Department of Bacteriology.

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My dear Luca,

I thought you might like to know that I have obtained a spontaneously occurring Hfr strain. This appeared in 58-161/F+(Spicer) under the following peculiar circimstances. I have found that F+, but not F-, cultures maintained on inspissated egg at 4° tend to die out slowly over a period of many months. Some weeks ago I found that 58/Spicer, transduced to F+ and kept on egg as usual, failed to yield growth when quite large sweeps of growth were transferred to broth. There was no evidence of lysis or plaque formation. I left the egg culture on the bench as a reminder to do something about it. About a week later I noticed that about 20 colonies had grown up on the area of confluent(but dead) previous growth. Several of these colonies were normally F+. One of them, however, was Hfr. The recombination rate is about X 1000 normal; it does not transduce F+ to W677/F-(25 colonies tested & compared with 25 colonies picked from a mixture with an Nfr culture of the same strain which gave 100% conversion under the same conditions); 25 Hfr X F- prototrophs appear to be F- (period of incubation not yet completed). In fact, it seems to behave exactly as your mustard-induced strain does. The interesting thing is that UV depresses the fertility of Hfr, a result which I must admit I anticipated. I have been thinking a lot about Hfr over the last few weeks and the more I think of it the more it seems to me to fit in to the view that the F+ agent ~~is~~ acts as a genetic vector. The theory now is as follows. F+ is a virus though not necessarily one which under any circumstances is lytic like a phage. It is liberated by the majority(or all)of F+ cells during the early stages of the growth cycle, and remains adsorbed to the surface of the cell; alternatively, it is liberated free but is very rapidly adsorbed on to other cells. When adsorbed by F- cells it is infective but its stability within a host cell depends on a rather delicate physiological balance so that, in the case of certain F- populations only a proportion of cells become infected, F+ being discarded by, or dying in, the remainder. A small proportion of F+ agents from Nfr strains become intimately associated with part of the chromosome(or one of several chromosomes) of the host cell so that, when these are liberated the chromosome is carried with them. The effect of UV is to increase the proportion of cells in which the F+ agent is associated with genetic elements(since UV decreases F+ transduction at the same time as it increases recombination). In Hfr strains there has been a mutation of F+ and the establishment of a new relationship between it and the cell so that all the F+ agents now become associated with genetic elements; i.e. those F+ agents which, in Nfr cells, become tied to genetic elements either naturally or as the result of the new equilibrium induced by UV, can be regarded as phenocopies of the genetic alteration which is Hfr. The Hfr virus, however, is inherently unstable in F- cells so that it cannot establish itself to produce Hfr prototrophs. I have been most interested to learn in this connection that, in Salmonella transduction which appears to be definitely due to phage carriage the recipient strain may remain phage sensitive although genetically altered. It is also a fact that only a proportion

of sensitive cells exposed to temperate phage establish a lysogenic relationship with it. I feel that F+ may exist in various "allelic" forms and that its stability within F- cells depends on a very delicate relationship between just the right F+ allele and the right physiological state of the cell. Hence your F+ strain which can be transduced by Waksman F+ but not by K12F+ and with which 50% prototrophs are F- — and my 58/F+ strain which is very poorly transduced to F+ as compared with W677/F+ and with which only 30% prototrophs are F+. I don't know what you think of all this — these are deep waters! I have probably expressed it all very badly. I forgot to mention that my theory as to why Hfr recombination is depressed by UV is that since all the F+ agents are already associated with genetic elements the proportion which do so cannot be increased by UV, while UV depresses the number of vectors which can make effective contact with F- cells. Incidentally my Hfr strain shows a 10-20 fold reduction in recombination rate when crossed with W-677/F+. Unfortunately it is $S^{r}Az^{r}$ so I haven't been able to test the effect of SM on its fertility. Could you send me your Hfr? I tested 20 colonies from a copy of it which I have and all were NfrF+. I was glad to hear of you and your work from Jim. Will you be coming to the S.G.M. Symposium on "Adaptation"? If you do I hope you will stay with us but please let me know as early as you can. Is there no chance of your getting a travel grant to go to Cold Spring Harbor? Both Jim and I think you should be there.

With every good wish -

Bill