assumed to result from the cytologically-observable, somatic pairing of homologues. The even rarer haploid segregants arose by step-wise, successive loss of whole chromosomes (Käfer 1961) in which '… each chromosome [segregated] as a unit' (Pontecorvo, Tarr Gloor & Forbes 1954). *Aspergillus* had provided a model system for which parallels were sought, successfully, in *Aspergillus niger* (Pontecorvo, Roper & Forbes 1953) and *Penicillium chrysogenum* (Pontecorvo & Sermonti 1953, 1954). Ponte (1954) coined the term 'parasexual cycle' for the mitotic events of heterokaryosis, diploid formation, mitotic crossing over, and haploidisation. The cycle achieved the same genetic end as was achieved in meiosis, the recombination of linked and of unlinked genes, but by different modalities. Ponte (1956b) saw the potential of this cycle in, for example, phytopathology, and industrial microbiology.[2] From this work stemmed the important idea that '… crossing-over might be a general feature of chromosome synthesis' (Pontecorvo 1952c), and the prophetic proposition that '… the possibility of applying mitotic analysis to higher organisms, better if in tissue culture, is clearly at hand' (Pontecorvo & Käfer 1958).

From the mid-1950s, Ponte concentrated increasingly on human genetics *via* tissue culture; it was as tantalisingly slow as he had anticipated (Pontecorvo 1959) but with characteristic determination he persisted in his belief: '… it is clear that, no matter what the difficulties and disappointments, if we want a breakthrough in human genetics, we have to concentrate on methods which bypass sexual reproduction (Pontecorvo 1962).

In 1968 Ponte moved to the Imperial Cancer Research Fund Laboratories which were directed by Michael Stoker, with whom he had had a close association in Glasgow. By this time many laboratories were engaged in human tissue culture, and cell fusion to give interspecific hybrids was a major tool in analysis. Ponte continued to make significant research contributions, drawing on techniques of plant genetics (Pontecorvo 1975) and concepts derived from his own work with *Drosophila* (Pontecorvo 1971, 1974). The importance of Ponte's contribution to somatic cell genetics, and the study of human disease and disorder, is emphasised in a series of papers given in his honour in his 80th year (Bodmer 1988).

Ponte received many honours, including election to the Fellowship of the Royal Society of London in 1955, Honorary Membership of the US and Indian Academy of Sciences, the Darwin Medal of the Royal Society (1978), honorary degrees from the Universities of Glasgow and East Anglia, and many invitations to accept visiting professorships.

As a director of research he was both demanding and generous; demanding in requiring precise and well ordered thought, generous in his encouragement and unstinting help to staff and students. He was impatient with what he called 'humbug' and he was intolerant of a blinkered outlook. He was irascible with administrative bureaucracy and ready to declare war on anyone suspected of promoting it. Ponte's scientific writing was terse and reveals little of the man himself and the values he espoused. But two late essays (Pontecorvo 1983, 1985) are more personal; they give fragments of his history, some of his philosophical views, and glimpses of his warmth. Ponte leaves a legacy of scientific achievement and, for those who knew him, a wealth of light and happy memories: the generous hospitality in their home with his much-loved family – his wife, Leni, who died in 1986, and their daughter, Lisa; Ponte's joy in activities as diverse as Scottish country dancing and the study of alpine flora; his humour in discussion; his sense of values, and the support given to many worthy causes, support given quietly and known to very few.

[2] By 1953 exploratory work on the parasexual genetics of industrial species was being undertaken in the USA and Japan. The National Research Development Corporation filed for a patent on the process, with any proceeds to be invested in the University of Glasgow and the Corporation. This was perhaps the first patent, certainly among the first, granted on a biological process: Patent number 719 313. 1 December 1954, price 2s 8d. Inventors: G. Pontecorvo and J. A. Roper. *Synthesis of Strains of Microorganisms.*

ACKNOWLEDGEMENTS

I am grateful to Bernard Cohen for copies of material he used in obituary notices for *Genetics*, the *Glasgow Herald* and the *Scotsman*. Some brief quotations have been made, without specific reference, from articles by Roper & Hopwood (1988) and Roper (1994). Permission to use the portrait included was granted by the Imperial Cancer Research Fund.

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[3] A full list of Pontecorvo's publications is not provided here as one is being compiled for publication in the *Biographical Memoirs of Fellows of the Royal Society* series.

https://doi.org/10.1017/S095375620000335X Published online by Cambridge University Press

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