Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

Guido Pontecorvo ("Ponte"), 1907–1999

Bernard L. Cohen

IBLS Division of Molecular Genetics, University of Glasgow, Glasgow G11 6NU, Scotland

GUIDO Pontecorvo died on September 25, 1999, age 91, of complications following a fall while collecting mushrooms in his beloved Swiss mountains; he was a significant contributor to modern genetics. He was also an irascible yet genial friend and advisor who attracted the great affection and admiration of colleagues and students worldwide and who, as head of department and Professor of Genetics, served the University of Glasgow with distinction from 1945 until 1968. It was characteristic that in 1955, when promoted to the newly created Chair of Genetics and also elected Fellow of the Royal Society, he circulated a note saying that henceforth the head of department should be known as "Ponte"—meaning of course no change; he was anything but pompous. Equally characteristic was his glee at being caricatured as a roman-nosed and kilted crow dancing on a bridge, recalling his liking for Scottish country dancing and the nickname "Crawbrigg," the Scots version of Pontecorvo coined by J. B. S. Haldane.

Ponte was one of eight children born to parents from old Italian (nonobservant) Jewish families. They lived frugally in Pisa, among a large, extended family on different floors of one house. His father and uncles worked in the textile manufacturing concern that had been founded by his grandfather and was, in the 1920s, the largest such enterprise in Italy. Ponte's siblings did well in various careers, and two also attained public eminence: Bruno, a nuclear physicist, and Gillo, a film director. Bruno's departure to the Eastern Bloc in the 1960s led to harassment of Ponte by some newspapers, which left Ponte distrustful of the media; his only known reaction was to say that he was not his brother's keeper.

According to his own biographical notes, Ponte's interest in biology was sparked by a high school (*Liceo*) natural history teacher, but the curriculum was mainly classical, so by the age of 16 he could, for example, read and enjoy Aristophanes in Greek. During studies in the Faculty of Agriculture in the University of Pisa, his interest in genetics was aroused by E. Avanzi, a plant geneticist. And in my recollection of a distant conversation, his orientation toward agriculture resulted from working a relative's chicken farm when he was a teenager. Undergraduate friends, among them Enrico Fermi (known even then as "the Pope" because of his infallibility), were also influential mountaineering and skiing companions. After two years' compulsory military service in the light horse artillery—and somehow the image of Lieutenant Pontecorvo exercising the commanding officer's horse seems not at all incongruous!—Ponte became assistant to Avanzi, now director of an experimental agricultural institute near Trento; he soon moved to Florence to lead the cattle breeding program of the Tuscan Ispettorato Compartimentale Agrario. Here, for eight years, he organized the recording and use of weight gain and draught ability data in a successful selective breeding program applied to the Chiana and Maremmana breeds. His developing interest in fundamental science can perhaps be seen in articles on limb growth, published in English-language journals (Pontecorvo 1938a,b).

In 1937 Ponte toured animal breeding centers, including the Institute of Animal Genetics in Edinburgh, then directed by F. A. E. Crew, where he met Alick Buchanan-Smith. A year later, when he was dismissed from his Tuscan post because of Nazi-inspired racial policies, Buchanan-Smith offered him hospitality and helped him obtain a scholarship (£150 per year) to support work on the inheritance of lactation duration in a well-recorded Friesian herd belonging to the Chief Scout, Lord Rowallan (Pontecorvo 1940a). Ponte's stay in Scotland was intended to last about a year, after which he expected to take up a Government contract for animal breeding work in Peru. While in Edinburgh, he had been joined from Florence by his Swiss art-historian fiancée Leonore (Leni) Freyenmuth, and they were married in December 1938, a happy union broken only by her death in 1986, aged 82; I recall his saying that

Address for correspondence: IBLS Division of Molecular Genetics, University of Glasgow, Pontecorvo Bldg., 56 Dumbarton Rd., Glasgow G11 6NU, United Kingdom.

Figure 1.—Guido Pontecorvo in 1978. Photo courtesy of the Imperial Cancer Research Fund.

Leni's Swiss family were not at all in favor of her marrying a then penniless refugee. With the outbreak of war, the Peruvian contract was cancelled, and they were thus stranded in Scotland but received continuing support from the Society for the Protection of Science and Learning.

Not only did the invitation to work in Edinburgh rescue Ponte from hardship, but it was serendipitous because H. J. Muller was at the Institute of Animal Genetics (1937–1940) *en route* from the USSR and, like Ponte, stayed in its guest house. Ponte was attracted by and became deeply imbued with Muller's clear thinking about the nature of the gene (Pontecorvo 1968a,b) and abandoned animal breeding to work for a Ph.D. under his supervision. Ponte's thesis, on the mechanism of induced chromosome rearrangement in *Drosophila melanogaster*, was examined by C. D. Darlington in 1941 and, as might be expected, his work with Muller involves the clever exploitation of biology and genetics (Pontecorvo and Muller 1940b,c; Pontecorvo 1943). These experiences changed Ponte's orientation from the application of genetic knowledge to its promotion.

After Italy declared war in June 1940, Ponte was interned on the Isle of Man along with other "enemy" aliens, including Scotland's resident Italian ice cream vendors and restauranteurs and many refugees from Hitler's Germany. He was fortunate not to be among those who were shipped to Canada or elsewhere, for example, on the notorious SS *Arandora Star*, many of whose passengers died when it was torpedoed on July 2, 1940. (Coincidentally, we share such an escape: in 1939 my passage to Montreal on the SS *Athenia*, also torpedoed with heavy loss, was cancelled at the last moment.) Since aliens were not then allowed to reside near the east coast, where there was a supposed danger of invasion, and since Leni was considered an enemy alien by marriage, she had been advised to move to Glasgow. There the wife of the Professor of Zoology, Edward Hindle, helped such refugees, and in January 1941, when Ponte was released from internment, Hindle offered research space in Glasgow's Zoology Department. Here, supported by grants from the Rockefeller Foundation and the Carnegie Trust, Ponte embarked on his "war work": fundamental studies of spermatogenesis and sex ratio in the human louse (Hindle and Pontecorvo 1942), the menagerie being fed, of course, upon himself. As Roper and Hopwood (1988) have pointed out, this work introduced him to the question of autonomous *vs.* nonautonomous gene action, later to be of fundamental significance in Aspergillus.

After a year lecturing in Edinburgh (1944–1945), Ponte was appointed to his first tenured post as the first and only Lecturer in Genetics in Glasgow, housed initially in the zoology department. In 1945 he won independence when the department of genetics was established, with one fifteen-year-old apprentice technician in two bomb-damaged basement rooms in the Materia Medica building and then in the refurbished Anatomy laboratories of the former Anderson College of Medicine, where it remained until 1967. Ponte's rapid scaling of the academic ladder continued with promotion to a readership (a mark of distinction in research) in 1952.

Around 1943 Pontecorvo became involved for the first time in fungal genetics, when he proposed to Professor Raistrick, then supervisor of penicillin development, to try to increase yields by the selection of irradiation-induced mutants. This was enthusiastically accepted, but rapidly fell foul of the high-level decision to transfer all penicillin work to the United States, where Ponte's proposals were soon put into effect by Demerec and Sansome. Despite the transfer of penicillin work, Ponte collaborated with Alan Gemmell (lecturer in Botany in Glasgow, 1941–1944) on the genetics of Penicillium, leading, for example, to genetic proof of heterokaryosis (Pontecorvo and Gemmell 1944).

The work with Penicillium reflected Ponte's interest in the largely neglected genetics of microorganisms; indeed, in 1945 he could fairly claim that his was the only British department in this field. The department's work addressed a wide range of topics, but came to be at least partly inspired by the idea that Muller's understanding of the gene as a continuum and of the potential

nonequivalence of the entities responsible for its mutational, recombinational, and functional manifestations (Raffel and Muller 1940; Muller 1947) could be tested by demonstrating intragenic recombination. Later, interpretations of new data bearing on these issues were divided: on the one hand, Pontecorvo and others preferred Muller's approach; on the other hand were some who supposed that alleles (such as Drosophila *Star* and *asteroid*) between which crossing over occurred—"pseudoallelism" to some; the "Lewis effect" to Ponte—might be adjacent functional units involved in a chromosomal "millimicromolar assembly-line" (Pontecorvo 1950, 1952, 1954; Lewis 1951; Haldane 1954). Ponte's interest in raising "the resolving power of genetic analysis" (Pontecorvo 1958) through the use of microorganisms had led him to test several candidates (*e.g.*, Aerobacter, Serratia) and eventually to pick the ascomycete fungus, *Aspergillus nidulans*, as a potentially ideal genetic organism, despite scorn from colleagues who thought that its homothallism would be a practical barrier (Pontecorvo 1946a). Thus, he was one of the few pioneers who deliberately and independently both advocated microbial genetics (Pontecorvo 1945, 1946b,c, 1947; Devi *et al.* 1947) and also went on to successfully develop and exploit the genetics of a new microorganism. The supposed difficulties due to homothallism were turned to advantage when Hemmons (1952) found that segregation of autonomously expressed conidial color mutations could be used to identify crossed cleistothecia and, by 1953, the utility of *A. nidulans* as a genetic organism had been comprehensively established (Pontecorvo *et al.* 1953).

That Muller had been right about the fine structure of the gene was demonstrated almost contemporaneously by linear intragenic linkage maps in Aspergillus (Pritchard 1955) and in phage (Benzer 1955), the latter deservedly more celebrated because of its site density and (later) introduction of the term "cistron." It is worth noting that, although the terms *cis* and *trans* were introduced into genetics by Haldane (1941) to replace Bateson's "coupling" and "repulsion," it was Pontecorvo (1950) who first applied them to the arrangement of recombining "alleles." Understandably, Ponte liked to emphasize that the new understanding of the fine structure of the gene as a linear array of elements that could independently recombine and mutate was developed purely by genetic analysis, with no input from biochemistry.

Another important contribution arose from Roper's (1952) discovery of stable *Aspergillus nidulans* diploids. This enabled the demonstration of mitotic crossing over (Pontecorvo and Käfer 1958), which, with haploidization (Pontecorvo *et al.* 1954), made genetic analysis in the absence of sex possible, even mapping new mutations to their linkage group in a single step (Forbes 1959). "Parasexual cycle genetics," as Ponte called the combination of heterokaryosis, diploid formation, mitotic segregation, and haploidization (Pontecorvo and Roper 1952), provided the first route to genetic analysis in organisms like *Penicillium chrysogenum*, *A. niger*, or *Fusarium oxysporum*, whose sexual stages were or are unknown. Thus, in theory if not in practice, genetic analysis and the breeding of better-yielding production strains of such organisms could proceed on a precise, scientific basis. Since then, *A. nidulans* has been of continuing value and "Glasgow" strains are in research use worldwide (Smith and Pateman 1977; Martinelli and Kinghorn 1994). In 1998, eighty-three papers from fifteen countries on genetic aspects of *A. nidulans* were published, and at the 1999 Fungal Genetics Conference, *A. nidulans* was, by a short head, the single most popular species subject in the poster session. And its genome is being sequenced (Kupfer *et al.* 1997).

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 (Pontecorvo 1958, p. 134). Human genetics from cell cultures, on which his work started in 1959, was sufficiently important to receive initial funding from the U.S. National Institutes of Health and the U.K. 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 parasexual cycle genetics is practiced 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 genetics department established in a new building 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, apart from influencing a generation of young cancer researchers, he devised a way to determine the preferential loss of chromosomes of one species in mammalian interspecific cultured-cell hybrids (Pontecorvo 1971, 1974), harking back to his Drosophila hybrid work with Muller, and went on to have one of those thoughts that, after the event, seem blindingly obvious but actually signify the existence of a well-prepared mind. Knowing that plant cells in culture could be made to fuse by adding polyethylene glycol to the growth medium, Ponte showed that human and other animal cultured cells responded similarly and defined the necessary con-

ditions (Pontecorvo 1975), thus facilitating the first, essential step of animal parasexual cycle genetics—a tiny advance perhaps, but a highly cited one.

The long-term vitality of genetics in Glasgow University owed much to Pontecorvo's talents and personality and was curiously amplified by the fact that transatlantic flights to and from the continent used to refuel at nearby, fog-free Prestwick. Thus, American and other geneticists could stop over free of charge and knew that they would receive a warm and civilized welcome from the Pontecorvos. The departmental guestbook shows that from 1945 almost every notable figure in contemporary genetics visited repeatedly, usually giving a research seminar. For example, Jim Watson passed through just one week after the appearance in print of his 1953 paper (with Francis Crick) on the structure of DNA. In the 1950s the center of gravity of genetics in Britain was sometimes said to be north of the border (and in Scotland, certainly lay toward the east). Glasgow attracted relatively few homegrown genetics undergraduate or research students, although those who did penetrate the cultural and professorial barriers were generally both very 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."

Within the University, Ponte belonged to an informal group that did battle in the Senate with the more entrenched professoriate who held the reins of business and directed academic affairs. Disdainful of administration, the wastepaper basket a filing cabinet, the fortunes of the growing department seemed to be managed by means of short and sometimes perhaps tetchy handwritten notes to the Principal. His approach is epitomized by the following quotation from a letter:

> Dear . . . , Thank you for suggesting to nominate me for the Library Committee. My fear is that if I went on that Committee, either I would have a stroke at the first meeting, or I would have to resign in protest with the same results as when I resigned in protest from the Amenities Committee. I wonder whether I can do more good (some would say more harm) by staying out and outwardly harassing that deplorable body?

The department had but two telephones and one half-time secretary. Yet it flourished! Although his distinctly Italian accent persisted, Ponte had an outstanding grasp of English (partly the result of private coaching when a schoolboy) and an enviable, scintillating clarity and impact, a skill perhaps more evident in conversation and writing than in everyday lectures. As Professor of Genetics, he followed the Scottish tradition of being personally responsible for the first course, giving fifty or so second-year lectures himself, year after year. Students of outstanding academic ability found that they were given something substantial to think about, but weaker brethren tended to be somewhat baffled. In the late 1960s, Ponte was a driving spirit (along with Adam Curtis and Michael Stoker) in a move for progressive, interdisciplinary biology teaching, which resulted in the Honors B.Sc. course called "combined biology," a misleading name that reflected the remaining strength of entrenched reaction. Transformed, when it was self-evidently successful, to "molecular biology," this was the first interdisciplinary, interdepartmental honors course of its kind in Britain and remains a leader in the field.

Ponte's academic distinction in genetics was such that, even though he had resigned his chair, the University later awarded him an honorary degree and, more recently, the distinction of being the only living person with an eponymous building, coincidentally named at the fiftieth anniversary of the founding of the Department of Genetics. In return, he presented the University with a handsome endowment for genetics student prizes and scholarships, funded by the sale of the cream of his reprint collection. As well as serving the Genetical Society of Great Britain as sometime Secretary and President, he was a founding member of the Institute of Biology and received many academic honors 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 (brilliantly published as Pontecorvo 1958) and Messenger lectures at Columbia and Cornell Universities, was an Honorary member of the U.S. and Indian National Academies of Science (among 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 alpines 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 friends who enjoyed their 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."

My thanks are due to the Pontecorvos' daughter, Lisa, for providing

a copy of Ponte's autobiographical notes, from which some of the details given here are drawn, and to John Clutterbuck for an update on Aspergillus. Only leading references are cited; a full list of publications and a more comprehensive scientific biography is expected to appear in due course in the Biographical Memoirs of Fellows of the Royal Society. It was a personal privilege to join the Genetics Department's teaching staff as Pontecorvo's Assistant in 1959 and to observe (without much understanding) at least some of the people and circumstances described.

LITERATURE CITED

Benzer, S., 1955 Fine structure of a genetic region in bacteriophage. Proc. Natl. Acad. Sci. USA **41:** 344–354.

Devi, P., G. Pontecorvo and C. Higginbotham, 1947 X-ray induced mutations in dried bacteria. Nature **160:** 503–504.

Forbes, E. C., 1959 Use of mitotic segregation for assigning genes to linkage groups in *Aspergillus nidulans*. Genet. Res. **6:** 352–359.

Haldane, J. B. S., 1941 *New Pathways in Genetics*. Allen & Unwin, London.

Haldane, J. B. S., 1954 *The Biochemistry of Genetics*. Allen & Unwin, London.

Hemmons, L. M., 1952 Investigations on the genetics of the homothallic ascomycete *Aspergillus nidulans* (Eidam), Ph.D. thesis. University of Glasgow.

Hindle, E., and G. Pontecorvo, 1942 Mitotic divisions following meiosis in *Pediculus corporis* males. Nature **140:** 668.

Kupfer, D. M., C. A. Reece, S. W. Clifton, B. A. Roe and R. A. Prade, 1997 Multicellular ascomycetous fungal genomes contain more than 8000 genes. Fungal Genet. Biol. **21:** 364–372.

Lewis, E. B., 1951 Pseudoallelism and gene evolution. Cold Spring Harbor Symp. Quant. Biol. **16:** 159–174.

Martinelli, S. D., and J. R. Kinghorn (Editors), 1994 *Aspergillus: 50 Years on*. Progress in Industrial Microbiology, Elsevier, Amsterdam/London/New York/Tokyo.

Muller, H. G., 1947 The gene. Proc. R. Soc. Lond. Ser. B **134:** 1–37.

Pontecorvo, G., 1938a A possible genetic mechanism in heterogonic growth of limbs in cattle. Nature **142:** 437.

Pontecorvo, G., 1938b Allometric growth of the forelimbs in cattle. J. Agric. Sci. **29:** 111–114.

Pontecorvo, G., 1940a A study of persistency in a herd of Ayrshire cows. J. Dairy Res. **11:** 113–120.

Pontecorvo, G., 1943 Hybrid sterility in artificially produced recombinants between *Drosophila melanogaster* and *D. simulans*. Proc. R. Soc. Edinburgh Ser. B **61:** 385–397.

Pontecorvo, G., 1945 Biochemical and industrial use of moulds—application of genetical methods. Chem. Prod. **8:** 41–43.

Pontecorvo, G., 1946a Genetic systems based on heterokaryosis. Cold Spring Harbor Symp. Quant. Biol. **11:** 193–201.

Pontecorvo, G., 1946b Microbiology, biochemistry and the genetics of microorganisms. Nature **157:** 95A.

Pontecorvo, G., 1946c The genetical control of nutritional requirements in microorganisms and its application to microbiological assays. Proc. Nutr. Soc. **5:** 182–186.

Pontecorvo, G., 1947 Genetic techniques in the development of microbiological assays. Biochem. J. **41:** xii.

Pontecorvo, G., 1950 New fields in the biochemical genetics of microorganisms. Biochem. Soc. Symp. **4:** 40–50.

Pontecorvo, G., 1952 The genetic formulation of gene structure and action. Adv. Enzymol. **13:** 121–149.

Pontecorvo, G., 1954 Genetical analysis of cell organization. Symp. Soc. Exp. Biol. **6:** 218–229.

Pontecorvo, G., 1958 *Trends in Genetic Analysis*. Columbia Biological Series, Columbia University Press and Oxford University Press, New York/London.

Pontecorvo, G., 1968a Hermann Joseph Muller. Annu. Rev. Genet. **2:** 1–10.

Pontecorvo, G., 1968b Hermann Joseph Muller. Biogr. Mem. Fellows R. Soc. **14:** 349–389.

Pontecorvo, G., 1971 Induction of directional chromosome elimination in somatic cell hybrids. Nature **230:** 367–369.

Pontecorvo, G., 1974 Induced chromosome elimination in hybrid cells, pp. 65–69 in *Somatic Cell Hybridization*, edited by R. L. Davidson and F. de la Cruz. Raven Press, New York.

Pontecorvo, G., 1975 Production of mammalian somatic cell hybrids by means of polyethylene glycol. Somat. Cell Genet. **1:** 397–400.

Pontecorvo, G., and A. R. Gemmell, 1944 Genetic proof of heterokaryosis in *Penicillium notatum*. Nature **154:** 514.

Pontecorvo, G., and E. Käfer, 1958 Genetic analysis by means of mitotic recombination. Adv. Genet. **9:** 71–104.

Pontecorvo, G., and H. G. Muller, 1940b Recombinants between *Drosophila* species the F_1 hybrids of which are sterile. Nature **146:** 199.

Pontecorvo, G., and H. G. Muller, 1940c The artificial mixing of incompatible germ plasms in *Drosophila*. Science **92:** 418 (and corrected authors' names, p. 476).

Pontecorvo, G., and J. A. Roper, 1952 Genetic analysis without sexual reproduction by means of polyploidy in *Aspergillus nidulans*. J. Gen. Microbiol. **6:** vii.

Pontecorvo, G., J. A. Roper, L. M. Hemmons, K. D. Macdonald and A. W. J. Buften, 1953 The genetics of *Aspergillus nidulans*. Adv. Genet. **5:** 141–238.

Pontecorvo, G., E. Tarr-Gloor and E. Forbes, 1954 Analysis of mitotic recombination in *Aspergillus nidulans*. J. Genet. **52:** 226–237.

Pritchard, R. H., 1955 The linear arrangement of a series of alleles in *Aspergillus nidulans*. Heredity **9:** 343–371.

Raffel, D., and H. J. Muller, 1940 Position effect and gene divisibility considered in connection with three strikingly similar *scute* mutations. Genetics **25:** 541–583.

Roper, J. A., 1952 The production of heterozygous diploids in filamentous fungi. Experientia **8:** 14–15.

Roper, J. A., and D. A. Hopwood, 1988 Guido Pontecorvo and his contributions to genetics. Cancer Surv. **7:** 229–237.

Smith, J. E., and J. A. Pateman (Editors), 1977 *Genetics and Physiology of Aspergillus*. British Mycological Society Symposium Series No. 1, Academic Press, London/New York/San Francisco.