Reasons for thinking that pleiotropy will be the rule rather than the exception in polygenic inheritance can be found in Mayr's recent book[11].

(4) When discussing my statement that differences in bristle number are neutral or almost so in relation to natural selection Thoday and Gibson clearly missed my reference to Waddington's book[12], where the experiments and conclusions of Clayton *et al.*[13] are discussed. In addition they can be referred to Falconer[14], where a lucid summary of the arguments concerning the minor direct selective value of chaeta number can be found. There the results of the "extensive experiments" (there are several replicates, a feature not found in other selection experiments on chaeta number) of Clayton *et al.* are one of the main arguments.

Now we come to the main point of my communication, which was the interpretation of Gibson and Thoday's results in relation to Mather's theory of the role of stabilizing selection in the origin of balanced combinations of polygenes.

Thoday and Gibson avoid going into this. They do not dispute my statement that Mather's theory involves stabilizing selection on chaeta number itself. According to this theory natural selection would favour animals with intermediate bristle numbers because deviation from the optimal mean value is disadvantageous. This would cause an association of plus and minus factors in balanced combinations.

In Gibson and Thoday's experiments the association of plus and minus genes is not caused by natural selection on bristle number itself but by lethality, not related to bristle number, of certain combinations of their 'factors'. This seems to me an essential difference.

Therefore the statement that their experiments "demonstrate and locate in a wild stock just such a repulsion linkage balance as Mather[5] has argued should occur...." is not justified.

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[1] Thoday, J. M., and Gibson, J. B., *Nature*, **201**, 736 (1964).
[2] Scharloo, W., *Nature*, **200**, 293 (1963).
[3] Gibson, J. B., and Thoday, J. M., *Heredity*, **17**, 1 (1962).
[4] Mather, K., *J. Genet.*, **43**, 309 (1941).
[5] Mather, K., *Biol. Rev.*, **18**, 32 (1943).
[6] Mather, K., *Symp. Soc. Exp. Biol.*, **7**, 66 (1953).
[7] Mather, K., *Biometrical Genetics* (Methuen, 1949).
[8] Thoday, J. M., *Nature*, **191**, 368 (1961).
[9] Mather, K., *Proc. Ninth Intern. Cong. Genet.*, 106 (1954).
[10] Gibson, J. B., Parsons, P. A., and Spicket, G. S., *Heredity*, **16**, 354 (1961).
[11] Mayr, E., *Animal Species and Evolution* (Belknap Press, 1963).
[12] Waddington, C. H., *The Strategy of the Gene* (Allen and Unwin, 1957).
[13] Clayton, G. A., Morris, J. A., and Robertson, A., *J. Genet.*, **55**, 131 (1957).
[14] Falconer, D. S., *Introduction to Quantitative Genetics* (Oliver and Boyd, 1960).

In the comment by Thoday and Gibson[1] on a communication by Scharloo[2], they quote a paper[3], of which I was an author, in a way which seriously misrepresents its conclusions on a point which is of importance in the theory of evolution.

Scharloo had said "extensive experiments have shown that differences in this character (chaeta number) do not have much selective value". In their reply, Thoday and Gibson say the "extensive experiments" are those of Clayton, Morris and Robertson, who only say that "it has been suggested that there is little direct connection between bristle number and fitness", quoting an earlier theoretical discussion. "They do not seem to have thought their evidence firm enough to justify a statement as strong as that required to support Scharloo's thesis".

They have chosen for quotation a sentence from a section on the theoretical aspects of the dominance relationships of the genes affecting bristle characters in *Drosophila*. Contrary to their final sentence, there are in our paper strong statements about our experiments which would justify Scharloo. On presentation of the results of relaxing artificial selection, we say, "It seems from these results that many of the genes controlling bristle numbers must have little or no connection with fitness". Again in the discussion, on the same page as the sentence quoted by Thoday and Gibson, we deal with the selective forces maintaining this genetic variation in our population in the following terms: "The results of relaxation of selection in lines selected for five generations, which showed that the line means had returned only about one-third of the way back to the original mean after nineteen generations of relaxation, suggest that these forces are not very strong and that many of the genes controlling the character must be effectively neutral in their effects on reproductive fitness. We have sufficient evidence on the effects of relaxation to feel justified in relying on the results".

Our last sentence would seem strong enough to support Scharloo's thesis on this important point.

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[1] Thoday, J. M., and Gibson, J. B., *Nature*, **201**, 736 (1964).
[2] Scharloo, W., *Nature*, **200**, 293 (1963).
[3] Clayton, G. A., Morris, J. A., and Robertson, A., *J. Genet.*, **55**, 131 (1957).

Our criticism of Scharloo's publication has done its work in eliciting replies and demonstrating that whether, and if so when and where, polygenic balance arises through selection operating on effects of genes on bristle number, or on pleiotropic effects of those genes, through linkage of those genes to others with more drastic effects on fitness or through random effects, is a more open problem than Scharloo suggests. Prof. Mather points out to us that it has also shown the dangers of taking statements out of their context, for his comment, quoted by Scharloo, that "Pleiotropy in the classical sense is therefore almost useless as a concept for application in biometrical genetics" followed a discussion of the difficulty, general with a biometrical methodology as distinct from classical, of analysing into their ultimate units groups of linked genes (or effective factors as Mather called them) which might indeed be expected to show apparently pleiotropic action (just as they can show apparent over-dominance) even where the ultimate genes themselves did not. The effective factor is the finest unit whose properties biometrical genetics will normally reveal; but its pleiotropy cannot be held to imply pleiotropy of the genes which compose it, and indeed in cases which Mather has analysed demonstrably does not do so.

We only wish to add two points. First, we had not believed Dr. Robertson attached so firm a conclusion to the results he refers to, because the conclusion can only follow on the assumption of a large number of genes none of large effect. That some of the relevant polygenes (or effective factors) are of relatively large effect is one thing we do claim to have demonstrated. Such genes might readily be fixed in some lines in short periods of selection and these lines could not return to the starting point under relaxed selection. Second, the two "genes" we described[1], and which Scharloo chose to discuss, clearly have extraordinary properties. They give a lethal interaction, show an apparent 20 map unit position effect[2], and the two 'loci' are polymorphic in populations all over the world. Extensive discussion of general theories of polygenic variation in relation to what may prove very special genes seems unwise. These two are among the first few 'polygenes' which have been closely located in linkage maps. Others have different properties[3,4]. More will have to be located and studied before it will become clear what the relative importance of different modes of selection have been.

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[1] Gibson, J. B., and Thoday, J. M., *Heredity*, **17**, 1 (1962).
[2] Gibson, J. B., and Thoday, J. M., *Nature*, **196**, 661 (1962).
[3] Wolstenholme, D. R., and Thoday, J. M., *Heredity*, **18**, 413 (1963).
[4] Thoday, J. M., Gibson, J. B., and Spickett, S. G., *Genet. Res.*, **5**, 1 (1964).