13th. October 1948.

Dear Dr. Odriozola,

Thank you for your letter and for sending me the photo taken in the train to Upsala.

About the series of agouti allelomorphs in the house mouse, I am not sure that I have advanced the question very much. I have tried out all of the ten different heterozygotes which can be made up with five allelomorphs for linkage with undulated, a closely linked recessive tail mutant which we found at Cambridge a few years ago. About 100 of each sex have been bred now from each heterozygote, in some cases more, the total being between 3,000 and 3,500. This would be enough to detect any gross differences between different heterozygotes in the crossover frequencies, and at present one can say that there are no such differences of significant magnitude. Consequently, if there is an inversion associated with any of the agouti allelomorphs it must be quite a short one, i.e. not more than about 4% in map length.

A second point can be tested on the same data, namely whether particular allelomorphs such as A^Y or a are associated with higher or lower crossing over. Although the differences observed seem comparatively high, e.g. on more than 1,000 cases each A^Y giving 6%, whereas A and A^L give little more than 4%, yet on the numbers

bred, which I shall not greatly increase, those differences are also non-significant. Even without a structural anomoly in this region it would, of course, be quite possible for gene effects of this kind to occur, and I should not like my data to be taken as excluding them. A^{Y} for example, which I think most probably is a short deletion, has many effects other than those associated with other alleles at the agouti locus, and just as there are sex differences in crossing over and differences due to age, or in Drosophila to temperature, so it is probable that some genes exert detectable effects in some regions.

I have tested this point fairly thoroughly as a preliminary to the work in view with the same chromosome using four closely linked loci, in the one case agouti, undulated, wellhaarig and pallid, which are easily compatible, except for some difficulty in recognising the agouti alleles on pallid homozygotes, and the second set consisting of kreisler, agouti, undulated and wellhaarig, where I think discrimination of genotypes will be easy, though it has not at present been easy to find sufficiently fertile and viable kreislers. These are circlers, apparently induced by X-rays in Paula Hertwig's laboratory. The locus I now know is to the left of agouti, perhaps as much as 10% away.

The other information that I can give on the agouti locus is that in one of my inbred lines homozygous for a, a doe was bred which phenotypically was a mosaic, parts of the skin resembling

aa and parts phenotypically A^L. She bred well, and of 63 young bred to a mates two were A^L in appearance, these not being mosaics, but uniform in respect of the agouti pattern. One of these has been outcrossed to a^t, to test the allelomorphism of the mutant gene with the agouti locus; and light-bellied-agouti young from the outcross have been backcrossed to homozygous a mates. Since so far nothing but A^L and a^t phenotypes have resulted there would seem to be no doubt that the mutant gene is at the agouti locus, phenotypically indistinguishable from ordinary A^L, and that it has arisen by a single event from the a gene at an early developmental stage in the mosaic mouse.

This observation, though a very nicely authenticated case of dominant mutation, does not altogether settle the question whether we should think of one locus or two closely adjacent loci, since the same event, e.g. the passage of an ionising particle, might affect both of two adjacent loci. The occurrence of this mutation does, however, render it far less likely that crossovers should occur between the locus responsible for A and that responsible for a^t, which up till now has been an open possibility, in view especially of the exceedingly close linkage observed between short ear and dilution.

Yours sincerely,