14th. December 1945.

Dear Dr. Garrett,

Thank you for your letter of November 27th. Race tells me that he has already sent you the earlier notes in which only slight and tentative references were made to the scheme I suggested. I enclose now three more, which I am afraid you will find almost equally slight, but you will understand that publication of long articles is liable to be very greatly delayed owing to paper shortage and other difficulties in this country. There is, therefore, a lot more to be said than these few publications make clear.

The notation, when I put it forward, was intended to leave open the genetical question of whether, as was at first assumed, we have a series of at least seven multiple allelomorphs, to each of which must be ascribed about two and sometimes three, active antigens, or whether these antigens each belong to a different gene, occupying three closely adjacent loci in the same chromosome. The frequencies observed in

European and white American populations do seem to speak strongly in favour of the latter view, for we have, in fact, three common genes or combinations with R_1, r and R_2, constituting about 95% of all combinations present, and a group of four genes at a second order of frequency, say 0.3 - 3 , all, as it were, in a cluster. Finally, the eighth possible combination, which I have called R_y, is obviously considerably rarer than the last group of four.

Now in respect of elementary antigens, all the common heterozygotes R_1r, R_1R_2 and rR_2 are doubly heterozygous. The ingredients of R_1r differing in Q and D, of R_1R_2 in Q and E and of rR_2 in D and E. These heterozygotes constitute about 54% of our population, and a very low rate of crossing over between the three hypothetical loci would produce and maintain against moderate counter selection just the four rarer genes which have been discovered, i.e. all three double heterozygotes would produce R_0 and the others would produce R', R_z and R" respectively, each in equal numbers with R_0. It is therefore suggestive that these four genes should be of the same order of frequency , and that R_0 should certainly be the commonest of the four, with a frequency

about equal to the sum of the frequencies of the three others. I have no doubt, therefore, myself that these four rarer allelomorphs, as they were at first thought to be, are really products of rare crossing over.

I think we may indeed go a step further and observe that R" is at least slightly the commonest of the three combinations less frequent than R_0, while its parent heterozygote R_2r is the least frequent of these three heterozygotes. This seems clearly to indicate (at least if differences in viability are not very great) that the frequency of crossing over between D and E is greater than the other two cross-over values, i.e. that C lies between D and E in order along the length of the chromosome, or else, what would have the same effect, that C is a minor structural anomaly, such as a small inversion, capable of reducing cross-over frequency locally, when C is heterozygous.

We are now in the position to consider the case of R_y, which should also, at least occasionally, be produced by crossing over. It could not be so produced by any of the common heterozygotes as could the other four combinations, but could be produced by the triple heterozygotes ~~R_1R'', R_2R' and $R\,r$~~

R_1R'', R_2R' and R_zr. If I am right as to order of the genes, the first and commonest of these, constituting perhaps 1% of the population, must be counted out, for it would require a double cross-over separating Q from D and E in order to produce R_y. The two triple heterozygotes available for this purpose seem to constitute in the sample at present available only about 0.3% of the population, and if these two each maintained a frequency of R_y equivalent proportionately to the frequency of R' maintained by R_1r and R_2 maintained by R_1R_2, then we could expect a frequency of R_y about 50 per million, i.e. about 1/60th. of the frequency of the least frequent of the other combination R_z.

This, I believe, sufficiently explains the non-discovery so far of R_y; for 96% of R_y genes will be in the three combinations R_1R_y, rR_y and R_2R_y, and these are all at present masked through giving serological reactions identical with commoner genotypes. For example, rR_y has the same gene content as R'R", but should occur of the above estimate of frequency in only about 38 persons per million, whereas R'R" might well occur in 300, consequently the great majority of persons of this phenotype if investigated through their relations should prove to be R'R", and

the few cases so far investigated have, in fact, turned out to be of this genotype. Again R_1R_y is at present indistinguishable from R_1R_2, about sixty times commoner, though the distinction will be possible serologically when, as I anticipate, the antibody δ is discovered, for R_1R_2 will be δ-negative. It is also indistinguishable from $R'R_2$ and will continue to be so phenotypically, even if and when δ becomes available. I suspect, however, that at this stage R_y may be found, for its frequency, say 44 per million, is about double what is to be expected from $R'R_2$. I imagine, therefore, that the discovery of R_y is improbable until δ is available, though if 20 or 30 cases of the phenotype R'R" could have their relatives examined, I think it would be found among these. The third and least frequent of the R_y genotypes, namely R_2R_y is intrinsically indistinguishable from $R"R_2$, which must be decidedly the more frequent genotype of the two, both being extremely rare.

The two genotypes can, however, now be recognised through Mourant's discovery of the antibody ζ or anti-e. They are logically in the same position as the commoner group R'R".

It was most annoying that through a rather inexcusable mis-statement of Levine's several writers in this country were mislead into thinking that he had obtained the specimen of the antibody δ. It is, however, now clear that his statement that all R_1R_2 individuals reacted negatively to his antibody was a complete mistake, and that in fact all R_1R_2 tested had reacted positively, consequently he must have obtained a specimen of the antibody γ and not of δ.

Recent work of Race has made it clear that the elementary antigen C has a third allelomorph, which he calls C^W. This allelomorph reacts with a special antigen $-^W$, or anti-C^W, which is not uncommonly present in what has been regarded as ordinary - serum. Consequently individuals of constitution CDe/C^WDe were at first classified as R_1R_1. It seems now clear both that anti-C^W and anti-C are separate antibodies and, as would be expected, that C^W occurs also in other combinations, at least it has been found in the combination C^Wde. C^WDE and C^WdE have not been found, but these would be expected to be exceedingly rare. On the single factor theory, therefore, we should to speak now of twelve rhesus allelomorphs, of which nine have been found, or on the three

factor theory, of three loci, with two, three and two allelomorphic genes respectively.

At the present time, I believe, great importance should be attached to the examination of all hospital patients who have recently had transfusions, since it is among these that the hitherto uncharted antibodies are likely to occur. In particular, most patients of apparent constitution $\underline{R_1 R_2}$ would be theoretically capable of producing and so further facilitate the recognition of the rarer genotypes.

The whole subject seems due for very considerable extension, and I hope that it will receive in the United States the attention which it undoubtedly deserves.

Yours sincerely,