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Dear Mrs. Box. — re "R. A. Fisher" —

I was so warmly, nostalgically pleased to read your graceful account of Luca Cavalli's introduction to bacterial genetics, and his due course to me. You may know that Luca and Alba are among my closest friends. They eventually moved to my department at Stanford; and I still see them often both there and here.

Your remark was most interesting, that "by early 1948 Fisher was planning to introduce ... bacterial genetics ..." This interests me as evidence of the prompt and tangible acceptance of my work (1946-1947), and especially as from such a substantial figure as he was.

(Biometrics Soc.)

I did meet him in Sept. 1947 at Woods Hole, and had some discussion about recombination in bacteria. What impression that made, I did not know — recall I was then 22.

My question is about any <u>documentation</u> you may have about the sources of his convictions: what part from reading the papers, from comments of others, perhaps from our personal meeting.

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P.S. "<u>Congression</u> of markers."

Have you noticed this usage in Fisher's writings? I am trying to trace the provenience of the term, prior to our application of it in the analysis of bacteria.

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R. A. Fisher
The Life of a Scientist

JOAN FISHER BOX

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taken on to his staff or dispersed in the later 1940s. Fisher himself was consulted about ARC animal breeding work again after Lord Rothschild became head of ARC in 1948. He was also much interested in the work of the small statistical unit formed in 1956 to serve ARC workers in the Cambridge area. As for academic statistics, students for the diploma in mathematical statistics were required to do a little applied work but, in practice, they spent the year almost wholly in preparation for the Part III examination.

The greatest blow to Fisher was his failure to regain the serological unit after the war. Plans with the university had to be renegotiated after the death of Dr. Taylor in March 1945. At the same time, the MRC had little interest in maintaining the unit in order to hand it back to its proper work, but rather wanted to take over its personnel piecemeal, for various purposes, as soon as the transfusion work ceased. Fisher immediately wrote to propose that a medically qualified assistant should be appointed to enable Race to carry on the work without a break; he suggested that Rockefeller Foundation funds allotted to the serological unit before the war might be used to pay the salary, thus recognizing the foundation's continuing interest in the research unit. The MRC responded favorably to the first part of the request, and Dr. A. E. Mourant, from the blood transfusion service at Luton, was appointed medical officer in the Galton Laboratory serum unit.

While the transfusion work was drawing to a close, Fisher was trying to get the university to offer Race the position of assistant director of research in his department and Mourant that of assistant in research. Despite their commitment to Fisher, the university were inhibited by the fact that the MRC was in a position to shut off financial support for the unit in order to force acceptance of their own plans; the university temporized and never formally made an offer to Race. Meanwhile, the MRC strongly presented its alternative plans to Race and offered him much more, both immediately and in the long run, than could be hoped of the university. In January 1946 Race accepted the post of director of a new MRC blood group unit at the Lister Institute in Chelsea. Six months later, Mourant accepted a post at the Lister as director of the new MRC blood group reference library.

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Disappointed of his hopes for serology, Fisher was the more eager to broaden the range of research in his department in other directions. A new line of genetical research was opened up at this time by the discoveries of the mid-1940s which mark the beginning of modern bacterial genetics. By early 1948 Fisher was planning to introduce research in bacterial genetics at Cambridge.

After pure bacterial cultures were successfully prepared in the later nineteenth century it had been recognized that bacteria share the attribute of heredity with higher organisms. Nevertheless, bacterial cultures grown from a single cell were notoriously changeable; when exposed to adverse conditions, pure cultures quickly gave rise to genetically stable strains adapted to the new conditions, and this apparent plasticity had been generally attributed to the effects of the environment, not to mutation. In 1943, however, Luria and Delbruck [82] published results that demonstrated the occurrence of spontaneous mutation, thus revealing that particulate genes in bacteria were entirely analogous with those of higher organisms. In 1946 Lederberg and Tatum [83] presented their discovery of the transfer of chromosomal material from one bacterial cell to another by direct cell-to-cell contact: some form of conjugation took place which gave rise to new combinations of the genes. Nothing was then known about the sexuality of bacteria, the shape of the bacterial chromosome, the manner of transference of chromosomal material, or its incorporation in the receiving cell, but, these problems aside, one could envisage the investigation of genetic linkages and chromosome mapping of bacteria by recombination studies and breeding programs similar in nature, though not in technique, to those with higher organisms.

Fisher knew nothing of the techniques of bacterial culture, and, as with the blood group work in 1934, his first step was to seek an expert capable of handling current techniques and developing methods suitable to the investigation of this particular genetic material. He considered the possibility of training a bacteriologist for the purpose, letting him spend a year with Lederberg, as Taylor had spent a year with Friedenreich in the 1930s, and to see something also of the pure culture work of Thornton at Rothamsted and of Winge in Denmark. As it happened, however, a man with the very qualifications he wanted, Dr. L. L. Cavalli (later Cavalli Sforza) was already making his way toward Fisher.

Fisher had met his name already in 1946, when Race wrote how impressed he was by the charming young aristocrat whom he met in Milan. Cavalli had introduced himself as a bacteriologist keenly interested in genetics and had mentioned that he was then grappling with the study of Fisher's statistical books. He was hoping soon to come to England, and Race was sure Fisher would want to meet him there. Fisher had also seen something of Cavalli's work when, as one of the editors of *Heredity*, he received an article by L. L. Cavalli and G. Magni [84]; the paper was published in the first issue of *Heredity* in 1947. In it the authors made application of simple statistical methods appropriate to the bacteriological material, so as to increase the precision of results and at the same time gain additional genetical information from them. It was just the sort of work Fisher appreciated most.

Cavalli realized his plan to come to England in March 1948, when he joined Mather in the genetics department at the John Innes Institute for a period of 6 months. In July he attended the 8th International Congress of Genetics at Stockholm. There he met Fisher for the first time and recalls that "to my great surprise, after five or ten minutes he offered me to take a job in his department at Cambridge. This was a wonderful surprise and I accepted immediately." In August he visited Cambridge, looking for a place to live with his wife and small son. In October he was officially appointed assistant in research in the department of genetics, Fisher having failed to get him the more senior position he had expected to be able to offer.

As it had been with the blood group work, so it was with bacteriology; the laboratory had to be set up and the first fumbling approaches made to research as the complexities and difficulties of genetic interpretation revealed themselves. Understanding would come years later, as it had come with blood group work. Whittingehame Lodge was, of course, quite unsuitable for making a bacteriological laboratory, but the basic equipment was bought, and Cavalli made a place for himself in part of the original laboratory room. A pure strain of *E. coli* was obtained, and 5 or 6 months after his arrival, Cavalli could start work. One of Fisher's activities in the United States in the summer of 1949 was the acquisition of the costly chemicals required, which could not at that time be obtained in England.

To Cavalli, it seemed remarkable how interested Fisher was in work of which he knew nothing from a technical point of view and how much insight he had into its genetic aspects. The bacterial chromosome appeared rodlike in current cytological studies; yet, rather early, in discussing the shape suggested by genetical reasoning, Fisher illustrated it as a large loop or inversion of most of the chromosome strand, with short tails. It was not until 1957 that Jacob and Wollman established that the bacterial chromosome is actually a ring.

The first clue about the nature of conjugation was the discovery in 1952 that chromosomal transfer requires the presence in the donor cell of an autonomous genetic element, the sex factor F (for fertility). The discovery of F made possible the recognition of two mating types, F^+ harboring F and acting as genetic donors and F^- lacking F and behaving as genetic recipients. When a population of F^+ cells is mixed with F^- cells, however, only about one in 10^4 donors actually transfers chromosomal material to recipients. For this reason the discovery of the mating process resulted only after the discovery of certain strains with a high frequency recombination (Hfr strains) which produce cells in which up to 100% of the F^+ cells are donors.

The latter discovery occurred in Cambridge in 1949. Using nitrogen mustard to produce mutations in his culture, Cavalli was thrilled by the appearance of a mutant strain with a much higher frequency of recombination than was ever observed before, which he called the Hfr strain. (A similar Hfr strain appeared spontaneously in the culture of W. Hayes 2 or 3 years later, and it is in this strain mainly that the mode of bacterial conjugation has been studied.) Fisher's reaction to the discovery was to suggest that a virus-like particle might determine sex in bacteria. At the time no evidence existed to support the hypothesis, but, Cavalli recalls, "Later, after I left Cambridge, it happened that three people, Josh Lederberg, William Hayes and myself, practically at the same time did discover indeed that there was a virus which is called F which determines sex in bacteria. In the strain I had found, the Hfr, that virus is anchored to the bacterial chromosome or, in fact, you can say becomes part of it."

If the F particle is free in the cell, it is only potentially a donor. When incorporated in the chromosome, however, it was found to be responsible for breaking the ring of the donor chromosome at its point of attachment, so that the chromosome becomes transferable. The orderly mode of transfer was discovered in the mid-1950s particularly by E. L. Wollman and F. Jacob [85] at the Institut Pasteur in Paris and W. Hayes in London. Once the theoretical basis of conjugation was clarified, many of the early difficulties of interpretation fell away.

These discoveries were years away when Cavalli was working in Cambridge, a one-man unit of bacterial genetics in a primitive genetical laboratory. Despite the excitement of his experimental results, Cavalli felt his isolation acutely. Not only was he in a genetical rather than a bacteriological laboratory, but he found it impossible even to talk with bacteriologists in England; because bacterial genetics was so new a subject, he was considered a crank by bacteriologists, as well as by most geneticists. He could talk to Fisher, but Fisher was no bacteriologist and could not share his technical problems and interests. Now that bacterial genetics has developed so far and become so successful, it is easy to forget the isolation of the pioneer in this or any other really new line of investigation.

Fisher did his best to make the Cavalli family welcome. From time to time he took them out to the best restaurants in Cambridge and, when Cavalli dined with him in College, was grateful to call him into his rooms afterward for a glass of port and an hour of conversation, and to regale him with new thoughts on geology, magnetism, and astronomy. Geomagnetism, like bacterial genetics, was a new subject and not yet academically respectable. Fisher was excited by the possibilities of both and very willing to give his moral support, with his interest, to the research workers in both.

In 1949 G. Maccacaro joined the bacteriological genetics unit, supported by a Rockefeller Foundation grant, and in January 1950 Cynthia Knight (later Booth) came on an international scholarship of the Rockefeller Foundation. Cavalli's appointment was with the University, however, and in the summer of 1950 Fisher learned that this appointment would not be renewed in the next academic year. His arguments, calling on the university to honor its promises to his department, rehearsing the special qualifications of Cavalli, expanding on their great good fortune in having attracted such a man and the luster his work in the new and very important branch of genetics must in later years cast on the university, these went for nothing. He returned from committee meetings red in the face, unable to give adequate expression to his feelings of outrage. It had been bad enough to receive Cavalli with such slight recognition in 1948 and to have failed to promote him; but to throw him out when the work was well begun was insupportable: insulting to Cavalli, humiliating to himself (who was made twice a liar thereby), and disastrous for the bacteriological work.

Fortunately, perhaps, Cavalli was offered an attractive position in Italy at this time. Jobs were scarce in Italy and, wishing to settle there sometime and eager to talk with his bacteriological colleagues again in Milan and Pavia, he took this opportunity and in October 1950 departed on unpaid leave from the University of Cambridge. Crippled by lack of university support, the bacteriological research in the department of genetics continued while Maccacaro remained at Cambridge.

In 1951 F. H. C. Crick and James D. Watson started working together at the Cavendish Laboratory in Cambridge. In 1953 their famous paper appeared showing the structure of the DNA molecule, the basic genetic material, in the form of a double helix. Meanwhile S. Brenner joined the Cavendish group and several times wrote to Cavalli Sforza inviting him to join them. It was too late. Regretfully, Cavalli realized that if he had stayed only a year or two longer in Cambridge, he would have found himself close to the fellow-scientists he needed, as Cambridge became the center of expansion of molecular biology. Instead, he began cooperative work with J. Lederberg, with such notable early results as their discovery of the sex factor in bacteria (1952) and their isolation of preadaptive mutants by sib-selection, a method of sampling subject to precise quantitative formulation (1955).

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By 1950, seven years after his appointment to the Chair, Fisher knew that he could hope for little university support for any new or ambitious enterprise in his department. The department would continue to be housed in Whittingehame Lodge, and his work on mice and on *Lythrum* would continue to be the primary research in the department. He was probably glad to remain in Storey's Way, for he loved the garden, and having found a gardener who would bring his ideas for the garden to fruition, he found constant delight and stimulus in his perambulations of the area.

When he first moved into Whittingehame Lodge in May 1944, the departmental garden was derelict, the paths almost ungraveled, and the bricks edging them crumbled away, the hedges either needing replacement of many dead plants or else wildly overgrown (the hedge of thuya was about 10 feet thick and it completely obliterated pathways alongside). The ploughed areas were infested with convolvulus. Despite its state of neglect what remained of the original plantings near the house was still lovely in its spring array. Cherries bloomed within view of the window of his office, formerly the drawing room. Ornamental crab apples ran southward, whose deep pink flowers glowed against the dark red of their early foliage, a striking contrast against the dusty gray-green beneath of a bank of huge rosemary bushes, heavy with fragrance. Beyond these, eastward, Punnett's orchard opened up, the old trees spangled with pale blossoms, and at their foot a broad wave of pale mauve iris flowers broke at the orchard's edge and surged uncontrolled across the unmarked boundary between Punnett's property and the departmental land. From the first Fisher liked to stroll round the garden or sit in the orchard to talk with his visitors.

During the war, with the aid of an old and rather feeble individual, hired as part-time gardener, the reclamation was slow. Fisher started work on one particular bed, and, removing two spits of earth to the other side of the field, he dug into the third, the untouched white clay subsoil of Cambridge gault. He felt double trenching was necessary to get rid of the convolvulus, for the further he penetrated, the thicker grew the food-storage roots of the weed. Wrestling with the resistant gault, he dragged out great knuckled roots, triumphing that the convolvulus could never recover. In this struggle, he broke the tines of three garden forks, the heaviest forks he could obtain, before succumbing himself to a nasty bout of sciatica. He never completed the job and the professional gardener he was fortunate enough to find in 1947, Mr. G. Harding (head gardener during the rest of his professorship), was grateful that the work had gone no further, for the intermixture of gault made the topsoil intractable for years afterwards.

Fisher was an amateur, but like any true gardener, he nourished his whole garden by his daily observation and care for it, his enjoyment of its beauties, his interest in its progress, and his plans for its future. It was to be years before it was brought under control, but with Harding's knowledgeable and sympathetic help, Fisher's ideas were gradually realized. He wanted adequate compost heaps, and Harding saw that adequate compost heaps were properly prepared and maintained. He wanted a herringbone pattern for a bricked garden path, and Harding saw that the path was laid, even to turning through a right-angle while keeping the pattern intact, exactly as Fisher planned it. He admired blue Siberian poppies in his sister's garden in Argyllshire and was sent some seed. Mr. Harding removed the whole topsoil alongside the library building, and replaced it with peaty soil, acid enough to produce a brilliant display of the poppies. He wanted the field he had first dug