WEDNESDAY MORNING SESSION

November 6, 1963

The session convened at nine-fifteen o'clock, Doctor James V. Neel presiding.

NEEL: We seem to have a quorum, so we will begin. This morning, we come to a discussion of the problems that arise from interpreting data of the type we have been considering in the past two days, and I think it is fair to say that these problems of interpretation have provoked about as much lively comment as any other issue in contemporary genetics. The Chairman would like to make two requests with respect to today's discussion: Firstly, in a good many of the exchanges, it seems that problems of definition have loomed rather large. It would be a valuable contribution, I think, if we could distinguish between problems of semantics and problems of substance, and, in this vein, please, would everyone who has something to say define his terms before he begins to use them?

The second request is much simpler. Please don't all talk at once.

The discussion will be opened by Jim Crow.

CROW: This is going to be grossly oversimplified, as several people will probably point out eventually, but I want to sharpen the question as far as possible, by so doing, and classify gene loci as being of two kinds. I will call them M, if they are what I call mutation, which means that the mutant alleles have this frequency determined by—well, I don't think I need to write this out—some relationship between the mutation rate and the selective action on these alleles; and, secondly, segregational, by which I mean that the alleles at this locus have their frequency determined by some kind of balance among selective forces.

I would like to exclude interdemic selection and mitotic drive from selection because, perhaps, they can be brought in later, but I'm interested here in any kind of frequency other than mutation that is maintaining the frequency
of these alleles. The most obvious, of course, is selection for a heterozygote, but this is by no means the only possibility.

I will use the word, "segregational," in preference to Dr. Dobzhansky's "balance," for the same reason I always have, but I would like to give it once; that is, these are all balanced and in one case you're balancing selection against mutation, and in this case you're balancing selection against selection and, to me, segregation seems to say it a little better.

DOBZHANSKY: May I enter a comment at this point? I prefer "balanced," because balancing describes what actually happens in the population. There are different kinds of balance; heterotic balance, where the thing is maintained by an advantage of heterozygotes, and, as Professor Crow says, there are many other kinds of balances, due to the variety of environments and all other things, so the word, "balance," I think, is describing the situation more logically than "segregation."

CROW: Well, may I suggest that this is a semantic or definition question and doesn't really concern the issue?

DOBZHANSKY: Right.

CROW: However, the rest of my discussion will be framed in connection with using the letter, S, rather than the letter, B, so I will continue using that. If somebody wants to say "S" stands for "balance," I have no objection.

Now, the questions that I would like to ask are--the fact that my terminology and approach here are largely those of Dr. Wright is no coincidence. It has to do with proximity and reading of papers.

The first question is, are the majority, or at least a substantial minority, of new mutants of class S?

The second question is--I would like to state the four questions and then, perhaps, have discussion, if necessary, as to whether these are really the right way to ask these
questions. Secondly, do the majority of loci in a population--

LEWONTIN: Or a substantial minority, again?

CROW: Yes. I think I can always add "or a substantial minority," because it hinges on that. Do the majority or a substantial minority of loci in a population have two or more alleles of class S?

WALLACE: When you say "loci in the population," do you mean after the effects of selection and all that?

CROW: Yes. Maybe, in an equilibrium population. Let me add that here.

Thirdly, is the concealed or inbred load--or I don't care whether we speak in terms of variances. If we speak in terms of loads, I'll speak of the load, and if we talk in terms of variances, I'll speak of the variance--or variability, mainly S?

Fourth, is it expressed load or existing load?

GLASS: In the third one, Jim, by "inbred," do you mean the load that would become apparent upon inbreeding?

CROW: Right; in particular, that would become apparent on inbreeding without intervening selection during the process, which is quite important here and, I think, one of the sources of the confusion which has taken place here. Is expressed load or variability mainly S? That is the fourth question.

DOBZHANSKY: May I ask a question? Does that equate load with the variability?

CROW: No. One is the mean change, and the other is the variance change. But, in an important sense, yes.

MÜLLER: The genetic variance changes.

CROW: Yes. I should say "genetic" here, very much; so we have "genetic" in front of "variability" both times.

ROBINSON: Are you implying that you are thinking always of components of fitness?

CROW: I think, for the moment, yes, Alan; components of fitness.
DEMPSTER: Can I ask what you mean by the inbred variability, since you don't like—I mean, more than one thing?

CROW: I have in mind the difference between one inbred line and another inbred line.

FALCONER: What do you mean by "new mutants" in the first question? Mutants that have never occurred before?

CROW: No, that are new in this population. Maybe, I should say "newly arising." They may be recurrences of previous mutations, for all I care. Are there any other questions of definition?

LEWONTIN: Would it be fair to paraphrase 1 and say, what is the nature of the recurrent mutational element that is being brought in all the time?

CROW: Yes.

LEWONTIN: That's what it really is.

WRIGHT: It sort of narrows it a little; that is, a really new mutation could be considered there, too. I don't see the necessity for restricting it to recurrent, even though that is 99.9 per cent of them.

CROW: All right; this is new, whether or not recurrent.

DICKERSON: What is new, anyway?

CROW: All I mean by it is that this allele was not already in this population at the time the mutation occurred. Now, what I want to suggest is that there are five internally consistent positions--

WRIGHT: In the last, it could be in the population. You just mean actual mutations that have been observed to occur, say, in an x-ray experiment, that these are the mutations that occur in the x-ray experiment, whether or not they are in the population?

CROW: That's right; I apologize. It is new whether it is or is not already in the population.
MULLER: Do you mean substantially mutations which have not yet come into balance with selection?

WRIGHT: After the occurrence.

DICKERSON: No, all mutations.

MULLER: They have not yet come into balance?

WRIGHT: But they are the kind that will come into balance by the M or the S.

CROW: Some are and some are not. We're really asking, what fraction of this kind.

DOBZHANSKY: I'm still worried about point 4, as to whether this does not introduce this shadow of optimal genotype. Does it?

CROW: Well, I don't know. To what extent? Is that relevant to this discussion?

DOBZHANSKY: Isn't it?

LEVENE: It might be when you're talking about expressed load. If you're talking about expressed variability, then, I think, there's no argument.

LEWONTIN: That's right; there's certainly no argument.

SLATIS: If it is a questionable point, then, it is relative to the discussion.

DOBZHANSKY: The Chairman asked us to define our terms, so what is an "expressed load"?

CROW: I'll state it as the fraction, not the absolute amount but the fraction, by which the genotype average deviates from the best genotype.

DOBZHANSKY: So you do introduce an optimal genotype in this?

CROW: Oh, yes.

WRIGHT: I think what Dr. Dobzhansky means is that "load" is a loaded word. [Laughter]

CROW: Well, I'll be happy to substitute some other word that means the same thing. [Laughter]

WRIGHT: That's all right, but it raises a question
as to how to measure it.

CROW: Yes. There are many questions as to how to measure it.

WRIGHT: But the question asks what to do about it.

NEEL: Let's accept the question for the moment and come back to the problem of measurement.

LEWONTIN: Perhaps, I could still clarify the question a little, or perhaps not. This is like the question one asks in any analysis of variance. One asks, what are the components which are the major ones making up the mean? In one sense, this is a nonsense question. The mean is there, and there isn't much you can do about it. But we still ask the biological question, which factors are mostly responsible for height, and what we really mean is, which factors are mostly responsible for the variation in height, but, in some sense, we also mean which are the factors that are most responsible for creating the average value of the characters you can see? It has this same meaning, exactly.

CROW: Yes. Let me say one other thing. The answer to this question would be exactly the same, I think, whatever my reference point, which might as well be the mean as well as the extreme genotype.

DOBZHANSKY: Let's reserve this for further discussion.

CROW: Because I'm perfectly willing, for the purpose of asking this question, to say that the amount by which the mean of any population deviates from any point you want to talk about, which could be the mean of some other population, for that matter--

DOBZHANSKY: It is the deviation of mean from the mean.

CROW: Well, it doesn't have much meaning. It would be zero over zero, and I don't think that's it. [Laughter] This is one of the reasons why I prefer not to define it this way, as you suggested.
DICKERSON: What would be wrong with simply calling it "genetic variability," in point 4?

CROW: It does seem to me that one is sometimes interested in the mean by which two circumstances differ, as well as the amount of variance created by this. This is certainly going to be related in this thing.

DICKERSON: But isn't that still a question? To what extent is this responsible for observed genetic variability?

CROW: Perhaps.

LEWONTIN: Between populations.

WRIGHT: But you've got that somewhere else.

DICKERSON: No, it's right there. He says "or."

CROW: Let me read it for you. This says--

DOBZHANSKY: Is this the law for an expressed genetic mean different from the population mean? Would that be a possible question?

CROW: If we don't know what question we're asking, we can't very well ask it.

NEEL: Jim, is there any other term which you could use for "load," because I think it is obvious that "load" does carry the clear implication of an optimum--

CROW: I think what Dick said makes sense to me.

NEEL: But is there any other term you could use in framing the question?

MORTON: "Load" is an old English word which means the same thing as a Latin word which comes from a wagon, or "to bear"; in other words, it is the same as "cargo." Cargo is something that is carried. No shipowner could consider an unloaded ship the ideal ship. It has no implication at all of good or bad. It is something that is carried along in the population. [Laughter]

NEEL: Before you entered the room, Dr. Morton, [laughter] there was an effort made to frame the questions in the most neutral terms possible, and it has become apparent
that the term, "load," does have connotations for some people. Now, mine is an honest question.

DOBZHANSKY: Well, let me try to compromise.

NEEL: Is there any other way to phrase it?

DOBZHANSKY: Would question 4 be acceptable to you, formulated as follows: Is the expressed genetic variability due mainly to S? That avoids any implication as to--

CROW: Except that I'm interested in means as well as variances.

LEWONTIN: Let me make a suggestion, again. The means have a meaning only from population to population, or as a deviation from some absolute, so you're really asking the following two questions: Is the expressed genetic variance within a population mainly due to S? And the load question is really a question, is the difference between any population and any other given population either real or hypothetical, also mainly due to S? You see, you are always expressing the load, the mean, with respect to some X point and, if you like, you can express it as the difference in means among many populations.

CROW: Well, this is pretty close, and I think it helps the discussion to keep this notion, yes.

MULLER: If we're willing to accept in 3 that the load is in the inbred, then, why aren't we willing to accept it in 4, a similar load in the ordinarily mated population as compared with the most fit genotype?--if we wish to define it so. After all, we cannot dodge questions of fitness. The question of fitness is the chief one we are concerned with here. There is no use using a neutral term that dodges fitness when we are concerned with fitness.

DOBZHANSKY: Well, Professor Muller, question 3 can be formulated logically by saying, "the deviation from mean fitness of a random-mating population." Question 4 cannot be so stated.

MULLER: No, it means the decline in relation to
mean fitness. You don't get it, usually, at a superiority in that respect from inbreeding. You may on a rare occasion, yes.

DOBZHANSKY: But it is defined from mean.

MÜLLER: Defined from mean fitness. The inbreeding, you don't get it from.

DOBZHANSKY: Not from optimal genotype.

MÜLLER: I would use optimal genotype synonymously with the highest fitness obtainable, or theoretically conceivable, under the circumstances.

DOBZHANSKY: Well, let's postpone that.

MÜLLER: You can't postpone it if you raise these questions here.

NEEL: Well, now, I wonder, for those of us in the group who might like to equate load with genetic variability at this point, is that for us a permissible procedure?

CROW: Well, for the purposes of the discussion, yes, but mean and variance, to me, have two different meanings, and I don't see how one can equate them.

DEMPSTER: That's right.

GLASS: Wouldn't "variability" be a broader term, that includes both mean and variance?

CROW: Certainly not. Variability is variability, and means are means.

DEMPSTER: I think that would be avoiding one of the most important issues.

CROW: I do, too.

NEEL: I'm trying to find a neutral expression so we can get on with the issues.

CROW: I think, Jim, if you think there is no such thing as an optimal genotype, if you think there is no such thing as a definition that measures the deviations from that, I'm perfectly willing to say that the deviation from point X that you would make is just as good as the optimal genotype that I would make, but it still has to be a mean
difference and not a variance difference.

NEEL: Well, then, as a fifth question, a question which we may never get to today, is there an optimal genotype? This is a basic question, as basic as any of the other four.

DOBZHANSKY: That is hidden in question 4.

CROW: The answer is no, but that doesn't prevent me from discussing the existence of a perfect vacuum.

DEMPSTER: Suppose one measures the fitness of an individual; suppose one takes a definition like this, which measures the fitness of an individual in all the environments in which the population is. Now, at each locus, we make every possible substitution of the genes in the population. We try every possible combination. The combination which we put in this population that gives the highest fitness is the optimum. This is a definition which you can't carry out, actually, in person, so to speak, but it seems to me it is an empirically possible definition and one can discuss it on this basis, if one wishes.

CROW: That's exactly what I'm thinking, and if that wasn't clear to everybody, maybe, you should state it again, because that is my definition for this purpose.

DOBZHANSKY: I would certainly take exception to that definition. Maybe, we should postpone it for the discussion.

ROBINSON: Well, now, there is another question on definition. Questions 3 and 4 are not clear to me. It seems to me that the key words are "concealed" and "expressed." What do you mean by "concealed"?

CROW: By "concealed," I mean what one would find in an individual who is homozygous.

ROBINSON: But that is only in terms of a moment in space, isn't that right?--because you're going to move now from concealed to expressed rather freely.

ROBERTSON: "Concealed" is inbreeding depression.
DICKERSON: That's what I was wondering. Couldn't you say "inbreeding depression"?

CROW: Yes, that's why I put the word, "inbred," here.

NEEL: Then, a related question is, if you keep the concept of optimal genotype, do you agree that the optimal genotype at this particular point in time and space may not be the optimal genotype a generation later?

CROW: Of course; this seems self-evident to me.

NEEL: But if you would accept, then, that the optimal genotype may change rather in the genealogical sense, rapidly--

CROW: Of course, this is the whole story of evolution, as far as I'm concerned.

NEEL: This is part of the question. Dr. Wright just made a statement. Would you like to repeat it?

WRIGHT: I think it is not merely at different times. There can be several different conceptions of the optimum genotype at the same time.

CROW: Oh, sure. I don't see any question about this.

ROBERTSON: Could I make a point, that in 4, there are two things, one referring to means, which is not an operationally obvious concept, that is to say, it doesn't say "do something and you'll get a measurement." The variability is immediately subject to doing something and getting a measurement.

CROW: That is true, yes.

DICKERSON: And variability implies a mean that is suboptimum. If you have variability, obviously--

CROW: I guess so, yes.

DICKERSON: --that means it is suboptimum.

MULLER: But only on the general principle of the natural cussedness of things, that most variations--it's downhill.
DICKERSON: There is no qualification on it at all.

CROW: I think that even Professor Dobzhansky will admit there are some genotypes in the population that are better than average.

DOBZHANSKY: And I hope Professor Crow will admit that some are better than the average.

CROW: That's what I said, exactly. [Laughter]

NEEL: Jim, could you now quickly move on? Now is the time to proceed. [Laughter]

CROW: I would like to say one thing, Professor Dobzhansky. I would like to paraphrase Burton Russell's statement that "I go to Edinburgh," and "Edinburgh comes to me," are the same statement. I would like to say that the statement that some genotype is better than the average is the equivalent of saying that the average is less than some genotype. Agreed?

DOBZHANSKY: O.K., fine. [Laughter]

CROW: I think much of the quibbling is over the assumption that these are different statements.

LEVENE: Jim, before you go on--

DOBZHANSKY: That is not quibbling at all. I take exception to the characterization of this discussion as quibbling. [Laughter]

LEVENE: Jim, I think that if you use the red and yellow chalk up there, it would be much more visible.

LEWONTIN: Can we discuss that? [Laughter]

CROW: Well, I think we have discussed the question. Whether or not this is visible, it is apparent. Now, if I may go on--I thought this part would be noncontroversial. [Laughter]

LEVENE: It was relatively noncontroversial.

CROW: I would like to say there are five internally consistent positions that one would occupy with respect to these questions. I will call the positions A through E. Position A would be that the answer to the first question
is "yes," that the majority or at least a substantial minority of the new mutants are segregational.

ATWOOD: In origin.

CROW: Yes, at the time of origin. I submit that if the answer to question 1 is "yes," then the answers to questions 2, 3 and 4 are also "yes," or you are immediately inconsistent.

ROBERTSON: Oh, no!

CROW: If the majority of new mutations are heterotic, to fix the ideas, then, more than that number of mutants will be heterotic because the heterotic ones will persist and the others will be eliminated; so, therefore, if the answer to this is "yes," the answer to 2 is "yes-yes."

ROBERTSON: Can't you answer "yes" to one of these and not the others?

CROW: You can answer it but not--well, let's go on. If 1 is "yes," and if 2 is "yes," I suggest that 3 is "yes," and if 3 is "yes," I suggest that 4 is "yes."

ROBERTSON: No, my own position is, certainly, if I may state it, three "yeses" and a possible "no" to these questions.

DEMPSTER: The first one is "no," though, isn't it? He hasn't come to that.

CROW: I think you're thinking exactly backwards, Alan.

ROBERTSON: All right; I retreat.

SLATIS: Jim, there is a possibility, though, of saying "yes" to the first two, without having to say "yes" to the third.

CROW: How?

SLATIS: You could argue that, on inbreeding, a second class of gene comes up.

CROW: That never mutates?

SLATIS: That has been mutating, but it has been the minority, a real minority.
CROW: Well, in other words, you are saying that there is such a thing as "no, no, yes, yes," and I'm going to get to that in a minute.

SLATIS: "No, yes, yes, no."

LEVENE: I think what Herman is getting at is that if the majority of new mutants are S, but with very, very small selective coefficients, and there are a number of other mutants that are not S, that are M but are lethals, then, on inbreeding, these rare lethals might produce more depression than all the S genes that have very slightly reduced fitness.

LEWONTIN: Oh, dear!

CROW: Now, let's see; I'm not sure I understood that.

SLATIS: I think you wrote it in 1958.

CROW: Well, that doesn't say I understand it in 1963, but go ahead. [Laughter]

SLATIS: I'm pointing out that you could have almost all the genes of the S type, but as you went toward inbreeding, they might balance out and contribute very little to the variability that you get on inbreeding, or to the shifts that you get on inbreeding.

CROW: That's all right, but--

SLATIS: A couple of genes, a very small proportion of all the genes, might be the ones that contribute to the inbreeding depression.

WRIGHT: I think he's right there, that the S genes, and there are only two of them, can't get more than a double depression from the heterozygote, while your M genes, you see, could get a hundredfold depression from the equilibrium condition in relation to the optimum, the best. I think Herman is perfectly correct there, that you could have a recessive. It would ruin your population.

CROW: Well, let me state it another way round, or may I write my other positions here first and then come
back to this?

WALLACE: May I ask a question before you do that?

CROW: I'm saving up questions to answer, but go ahead.

WALLACE: When you talk about S, now thinking in terms of S in the sense of deviation, 1 - S, 1 - T--

CROW: No, no, S.

WALLACE: Yes, I know that, but are you thinking in terms of large effect or small effect or doesn't it make any difference to you?

CROW: I'll tell you what I was thinking. I was thinking, in order to frame up the issue, I would like to assume that both kinds of loci have about the same kinds of effect, and, in effect, this is what is being challenged, and, I think, appropriately, and that is why I would like--the magnitude of S is about the same in both.

FALCONER: I just realized that questions 1 and 2 are framed in terms of number of loci, and 3 and 4 are framed in terms of magnitude of effect of the gene.

CROW: Yes, purposely.

FALCONER: We have to keep that clear, I think.

SLATIS: But this was your argument five years ago, that the large number of loci that might contribute to normal variation might be completely overruled by just a couple of loci that had enormous effects, but they were rare and the effects turned up only on intensive inbreeding.

CROW: No, no.

DEMPSTER: What he said was that there might be two or three segregational loci that contributed very greatly to the variability, but that, on inbreeding, the maximum inbred load that one locus can possibly contribute is, I think, the clue to the mutation. If you have a lethal locus with a certain mutation rate, the frequency of the gene in the equilibrium population is 1/S. If you let S equal l and
multiply it by S, you get the spirit of the thing. If you got a mutation rate of 1 in 10,000, it would be very high. The absolute maximum inbred load would be 1 per cent, whereas segregational loci have to have very small Ss and Ps in order to contribute that small load. Almost any segregational locus will contribute more load on inbreeding than a mutational gene. I think that's it.

CROW: Thank you, Everett. Yes, this is what I would have said had I thought of it.

WRIGHT: But, in your 1 there, there is nothing said about the effect of these genes; merely the majority. That is the point there; to be consistent with your "yes" for 1, if this majority of the heterotic loci have exceedingly small effects, while there are a few mutational ones which, when expressed under inbreeding, had very devastating effects, the heterotic effects, or the deviation from the optimum, would be merely doubled under inbreeding, and the expressed effect--

CROW: I think you're right, Dr. Wright.

WRIGHT: The main point is that you have said nothing about effect in the first, so this majority, the heterotic, may have negligible effects. Then, you jump to effects with inbreeding.

MORTON: Your "yes, yes, no, yes," is a tenable position with certain other assumptions.

CROW: Yes, I think I have to say that, and the assumptions are that the magnitude of individual effect is far different for one class of locus than it is for the other class of locus.

WRIGHT: There is nothing said in 1 about that.

MORTON: Or it could be tenable in another way, that you are not measuring fitness with some component. There are lots of ways of making it--

CROW: Nonetheless, I said I was going to simplify it, and I would like to continue this way. It seems to me,
without bringing in this kind of assumption, which may or may not be realistic—well, let me go ahead with my discussion, anyhow.

Another possible position is, we may have to say that these "yeses" on 3 and 4, and 1 and 2 are apples and oranges, and there is not much relationship between them, but I don't think this is true, because I'm not willing to make the _ad hoc_ assumption that these are totally different classes of mutants in terms of their effect on the organism.

If the answer to 2 is "no," then 3 can clearly still be "yes," for the reasons that have been brought out, and if 3 is "yes," then 4 is "yes"; that is, because of the tendency for heterotic mutants to persist and classical mutants to be lost, it is possible that this [question 2] is "yes" and this [question 1] is "no." Then, 2 can be "no," 3 and 4 can continue to be "yes," for the same reason, that heterotic loci contribute more to inbreeding depression than classical loci do, per locus; therefore, this 2 can be "no" and 3 can be "yes." The heterotic locus is likely to be at a higher frequency in the population than a classic locus, and therefore, on the average, it will contribute more to the inbreeding effects.

ROBERTSON: Will you say that again?

LEWONTIN: Given an equal effect, the numbers of heterotic loci might be very small, but the total variance associated with them might be very large.

ROBERTSON: Oh, yes, that's right.

WRIGHT: But you have to add a comparable effect under 1, if you're going to make these definite answers.

CROW: If the third and fourth answers go with answers 1 and 2, I have to say "of comparable effect." Perhaps, I should just say it up here. Should I put "comparable effect" in the statement up here?

WRIGHT: I think it rather spoils the question to put it in, though.
CROW: Well, maybe, it points up the issue, Dr. Wright.

WRIGHT: Unless you put it in, I think, for example, in the first one, 3 can be just anything.

DEMPSTER: I don't think that is quite true, Professor Wright. I mean, you speak of the maximum effect in one case being 50 per cent and in the other case a very much larger per cent. I think we have to think in terms of the degree of effect rather than the percentage. You're comparing the percentage at random mating with the percentage under inbreeding. If you have the maximum possible effect that you can have with a mutational locus equilibrium, unless you are measuring some other component, it is 1 per cent, and that is with the enormous mutation frequency of 1 in 10,000. To have that small an effect of segregational loci, you have to have the S and T in the neighborhood of 2 per cent, and I would submit that it is unlikely that you've got segregation loci that are held in the population, let's say, by something like .1 per cent, because mutation then begins to be important.

It seems to me, therefore, that, substantially speaking, you don't really have to say much about the degrees of effect of these two classes of loci, because there is hardly any range there, where their relative degrees could be so different that that statement wouldn't be true in the order in which he has put those "yeses" and "noes."

WRIGHT: I would be inclined to answer him under 3, I think, under just the ordinary situation.

CROW: That's all right, but you probably would--

WRIGHT: "Yes" for 1 and "no" for 3, in the first column.

NEEL: Why don't we let Jim put down the five alternative formulations he wishes to pose, and then see how heavy the pressure is to put on other formulations? We may end up exhausting all the combinations and permutations.

CROW: That's what I'm going to do. Position D is
all "noes" and E is all "noes."

DICKERSON: If you have a question on the first case, under 3--

CROW: I was merely trying to write these in a probable hierarchy.

WRIGHT: Your line between Y and N is just a diagonal.

CROW: Right. Well, I'm inclined to agree with what Dr. Dempster says, that unless you assume a quite different order of magnitude of the mutants involving the two kinds of effects, this is the logical system. Now, I can contrive systems where it is not true.

MORTON: I don't think that is true, because the first two questions can be formulated in a way which is completely unreasonable, that is, in terms of effects that you can't measure. They can talk about isoleles, we'll say, as always maintained.

CROW: Well, I did have one thing in my notes that I thought I would bring in, but I was going to say I would omit from discussion, selectively neutral isoleles as being pretty much beyond the pale of investigation, by population methods, at least.

NEEL: But do we know that isoleles are selectively neutral?

CROW: I would say that selectively neutral isoleles do not exist.

DEMPSTER: There are mutational loci, aren't there?

LEWONTIN: Alleles must be defined as those states of the gene which are distinguishable to natural selection. It seems to me that everything else--

[cries of "No, no!"]

LEWONTIN: Well, within the population at a given time.

BODMER: They may not be distinguishable at one time and they may be expressed later in interaction with some other loci.
NEEL: Actually or potentially.

BODMER: Yes.

LEWONTIN: Actually, the questions we do ask about a population and measure about a population are with respect to the current selective forces. If we're going to ask, "What is the potential of this population for future evolution?" then, I agree entirely that the whole range of possible changes of state of DNA is important. But you don't ask those questions in experimental practice. When you say, "Is the expressed load or expressed genetic variability mainly S?" you can talk only about the alleles which have been and are at the present time distinguished by natural selection. If no selection has arisen yet which will distinguish between two isoproteins or isoenzymes, then, as far as natural selection is concerned, they are both the same.

NEEL: But, Dick, they may have been selected in the past.

LEWONTIN: Indeed, they may. All Jim is saying is that if there is no selective difference between them, you count them as one.

BODMER: But, in experimental practice, you have a sort of uncertainty principle. There is a limit--

LEWONTIN: This is unfortunate.

BODMER: --to the selective difference which you can detect, and there may be a very large number of alleles which will be below the limit of the selective difference which you can detect and which are, nevertheless, important.

CROW: Then, one tries to invent techniques to do this.

LEWONTIN: All Jim is trying to eliminate is--

CROW: Those which are neutral.

LEWONTIN: --those which by definition are indistinguishable to natural selection. If there are some distinguishable to natural selection but which are unfortunate enough to be unable to distinguish, this creates a kink in the
external problem. All he's trying to do is find a way out of this difficulty.

WRIGHT: In questions 1 and 3, if you say "comparable effect," do you mean comparable effect in the heterozygote, or what? If you mean in the heterozygote, then, you could have a great many Ms that have slight effects, and, perhaps, a majority of Ss, if you're going to answer "yes," that have the same slight effect. The latter will go up in the other homozygote, while this M, we will say, is devastating that homozygote. It's almost a recessive lethal, or something of that sort. But it has comparable effects when they occur as heterozygotes.

In the inbreeding effect, the M, of course, will bring out the devastating homozygotes, and be a tremendous depression. In the Ss, the depression can't be more than twice the depression of the homozygotes with respect to the heterozygotes, or I'm thinking of exactly a gene frequency of 50 per cent, but it will be about two times, so that it will not produce very much inbreeding depression if the effects on the heterozygotes are about the same. The other will produce a very great depression in inbreds.

CROW: Measured only as a fraction of what it was doing in the outbred population, but not in absolute terms, Dr. Wright. It depends on the gene frequency.

DICKERSON: Yes, that's it.

CROW: You see, your mutational alleles are going to be low gene frequency and your segregational alleles are not.

WRIGHT: But, on your own principle, the inbred depression can be a hundred times the difference between--

CROW: It will be a hundred times the effect of that same locus on the hybrid population, yes, but if that is very small, the hundred times is a very small quantity. It is not necessarily two times larger than the large quantity.

WRIGHT: But we're assuming that the others have
a comparable effect.

CROW: No, no! The comparable effect of the gene, but the locus will accumulate--

WRIGHT: It depends whether you mean in the heterozygote or in the homozygote. If you're talking about the heterozygote, then, this would be "no"; if you're talking about the homozygote, then it will be a different answer.

CROW: No, the difference has to do with the fact that one kind of locus will accumulate to a high frequency in the population and the other will not.

MORTON: But, Jim, let's take a hypothesis that all genes are heterotic, but some are more heterotic than others. Then, a gene that is lethal in the homozygote has a slight advantage, an advantage, we will say, which is not measurable in the heterozygote. These are radically different effects. I'm not sure that the first two principles are formulated in such a way that I would know whether you're counting that as a segregational or mutational load. Whenever the heterozygote is so small that mutation must also be invoked to keep the gene in the population, you are in an area that isn't investigatable, but these genes, presumably, unless you define them out, will contribute to your first two propositions.

LEVENE: I would like to ask another question. Are we assuming that there are two alleles that are a locus?--because Dr. Wright has been saying that segregation can only depress by a factor of 2. This is true only if you have these two alleles.

WRIGHT: Yes, that's right.

CROW: Yes. I'm not assuming this. I think it's clear enough that one can invent situations in which this hierarchy is not necessary. Well, let's go on with the discussion from here. What I wanted to do was to ask two other kinds of questions. Why do we want to know the answers to these four points? Second, what kind of experiments have been done or are proposed to be done, which, at least in principle,
could answer some of these questions, and which of the ques-
tions do the experiments bear on?--because, once again, I
think, whether this is strictly right or is not--and I agree
it is not strictly right, but I think it is probably right
for most situations that one thinks are realistic--it is still
possible that some people are talking about this [question 1]
and other people are talking about this [question 4], and don't
realize that they're talking about different things, or at
least there is a possible shifting of grounds.

Now, excuse me for being personal for just a
moment, but I would like to identify what my own view has been
at various times in the past and what it is at present. When
I express a view, this doesn't mean that it is a dogma or that
it isn't capable of being changed. I am simply saying what I
think is the most likely picture of nature at the particular
time.

In 1948 and in 1952, I wrote papers that argued
essentially for view "D" here. The argument was primarily
that hybrid corn was enough better than the average of random-
mating corn that removal of concealed classical mutants was
hardly sufficient to account for this. There have been two
factors since 1948 that have mitigated that statement somewhat.
One was my lack of realization, or anybody's, pretty much at
that time, that partial dominance was a ubiquitous thing, and
that changes by a factor of 2 were the kind of estimate that I
was using.

The other one is that, with more study of mutation
rates--I think, I was choosing too low a value for the mutation
rate to mild use as opposed to drastic changes, so, if the
mutation rate, as I took it then, was too low, and if the amount
of dominance or complete recessivity was not so much the rule,
much of the force of that argument disappeared, and my position,
if I can call it that, shifted to one of uncertainty between
these two alternatives, and that is where it still is [D and E].

I apologize for being personal, but I want it clear
that I have never argued for a view like the one that this view [E] was correct.

LEWONTIN: At the present time, you think, the choice is between D and E; is that right?
CROW: Yes.
MILLER: That is where you and I differ, to some extent.
CROW: I think Dr. Miller might take view E. Am I right?
MILLER: Yes.
CROW: I think, if anybody else would like to express an opinion as to where he stands on this, I would gather from the discussions with Dr. Wright—but he is perfectly capable, as you know, of speaking for himself—that probably he would be here or here [D and E] or somewhere in between.
DICKERSON: That would be the democratic way to decide it, wouldn't it? [Laughter]
CROW: Yes.
LEWONTIN: I would like to point out that if we use the statistical principle of ignorance, the answer to question 4 is clearly "yes," the answer to question 3 is probably "yes," the answer to question 2 is probably "no," and the answer to question 1 is certainly "no."
CROW: Based purely on these statistics?
LEWONTIN: Yes. [Laughter]
LEVENE: As a statistician, you would take No. 3?
LEWONTIN: Yes.
DOBZHANSKY: Well, now, if I may add my voice, I would put myself in the category of C, with the reservation that question 4 is formulated in a way which I find difficult to answer. Otherwise, I would favor C.
CROW: Well, this is Dr. Miller and this is D, so you can take whichever you like. I think everybody is prejudiced in this by saying, if somebody knew the answer to A, we wouldn't have any argument.
SLATIS: Is someone willing to argue for A?
CROW: That's Bruce.
WALLACE: Yes. No. 1 is the one I'm trying to get at, personally. I don't care where my personal views fall. I feel that is unimportant. The interesting thing is the experiment, and I interpret my experiment as saying "yes" to No. 1.
CROW: That's right. Now, let me proceed from here, because--
WALLACE: Given that one additional factor, that the alleles involved in the experiment are those taken from the population to begin with and not from some laboratory stock.
CROW: I would like to ask why we want to know the answers to these four questions, in addition to just the fact that we want to know anything we can find out, for its own interest. The relevance of question 1 has to do with the assessment of the impact of mutation on the population, as, I think, everybody has clearly realized.
Question 4 is pretty largely irrelevant to that particular point, but is very relevant to the question of the choice of breeding system for future selection in livestock populations or plants, or short-range evolution in any species, I would say.
Questions 2 and 3 seem to me to be of considerably less intrinsic interest than either 1 or 4. It seems to me that 2 is most useful because, with one answer to 2, it pretty clearly implies the answer to 1.
Question 3 is useful because the answer to 3 pretty clearly implies the answer to question 4.
I had a little bit of reservation that has come out far more strongly here, as to the possible fact that there is a logical gap between these two things and these two things [questions 1 and 2, and 3 and 4], but, to a large extent, I think, it is fair to say we are interested in 2 because of its
bearing on 1, and we are interested in question 3 because of its bearing on 4; at least, to my own way of thinking, this is to a large extent true.

LEWONTIN: Excuse me, Jim, but if I may state a position which, I think, Dr. Miller stated, it is that question 1 has another importance, in addition to its bearing on 2; that is, it would be the immediate question of the damage done to the population by mutagenic agents.

CROW: I think, Dick, I said the opposite of what you said. I said I am not especially interested in 2 so far as it bears on 1.

LEWONTIN: Oh, sorry! But one might ask question 1 quite independently of 2.

CROW: Oh, sure, but this is what I'm saying, that 1 is interesting in its own right, because that is the question that will tell us the most about the effect of a change in mutation rate on the future population, it seems to me. Question 2, by itself, wouldn't really tell us very much about that. But 2 would help us answer 1, if it had a certain answer.

DOBZHANSKY: Excuse me, but there is one word which may cause trouble, if I may point this out;"mainly," in question 3. You say "mainly." Would you agree to change it to "substantially," "substantial fraction"? "Mainly" may be misunderstood as meaning 99 per cent.

CROW: By "mainly," I mean more than half.

DOBZHANSKY: It is substantially.

CROW: Mainly is substantially. I would rather say "more than half," if that's what you wish, but it is unambiguous.

DOBZHANSKY: Could we say 40 to 60 per cent?

CROW: Is "more than half" all right?

LEWONTIN: That's not 40 to 60 per cent.

DOBZHANSKY: No. I would be in doubt.

NEEL: But at least it makes the question less ambiguous.
CROW: More than 25 per cent, or something?

DOBZHANSKY: Why not say "substantially"?

[Laughter] It means all sorts of--50 per cent is not a sacred percentage, is it?

CROW: I don't favor it, particularly. Let's say "substantially."

GLASS: I think "substantially" is just as vague as "mainly."

NEEL: And to put an exact figure in gives us something to shoot at, so let's say "more than half."

LEWONTIN: My only objection to that, Jim, is that, precisely by giving you something to shoot at, it may be giving you a false target. People may start to argue whether it is 40 or 60 per cent, which may not be worth arguing about.

NEEL: Is that any worse than arguing about what "mainly" or "substantially" mean?

LEWONTIN: The real question is not whether it is 40 or 60 per cent, but whether it is 1 per cent as opposed to something larger, 25 or 30 per cent. It is an order-of-magnitude question rather than--

BODMER: You could frame it this way: You could say, "Is there a difference of order of magnitude between 1 per cent and 20 or 30 per cent?"

DOBZHANSKY: But 30 per cent for some purposes is a substantial percentage.

CROW: Yes, but if the corn breeder learned it was 20 per cent, he would follow one breeding procedure, and if he learned it was 50 per cent, he would follow another.

WALLACE: I'm a little confused by your remarks on category 1, and why it is important. Would you repeat them?

CROW: I don't think I said anything that hasn't been said many times, that if the majority of mutants are M, then, the impact of the mutation on the population is proportional to the mutation rate. If the majority are S--
WALLACE: But you say "a substantial minority." Does that leave a substantial majority of M? As long as the argument runs that mutation of any magnitude is important, how will the argument be changed if there is a substantial minority of mutants that are S? That's my question.

CROW: Well, could I say it this way, that if S is 50 per cent, then, the Haldane principle applies to the extent of 50 per cent of mutants, and it does not in others. There is 50 per cent uncertainty introduced by this effect.

ROBERTSON: You should put in the condition here that this statement is a large-population statement. The moment you get down into the small thousands, it ceases to be true.

CROW: That's true, though, Alan, for practically anything else we could say, it seems to me. Agreed, but--

WALLACE: But isn't it true that the correction is a relatively simple and straightforward one? It depends upon the proportions themselves.

CROW: Yes.

WALLACE: I don't know what a substantial minority is, but let's say it's 10 per cent; then, we know that 90 per cent of the original argument holds, and, as long as we said that irradiation at any level was important, then 90 per cent of that is presumably still important.

CROW: I would say even more than that, that the error is inherent on the assumption of the impact on the human population of errors far in excess of 10 per cent for other causes, so I wouldn't worry in the least about this.

MORTON: Jim, you made a statement that wasn't challenged by any of the quantitative geneticists. I assumed we were talking here about fitness; is that right? Or are we talking about any character?

LEVENE: Fitness.

MORTON: Then, you said that the corn breeder would do something different if the segregation load were 20 per cent
than if it were 60 per cent of the inbred load. But, surely, the corn breeder is interested in yield, isn't he?

CROW: At least, what I would like to say is that fitness arguments are not totally irrelevant to yield, because it has been subject to selection.

MORTON: But would that, in fact, that kind of quantity, tell you anything? This is an interesting point. If a corner breeder found that, measuring fitness, if he could do this in some way, would he make a different breeding plan if he knew that the inbred load was mostly segregational?

You see, he is dealing always in corn with hybrids, but the inbred load is mostly segregational and mostly mutational. I think it would be irrelevant.

CROW: I'm talking about the random load, for one thing.

MORTON: Point 3.

CROW: No, I'm sorry; I meant 4.

SLATIS: I think he meant point 4.

LEVENE: The point is that when you're dealing with corn, yield and fitness are exactly the same thing. Whether a particular seed has lots of descendants depends on yield and nothing else.

CROW: Well, at least, there is a correlation.

LEVENE: Viability is part of yield.

LEWONTIN: You never grew corn.

DOBZHANSKY: I never grew a corn plant, either, but, Dr. Robinson, let me ask you a question. Would it be fair, for purposes of population genetics, to define fitness of domesticated animals and plants as fitness for the purposes for which they are raised?

ROBINSON: For the purpose for which they are raised?

DOBZHANSKY: Yes.

ROBINSON: Not necessarily.

DOBZHANSKY: Or usefulness to man.

ROBINSON: No, not necessarily, because, I think,
this changes. Man changes his requirements for these plants and animals.

DOBZHANSKY: Environment changes of fitness of wild animals and plants also occur, but, at any given moment, shall we say, fitness of corn or of poultry is defined as the yield, the number of dollars.

ROBINSON: Well, let me speak to this. You see, earlier, we tried to equate yield to fitness in corn, but, on the other hand, you can argue the point, and effectively so, that this is not true, for this reason: Without man, an ear of corn that has a relatively small number of seeds may be more fit in that, if it were dropped at the site of the plant and a small number of seeds were here, then, these might grow and reproduce better. On the other hand, a very large ear, with a high number of seeds, may be so competitive for that particular site that this would be detrimental to the plant. Now, that is without man in the picture. This is just natural reproduction.

With man, and if you make certain other assumptions here, then, I think, the higher number of seed expressed in yield would be a component of fitness here.

DEMPSTER: The question of whether or not some kind of equilibrium has been reached under man's selection has been going on long enough.

CROW: Well, may I go to some experiments now? I would like to mention several experiments that are familiar to everyone in the room, and say then, to me, the question they bear on, and also the possible answer they could give to this if there were no questions about experimental details and things like that.

I will list the experiment, the question that it seems to me it bears on, and list the possible answer that it could give; that is, there are two kinds of experiment, those that can answer the question if it is "yes," and those that can answer the question if it is "no," and those that are
meaningful in only one direction.

I will list, first, the Wallace experiment, consisting of comparing a fly that is homozygous for two chromosomes, one of which has a history of irradiation and the other of which does not, with the fly homozygous for the same two chromosomes when one does not have a history of irradiation. That bears clearly on question 1, and it could answer it either way, it seems to me, yes or no.

A second kind of experiment is the one that Comstock, Robinson, Gardner and others have done at North Carolina and other places, where they answer a question related to yield or some other character in the corn itself. I'm talking about what I think you called your plan 3; is that right, Cotton?

ROBINSON: Crossing back and forth.

CROW: Where you double-cross and put these back together again and permit randomization of linked combinations at a predictable rate over a period of time.

ROBINSON: That's right.

CROW: This seems to me to bear quite unambiguously on question 4, and I think it, too, can provide either kind of an answer; that is, if corn yield is primarily due to heterotic genes, at least, the linkage equilibrium will not disappear. The linkage bias, perhaps, I should say, will not disappear. If the apparent overdominance is primarily due to linkage, it will disappear at at least a somewhat predictable rate; so it seems to me that is a meaningful experiment, at least, and, whichever way it goes, it bears on the question.

LEMONTIN: Do you agree that that answers question 4 only in the case where you are dealing with things taken out of an equilibrium of a pollinated variety?—because, if you take just two long-time inbreds, these two long-time inbreds are, after all, a small sample of the kinds of gene action which existed in the population. You will get a variety, an array, of answers, if you do this with many different sets of inbreds.
CROW: Yes, to the extent that the inbred lines you start with and put together can be regarded as reconstituting a random population.

LEWONTIN: Yes, that's important.

NEEL: I'm sorry to interrupt this train of thought, Jim, but I'm doing a "delayed take" here. Isn't there a fifth question which lies behind a good deal of the disagreement? This is the question of the proper frame of reference in answering all four of these questions. Is it the population mean, or is it the best genotype? If it is the best genotype, do you shift standards as you go from segregational to mutational systems? Before we can just discuss any of these, what is your frame of reference in trying to answer these questions?

DOBZHANSKY: I very much agree with our Chairman. This is what I tried to say. But I take it that we have postponed this crucial question for discussion later. Is that correct?

NEEL: This is certainly the question or the issue about which more blood is being spilled right now, in a sense, than any other.

CROW: We'll get to it.

ROBINSON: Yes, that is the question.

CROW: Let me say that neither of these two experiments is the last bit injured by any amount of discussion on the subject. Coonstock's measurements are entirely on variance, and Wallace's on scale. I can't see anything ambiguous about Wallace's measurements.

MORTON: It would answer the question if it involved a whole possible spectrum of variances, but, since it doesn't, it can't. I submit that one could not reasonably answer the first two questions if they were expressed in a general way, by any experiment that we could now perform, under any circumstances. You don't have any way of getting information on the first two points. There is a bias there.

LEWONTIN: What is the bias in the argument of
NOZTON: At least with respect to certain rather gross types of mutation.

MULLER: Yes, and you're measuring fitness as defined under certain particular conditions, of course, which you always have to do.

LEWONTIN: Doesn't the strength of your argument, Newt, depend on this difference between chromosomal and locus effects, if you gave a gentle enough treatment so you could assume that nearly every chromosome treated had at most one mutant?—because, in fact, the mean number of mutations induced by this level of radiation is probably less than one per chromosome.

LEYENE: But we don't know what the mutation rate is for, let's say, polygenes, and you may have a lot of those induced.
LEWONTIN: But this isn't the question that was raised. I'm trying to find out what the question is.

DOBZHANSKY: I'm surprised that Dr. Wallace doesn't say anything about it, but isn't it true that his experiments bear on question 1, under certain special circumstances?

CROW: Isn't that true of any experiment at any time?

DOBZHANSKY: I think Dr. Morton is perfectly right.

MORTON: The mutations that are induced are tested only in heterozygotes. They are never observed in homozygotes, so I don't think one can talk about a heterotic gene unless you see it in a homozygote.

CROW: I'll accept that.

WALLACE: If I say that the mean goes up, though--

MORTON: You're comparing a homozygote with a heterozygote. You're not comparing or saying anything about the other homozygote.

LEWONTIN: Do you believe these mutations he has induced will, in fact, cause an increase in the other homozygote? That seems unlikely. The reason he didn't bother to do it is because, I think, if there is one thing that everybody in this room accepts, it is that newly arising mutations, when made homozygous, will be lousy.

MORTON: I'm not sure this is so.

LEWONTIN: Do you think that the frequency of newly arising mutations which are better than the old ones in the homozygous condition will throw this out?

WALLACE: Then, we can throw out the idea that ? equals the square root of S, and so on.

MORTON: But you are assuming in this argument that genes have a very small effect; that although their mutation rate has never been measured, in fact, the mutation rate is not appreciably greater than the lethal rate, for example. Is that right? If it were true that there were a very high probability but infinitesimal mutations, so-called, if these
were what was being measured, you don't know how they would behave in homozygotes.

DEMPSTER: That is always true. You are always making some kind of assumption when you interpret an experiment. These assumptions may be wrong, but they are reasonable first assumptions to make. If we can say that mutations of small effect are not very frequent, then, we can give a probable answer, yes or no, perhaps; I mean, it doesn't give an absolute answer, but you'll never find an experiment that gives an absolute answer to anything.

MULLER: If you take Jia's original assumption, that there is a similarity in the amount of effect of these different classes, then you can do it.

MORTON: I submit that the question, in general terms, is not meaningful. It will be made meaningful only by introducing an arbitrary assumption. Perhaps, the question is not really useful.

DEMPSTER: The assumptions are not completely arbitrary. For example, the first suggestion you made, that you want to know what happens in the homozygote—if you make the assumption that most new mutations with small effects when introduced by radiation are favorable in the homozygote condition, this leads you to an untenable assumption.

MORTON: If you don't know how many mutations have been induced by 500 r, how do you know how many are lethal? Since you can't count mutations, it has no bearing on this.

MULLER: You can count them up to a certain limit of sizable effect.

MORTON: You have to assume an awful lot.

DEMPSTER: I agree. If you say there are a large number of mutations produced that are, say, completely recessive and have an effect of about one part in a million, you can't answer this question, but you can say--

MORTON: And that shows the superiority of the
third and fourth questions, and you might get some information.

NEEL: Wait until we get to the third and fourth questions.

DEMPSTER: You can say either there is a tremendous number of mutations produced that have very small effects, recessively, or you give an answer, yes or no. There are a few other assumptions. I am greatly simplifying it, but you've gotten some information that bears on the question. I think that's all Jim is trying to say.

BODMER: Isn't the more important question, in a way, the fact that the mutations you induce will not give you a spectrum of mutation type which is at all comparable to what occurs spontaneously?

MULLER: Except that we have evidence that it is spontaneous.

BODMER: Not from microorganisms.

MULLER: I'm thinking of Drosophila.

CROW: It bears on question 1, as far as mutation-induced effects are concerned, which is all you're really trying to say.

ROBINSON: Before you leave No. 2, on the corn, you brought it up in 1948 and 1952, and, where you are asking for other information, you may bring it up, but, you remember, in terms of the 1948 and 1952 papers, the question about corn in the open pollinated varieties, and then the random set of lines—this is one reason we produced this material, to make them in terms of all possible crosses and see what the maximum performance of these was, in terms of mean performance. Most hybrids might come out of that population, because, you remember, in terms of your hypothesis—I don't know whether this will fit in here, but that has been done. We have an array of hybrids, and it seems to me that bears on the question of whether you are in D or E. Isn't that right?

CROW: I think it does, yes. I have overlooked it,
as a matter of fact.

MORTON: So it would be acceptable to everyone to modify the first one and say that the majority or at least a substantial minority, assuming that most mutations which have not been measured and, in fact, cannot be measured by this procedure, I can imagine, do not, in fact, exist. The question is meaningful when so phrased. [Laughter]

CROW: I think that is a fair statement, but you could say the same thing, really, about a whole variety of experiments.

MULLER: No, assuming that they can, for practical purposes, at this point, be affected, you can say.

ROBINSON: I suggest we go ahead.

CROW: There is not going to turn out to be any further experiment in this further discussion.

Let me mention, as the third point, one of my own, but I would suggest deferring discussion of it, because I'm sure it will lead to some. I would like to say where I think it bears on what Newt and I have called the B plus A over A ratio of Morton, Miller and myself.

This bears on question 3 and not on 4, or at least it would have to take some rather unusual values to tell you very much about 4. This is what I would rather say. It can answer the question only one way, which, it seems to me, is important to say. It can give you an M answer, but it can't give you an S answer, except under what seems to me--well, it can give only a "no" answer, unless the typical number of alleles is quite high.

LEWONTIN: Jim, I would like to defer that, except that I want to say something now. I believe, in fact, if you look carefully at question 3, it can give both a "yes" and a "no" answer. What it can give a "no" answer to is essentially question 2, on the number of loci. But, I believe, if you talk about the genetic variance or the average effect, it really turns out to be pretty symmetrical in that respect.
CROW: I think we are agreed, but let me see if we are saying the same thing. If the value here is high, it points in one direction; if the value here is low, it may be that $A$ is inflated, by causes that are unrelated to genetic factors that you are trying to study. If you have some way of removing the environmental part of $A$, then, I think, a low value is meaningful.

LEWONTIN: So I say, under the ideal situation, a situation under which the $B/A$ ratio can, in fact, be a two-sided test of hypothesis 3 but not of hypothesis 2.

ROBERTSON: Will you specify for us exactly what $A$ and $B$ are?

CROW: Well, $A$ is the measurement of whatever you are measuring on the inbred coefficient, and $B$ is the other end of the constant regression equation.

NEEL: Do you now or later want to say what you mean by "high"? You say, if it is high, this answers the question.

CROW: Oh, 10 or something like that. I would say, if it is 10 or more, it argues in favor of Y. If it is 2 or 3 or less, and $A$ as an environmental component of $A$ is not the reason, I would argue that it argues for the other letter, and it bears more on 4 than on 3.

NEEL: I would challenge that from your own formulation, that 10 just gives you a critical ratio.

CROW: All right.

NEEL: That 10 would be a critical ratio, and dividing point of relative importance.

CROW: Well, make it 6, you mean?

LEWONTIN: Or 20.

WALLACE: I'm a little bit confused. Did you say it would answer 10 to 3 or to 4? You've switched questions.

CROW: I've forgotten what $N$ and $Y$ means; that's the trouble. I think I wrote it backwards. If this can offer evidence against $S$, which means "no," yes to question 3. If
it can offer evidence in favor of $Y$, it is primarily "no" to question 4. I haven't thought this through.

LEVONTIN: I would like to say something about this later.

CROW: Let me take this part out for the moment. In any event, a high value of this argues that the answer to question 3 is $N$. Perhaps, a very high value argues that the answer to question 4 is also $N$, but more strongly for 3 than for 4.

Now, experiment No. 4—and some of these are classical experiments, but I would like to list them, anyway—

MULLER: You will take up later whether $A$ is discernible?

CROW: Yes. I think this is something we do want to discuss, but it could lead to quite a long discussion. At least, if the discussion is proportional to the number of words that have been written about it, it might run for quite a while.

Let me list the people who did the experiment.

I'm thinking of the direct effect of heterozygous effect of newly arising mutations done by Stern and Novitsky and their group, on the one hand, and by Muller and Campbell, on the other.

DOEZHANSKY: Nobody else? [Laughter]

MULLER: He was too modest to go into it.

CROW: Whom am I missing? Quite seriously, for new mutations—

WALLACE: Well, the other day, Wallace was mentioned. [Laughter]

CROW: Yes. Excuse me. I was thinking of additional experiments. I was distinguishing between heterozygous effects and new mutations.

WALLACE: Are you restricting this to new ones?

CROW: I'm restricting myself to the following experiment: where you induce a mutation, discover that it is
truly lethal, and test that in the heterozygous state.

WALLACE: We shouldn't forget the Stern's, on the spontaneous, because that is important.

ROBINSON: Where would Sprague and Schuler go?

CROW: Was that the same kind of thing?

LEWONTIN: No, double haploid, in other words, with the chromatic mutant.

ROBINSON: It wasn't all double haploid, was it?

DEMPSER: Schuler's experiments have touched on that.

MULLER: You also have the James experiments in yeast.

CROW: I don't have the Schuler experiment well enough in mind to discuss it, so someone else will have to do it. But is there anyone from Dr. Dobzhansky's laboratory who has done this experiment? I really didn't think I was overlooking anybody in this respect, who has induced the lethals or found them first, and then put them in the heterozygous state and tested them.

LEWONTIN: Cordeiro.

CROW: Are they newly induced?

LEWONTIN: No, they were population lethals. I'm sorry.

CROW: I think I was right in the first place. I'm not trying to be all-inclusive, anyway, so if somebody's priority is hurt, that's not the main purpose of this discussion. This bears on question 1 for lethals only. Most of Stern's were probably spontaneous, and most of Miller's.

MULLER: Excuse me, but James also applies to nonlethals.

CROW: Stern's experiments were mostly spontaneous, although they may have included a few radiation-induced. Miller's and Campbell's were all radiation-induced, but UV more than x-ray.

DOBZHANSKY: Was that published?
MÜLLER: Not in extenso, but I gave the conclusions in my 1956 paper.

DOBZHANSKY: Could one see the data?

MÜLLER: Certainly.

DOBZHANSKY: It would be good to have them published.

CROW: Well, they are available in some kind of mimeographed form, aren't they, for people who want them?

MÜLLER: They are available. I'm not sure that it's mimeographed, but I have some carbon copies.

CROW: The fifth experiment is of the kind that Cordeiro, Hiraizumi and I did, and some other experiments from South America, and several others. These have to do with doing the same kind of experiment, identifying the lethal first, and then directly testing its heterozygous effect. These bear on questions 2 and 3, it seems to me, with a possible "yes" or "no."

LEWONTIN: Don't you think they bear on No. 4?

If we discover that lethals are semidominant, for example, they have nothing to say about the expressed load.

CROW: Well, I guess, they bear on 4 in the fact that the right answer to 3 will tell you something about 4. They bear one way on 4, it seems to me.

DOBZHANSKY: Wallace's experiments have not contributed anything to that?

CROW: I've already talked about Wallace.

DOBZHANSKY: I mean, experiment 5.

WALLACE: We're being modest. He put my name up first, and we're not putting it up every time it appears.

CROW: I'm not trying to list every person who did this kind of experiment. It would take me the rest of the day.

DOBZHANSKY: Is that not somewhat selective?

LEWONTIN: I think it's an important point. It is important for us to decide on whether Wallace's experiment bears on any other experiment.
WALLACE: Wait a minute! What experiment are you talking about?

DOBZHANSKY: I mean the experiments published in 1961 and 1962, which were testing for heterozygous effects of lethals, sublethals, and semi-vitals, and so on.

WALLACE: I don't care whether I'm on there or not. I know what you're talking about, and I'm perfectly happy.

MULLER: We have to remember Falk, also, in connection with this. He is a very fine worker. He is the better worker in the field.

WALLACE: Yes, but Falk up in 30.

CROW: I'm sorry, but I'm trying to identify the kind of experiment, not credit the intelligence behind it.

On No. 6, I have the kind of experiment that, as far as I know, was first done by Dobzhansky and Wright, but since has been done by a great many people, which is the comparison of frequency of allelism, mutation rate, and frequency of lethals in the population. I'll put down Wright and Dobzhansky, plus everybody else in this room at one time or another.

It seems to me that this bears primarily on 2 and 3. I realize that you can't answer 3 without it telling you something about 4, but it seems to me that the immediate bearing of this particular experiment is on 3. What I'm talking about now is an experiment in which you obtain the following data: You make chromosomes homozygous from natural populations, you measure the frequency of lethals among such, which means that you are measuring the gene frequency in the equilibrium population rather than the phenotype frequency. You learn the mutation rate either in the same experiment or from some other source. You also measure the frequency of allelism, and you compare the frequency of lethal mutants in the population with what would be expected on the basis of the occurrence of the mutation rate and the rate at which these
have been eliminated. I think Wright and Dobzhansky were the first to argue this, maybe, I should say to suggest it.

DOBZHANSKY: I'm sorry, but that bears on No. 1, not on 2 or 3.

LEWONTIN: Not newly arising mutants.

CROW: These are in equilibrium.

DOBZHANSKY: Sorry, mutation rate. You determine it by newly arising mutants, obviously.

CROW: Right, but that doesn't mean that the experiment bears on that.

DOBZHANSKY: Well, then, you compare it with the possible rate of elimination due to homozygosis, not for newly arising mutants but of mutants which are in the population; so what you're dealing with is question 1.

CROW: I have to disagree. It seems to me that it bears on question 3.

DOBZHANSKY: I have to disagree, very clearly.

WALLACE: I would like to ask a question in connection with question 2. Suppose you find that—you are computing an average \( H \) out of these data, right? Suppose you find that it is slightly negative, which means the lethals are slightly heterotic. Let's assume that is what one finds, although no one has done it, apparently. Does that say the majority of loci in equilibrium populations have two or more alleles in class S?

CROW: Only if one equates the size of mutant effect in the two systems, as we have said. It bears more directly on this one.

WALLACE: I think that's the question. Isn't it possible that the \( H \) you get, let's say, which is a negative value on the average, is due to a small number of loci?

CROW: Yes, with a big effect averaged over a much larger number with a small effect. Perhaps, I should put parentheses around both 2 and 3 here.

DOBZHANSKY: I think we should be able to agree
at least with this. You are comparing mutation rates, obviously, for the newly arising mutations; correct? with the computed elimination rate on mutations which you are finding in the natural population. Right?

CROW: Yes.

DOBZHANSKY: Doesn’t that bear on question 1?

CROW: [Laughter] No. Maybe, somebody else could explain it.

DOBZHANSKY: Suppose half of the mutations which arise are deleterious and quickly eliminated, and the other half are retained in the population. The rate of homozygosis of this second half and the rate of mutations producing them would not be the entire mutation rate, but only part of it.

LEWONTIN: Excuse me, but, in your experiment, did you test the heterozygous effect of newly arising mutants, or did you just use the mutation rate as a parameter for the rest?

DOBZHANSKY: That is precisely what you do. You must use the mutation rate.

LEWONTIN: But you do not ask the question directly, what is the average heterozygous effect of the new mutants in your experiment?

DOBZHANSKY: Consequently, you get the average heterozygous effects of mutants which arise, not of the mutants which are in the population.

CROW: No, you get the heterozygous effect of the mutants that are in the population. Look, you were the first person to do this kind of experiment, or you and Professor Wright. Maybe, he did the algebra.

ROBINSON: Maybe, this is putting the question another way, but I started to ask this question originally, and I think this is the argument. Where does the experiment that bears on mutation rate fit into this?

CROW: I don’t want to get involved in a lot of algebra, and it may not be possible--
ROBINSON: I mean, which one of these four? I think that is the argument here.

CROW: Well, I've just about exhausted my ability to say this, but let me try it again. The items of data that one uses here are the frequencies of lethals in the natural populations, and the frequency of allelism amongst these lethals in a natural population. Then, one brings in as another necessary parameter, the mutation rate as measured from some independent experiment, almost always. Now, one can predict, thinking of a single locus, the average dominance of this particular locus, but the particular gene whose dominance you are measuring is a gene that is in the population.

LEWONTIN: But, Jim, I think, I've just realized what Dr. Dobzhansky is saying. He is saying that, nevertheless, the difference between the standing number of lethals in the population and what you get by mutation must be due to elimination of mutants, or to an accumulation of mutants, whichever way the difference happens to go, and therefore it is evidence, in fact, of the way in which these mutants are acting when they arise.

CROW: Yes, through the other question.

LEWONTIN: Suppose newly arising mutants, on the average, are heterotic. Then, you will find a vast number of lethals in the population as compared with the rate of mutation. If they are semidominant, you will have a filtering out of them. It can, in fact, therefore, bear on question 1.

CROW: O.K., in the sense that an answer to question 2 is always bearing on 1.

DOBZHANSKY: No, I don't think it bears on 2 and 3 at all.

LEWONTIN: In the sense that the comparison of the rate of arising with the standing number must be a result of the selection process between the time the mutant arises and the equilibrium situation.
CROW: Yes, Dick, but there is another point that you haven't mentioned, that comes into this. If you are doing this for a single mutant, that's fine, but now, what you're doing is averaging second chromosomes in the population. How are these weighted? They are weighted by the frequency of the occurrence of lethals in that population. That means they are going to be most heavily weighted in terms of those mutants which have persisted in the population. Therefore, you are measuring the average dominance of those mutants which have persisted in the population long enough for you to pick them out.

LEWONTIN: That's true.

CROW: So, then, you are measuring the average dominance of a group of mutants that have persisted in the population rather than the average dominance of a group of mutants at the time of arrival. This is different.

NEEL: Coffee is waiting.

CROW: This is a good point to discuss over coffee, but I'm pretty sure I'm right about this.

LEVENE: You're both right.

[Recess]

NEEL: I think it would be quite noncontroversial if I were to write a letter to the Macy Foundation, expressing our appreciation for the last three days. [Applause]

DICKERSON: It may be too early to say. [Laughter]

CROW: The one surviving person is empowered to write the letter. Well, let me rather quickly put down my remaining points. I am conscious of having taken up too much time already.

MULLER: I think most of us would agree that we and not you took up the time. [Laughter]

CROW: There are some kinds of experiments that have been used at various times by corn breeders that, it seems to me, may have some bearing on the question, although they have not been widely discussed. Dickerson has done a little bit of
this kind of work. I have in mind some of the ideas growing out of the suggestions of Hull on constant pair regression techniques, that bear on question 4, it seems to me. It would be more probable to be definitive if the answer were "yes" instead of "no," that is, this tailing off at the top of the regression, if it were sharp, would argue for overdominance. In the absence of that, I think, it is consistent with several hypotheses. However, this has not been widely used, and I'm putting it in here mainly because of the fact that it has played such a large historical part in the discussions among corn breeders in this country.

I also think that experiments such as--I don't know what to call them, but the kind that Ritchie and Sprague and others have done, of recurrent conversion improvement--

ROBINSON: Call them "conversion improvement," I guess.

CROW: In fact, some of the strongest evidence existing ten years ago, it seems to me, for partial dominance or at least not overdominance of corn yield came out of this kind of experiment, and I was the most shaken in 1948 by Ritchie and Sprague's papers, more than by any other data existing at that time, in arguing for overdominance as an argument in corn yield. Anyhow, it bears on question 4, on positive regression. Regression argues strongly for "no." I think no slope at all is uninterpretable on this, and this is part of the problem, too.

LEWONTIN: For the benefit of the Drosophilists, I take it, the Sprague and Ritchie experiments are essentially the same as regressive homozygous on heterozygous?

CROW: In principle, yes, but this is the effect of seeing the selection for combining of one type, if it makes it improved in ability to combine with other types.

LEWONTIN: Would you include this regression of homozygous on heterozygous?

CROW: I was coming to that. I was going to
LEWONTIN: Because that is always one-sided.

CROW: Yes, regression of homozygote on heterozygote.

ROBINSON: What is the difference between that and No. 7?

CROW: What Hull did was to do regression of homozygote on heterozygote, holding the one parent constant through a whole series, whereas, now, these are general regressions of homozygote on heterozygote, done mainly by Wallace and Dobzhansky in Drosophila. This bears on question No. 4.

It seems to me that this can provide a "no" answer if the regression is strong and positive, but that a "no" slope is uninterpretable in terms of these kinds of questions. This may be debatable, because I'm not sure whether Bruce would agree with this statement. As a matter of fact, I'm pretty sure he wouldn't. Let me leave this one out, because it is in the future rather than the past, but I would like to mention it, nonetheless; that one approach to the question is that if we know the nature of lethals in the population, that is, if we can assume that the typical lethal is partially dominant, and let's just assume for the moment that we do know that--if we know that, then, we can ask the question about whether the typical detrimental is also partially dominant by the relative rate of accumulation of detrimental in the population, and comparison with lethals in the population.

The information I need to know to answer this is the ratio of the load due to detrimental to that due to lethals for two populations, on new groups of mutants and an equilibrium group of mutants.

Now, I have been stymied in this kind of experiment because of the difficulty of getting a measurement of this quantity for new mutants. It ought to be done for spontaneous mutants if you're going to make the population comparison for
spontaneous mutants. This means that, operationally, this is a very difficult experiment. Nobody, so far as I know, has any convincing data on it. It seems to me, though, to be about the most unambiguous approach to this on Drosophila, by Drosophila methodology.

There are two important points--

WALLACE: What symbol are you going to put down there?

CROW: Let's say D/L, and D stands for detrimental load, and L stands for lethal load, in new versus equilibrium.

LEWONTIN: What question does this answer, Jim?

CROW: It answers question No. 1, I think.

LEWONTIN: I think, in the same way that Wright and Dobzhansky answer question 1; right?

CROW: It answers question 1 in an average sort of way, and if one kind of locus is ordinarily having a big effect and another kind of locus is having a small effect, this average can be misleading, as has been abundantly pointed out this morning.

Finally, or next to finally, there is the direct measurement of the segregation load, mainly by Morton, for specific human traits. The idea here is primarily Morton's. I had it all algebraically and didn't know what it meant. He saw what it meant. The idea is that if the population is at equilibrium, and if you define segregation load as I have defined it, then, you can estimate this from a surprisingly minimal piece of information; namely, the frequency of the trait under consideration, if it is due to a homozygous recessive, and the deleterious effect of that particular trait in the homozygote. From this information, you can estimate the segregation load, irrespective of the number of alleles involved in the locus or irrespective of the mechanism that maintains them, as long as it is at equilibrium, under selective balance.

It seems to me like a very powerful principle.
This is a minimum estimate. It is an inequality rather than an equality. But this does mean, given the facts, say, that phenylketonuria is lethal in a natural population, then, you can estimate the segregation load that would be required to maintain phenylketonuria, if it were at equilibrium under this mechanism.

It seems to me that this bears on question 2, in one sense at least, that there must be—although I don't have any better idea than anybody else exactly how to define it—an upper limit somehow on the total amount of variability or the total load that a population can have, and, the more segregation loci there are, as Dr. Wright has frequently pointed out, the less selection can be brought to bear on any one of them. The more random drift becomes important, the more difficult it is to explain the population structure with too many polymorphisms in it. But I don't know how to set a meaningful limit on this. Perhaps, we could discuss what approaches we have to that question. This is what I would rather like to do, at least for the remainder of the day.

In any event, that bears on question No. 2, it seems to me, and we can answer it in only one direction; that is, if it looks as if there is too much of the segregation load, then, some of these must be maintained by other mechanisms, and so no answer is the "yes" answer.

NEEL: But, Jim, I think, there is one problem. In one of your papers, you have referred to the traits that have been worked with, as muscular dystrophy and so on, as having been selected because they have the frequency at which they could be maintained by recurring mutation, and I would say that your arguments extrapolated from such traits have no value, because you already have a very special selected class. If you can show that muscular dystrophy is not being maintained by segregational load, I don't know—

CROW: Does it show it very much? This may be right.
NEEL: I don't know the conditions that you're talking about here.

CROW: If one is willing to say that one simply shows what is already obvious by this mechanism, I have no objection.

NEEL: But in one of your other papers, you have said these were selected because they had about the frequency where they would be maintained by mutation, so you end up showing they have the frequency about where they should be maintained by mutation.

CROW: And, if this isn't true, there is a measurable segregation load, which seems too large. Therefore, I simply reinforce what already seemed comparable. This is not circular reasoning, though. I want to make a distinction. I am reinforcing a conclusion that already seemed probable, so it is not circular.

NEEL: That this very special class is probably maintained by mutation, which nobody would ever have disputed.

CROW: All right, but I think human genetics is not so well established but that some well-established conclusions can still be checked.

DEMPSTER: I question that remark, because I'm sitting very close to a person who, on occasion, told me he thought it was not improbable that the fitness of the population was due to a number of these rather drastic genes. They have rather drastic deleterious effects on homozygotes. He didn't say this was true, but he put it as a very plausible hypothesis. Wouldn't you agree with that, Dr. Dobzhansky, that you have entertained quite seriously the hypothesis that the well-being of man is dependent, or might be dependent, to a very considerable extent, on heterozygosis for a number of genes which are quite deleterious to homozygotes?

DOBZHANSKY: Only after several cocktails. [Laughter]

MULLER: Isn't that when people's true nature comes out? [Laughter]
DOBZHANSKY: Professor Muller, you have scored a point. [Laughter]

CROW: Well, if there is nobody here to defend the possibility that most ordinary recessive genes are segregational, we'll drop it. I think this means that the people in this room are honor bound not to raise this as a hypothesis in the future, or at least not without disclaiming what they said here.

MULLER: That most rare recessives are.

CROW: That's right. To me, it is not that self-evident, Jim. I don't want to be a segregationist, but--[laughter]

CROW: You want to be an integrationist?

CROW: Yes. Well, the twelfth possibility, I want to say, too, is not totally irrelevant.

WALLACE: What is that?

CROW: Minimum segregation load. It seems to me that there is a place for a little bit of theoretical work that Moto, Kimura and I have done recently, bearing on the question in this fashion: Suppose we ask how much selection it takes to maintain a polymorphism, loading the difficulties in every way we can to minimize the amount of selection. What can a population do, if it would like, as it were, to maintain the maximum number of polymorphisms? One thing it can do is to have as many alleles as possible, assuming that all mutually heterozygous combinations are beneficial, and, if it turns out that there is a locus or there are several loci which have this property, that there are multiple alleles, any combination of which is beneficial and any homozygous combination of which is deleterious, then, the larger the number of such alleles in general, the smaller will be the segregation load, just because the more alleles there are, the larger the ratio of homozygotes to heterozygotes.

The limit placed on this process is random drift, I think, because the tendency for alleles to be lost from the
population by random drift is not very large when the number of alleles is small, but, when they get to be large, this becomes very large, because the random-drift effect, as Dr. Wright, Kimura or somebody has shown, is proportional to the square of the number of alleles involved in the multiallelic locus; so, once you get up to twenty or thirty alleles, random drift becomes very important even in the large population and even with fairly strong selection.

Therefore, one could ask for a given selective advantage of homozygotes, and let the population have at its disposal all the alleles arising by mutation that it can make use of. What, in fact, will it do? There will be an equilibrium reached by most of the random drift and, again, of new alleles given mutation. One can ask what the segregation load would be in such a system. You see, clearly, there is going to be a segregation load. If you increase the number of alleles, they tend to be lost by random drift, so these will come to equilibrium at a certain point and, at that point, the segregation load will be minimized.

WALLACE: Won't there also be the load which will be 1/N, the number of alleles which are maintained times the selection you put in?

CROW: That is exactly it.

WALLACE: That is a chance load; in other words, you can think of a load imposed by chance. The chance loss of these alleles must impose a certain load. It is the frequency of homozygotes times the deleterious effect of the homozygotes, because if all the alleles have been kept--

CROW: This is purely what I am defining as the load.

WALLACE: But that is chance.

CROW: Call it chance, if you want to.

WALLACE: Because the alleles aren't there, because they are lost by chance.

CROW: Well, I'm talking about an existing
population relative to a population made up only of homozygotes.

WALLACE: That's right, but since you said these alleles are lost by random drift, this is a chance load.

CROW: I don't care what you call it, but I think we agree as to what we are measuring. The magnitude of this can be quite small. Let me see if I can find my notes, to give you just one illustration. Suppose I take the S value to be .01. By that, I mean that the homozygotes are 1 per cent less fit than heterozygotes. The minimum segregation load for such a locus in a population---I took a population of effective size, 10,000---excuse me a minute. I'm not sure about that and I would like to check it.

Yes, I took an effective population number of 10,000, with selected disadvantage of 1 per cent. If we say that a substantial minority is 50 per cent of all loci, in other words, say, 5000 loci, then, for 5000 loci, the segregation load is about 6. The load per locus under this assumption is \(1.2 \times 10^{-3}\).

WALLACE: How many alleles are obtained there?

CROW: I've forgotten, but it is quite a large number, 20 or 30 or something like that.

LEMONTIN: In such a large population?

CROW: Yes, this is a large population and it can maintain a large number of alleles. I'll look up in a minute what the number of alleles is. Anyway, the load imposed by maintaining this number of alleles, whatever it is, is 1000. Therefore, if I have 5000 loci, if they are independent of each other at least, this would be 5000 times this, or, roughly: \(e^{-6}\), which is .002.

This is the kind of argument I am trying to make, that this seems to be like an improbably large load for a population to bear. This would mean that the average of the population has a fitness of .552 relative to the individual who is heterozygous at all the loci.
LEWONTIN: It isn't the load; it is the proportion of individuals.

CROW: But the load is .998.

LEWONTIN: The proportion of individuals?

CROW: Yes, so all I have to say is that if this is true--now, remember, we're assuming independence of action of these genes. The effect of synergism or the effect of epistasis depends a little on the direction of it. But it seems to me, as a qualitative argument, this has some weight; that is to say, if there are this many segregating loci, then, if I could obtain an individual heterozygous for every loci, it would be 500 times as viable as the present average of the population. To me, it is inconceivable to think of a fly with 500 times the fitness of the existing mean; ergo, I would rule out this kind of hypothesis on this kind of ground.

LEWONTIN: But let's emphasize this in answer to question 2, which is the number of loci and not the relative contribution to the total load.

CROW: That's right.

LEWONTIN: That point has been missed too frequently, I think, not to repeat it.

CROW: That's all I have to say by way of introduction. [Laughter] Now, I'll start my main talk.

DOBZHANSKY: Professor Crow, would it be possible to introduce point 13--which is an unlucky number--but has the comparative study of genetic loads in different populations of a species and different species, living in different ecological conditions, anything of interest to contribute to this general problem?

CROW: Well, it is not obvious to me how it contributes to these particular questions, Dr. Dobzhansky. It may have tremendous interest, but for other reasons.

MORTON: There is one case I can think of easily, and that is Wernicke's studies on two types of bees, those where there is a balanced lethal sex determining system and those where there is not. The loads seem to be quite consistent
with the mutational hypothesis.

MULLER: In studies on bees by whom?

MORTON: Werniker. At least, that is how he interprets them. I wouldn't agree with him.

CROW: These are simply the things I can think of. I'm sure other people will have other experiments.

BODMER: I would like to bring up, tentatively, some information in biochemical genetics, a little bit more detailed knowledge of the way the genes work that we have now, and what bearing that might have on this. It is difficult to formulate something specific, but I think, certainly, to my mind, intuitively, it argues strongly against 1, what knowledge we have nowadays in terms of the way genes work. To my mind, it makes it very unlikely, for example, that 1 is a possibility; so it seems to me that one should really add to this list something to indicate that we do know a little bit about how genes work nowadays.

DICKERSON: Primarily or secondarily?

CROW: We have known quite a bit about how genes work for quite a while. I have laid down for myself a set of rules, that I was trying to specify here experiments of a population genetic type. It is perfectly clear to me that once one knows enough about DNA and proteins, the answer to question 1 should be known. Maybe, we should simply shut up until that time comes.

BODMER: I don't think that is so.

LEVONTIN: I disagree entirely. You may not know what the primary products, protein products, of a heterozygote may be, but to ask what effect this heterozygote may have on fitness is not a question of knowing all about DNA, sir. It is a question of knowing all about development in physiology, in different environments. That is a much different question.

BODMER: You would have to combine the two sorts of studies.

CROW: I agree. Anyhow, question 2, I can conceive
of answering by biochemical methods. You simply ask whether an existing population is polymorphic.

LÉVONTIN: That's right.

NEEL: Jim, would you accept another line of evidence here? That is, the study of the structure of natural populations. For instance, you have put down that $N$ equalled 10,000 with respect to man, and $N$ probably equalled 50 for most of his time on earth. Yet, we see these extreme polymorphisms. This is true for many of the small mammals we have been talking about. Don't you get some valuable circumstantial evidence out of defining the structure of populations?

CROW: It is certainly worth pointing out that if $N$ were changed from 10,000 to 100, this quantity would change to $e^{-600}$.

DOBZHANSKY: Mr. Chairman, this is identical to what I have suggested, and which was rejected.

NEEL: I'm sorry not to have had the perspicacity to recognize at the moment that we were on the same side.

CROW: Let me go first to Kim, who said something I didn't hear just now.

ATWOOD: I don't know what I said, but I object to the cavalier attitude with which the remark about the molecular age has been rejected. The point is that if No.1 were true, you would have to say that, in given individuals, the population of protein molecules of a given species is polymorphic. This is just not the case.

CROW: I agree.

NEEL: So it is perfectly obvious that 1 is false. If the answer is "no" to it, and we can just say, a priori, it is "no," because the reason it is "no" is pushed far in the background, we don't even know where it originated.

ROBINSON: Jim, when you were discussing the 1948-1952 work, you remember, in terms of whether, on No. 4, you put a Y and N in terms of corn, the hypothesis which you put forth then involved this question of population structure.
The best possible hybrid which might be developed from lines out of an equilibrium population, you remember, is that 5 per cent figure. Now, in the first place, you've changed this--

CROW: Well, I changed it only by saying I didn't forget partial dominance. I really don't know about the partial dominance.

ROBINSON: All right. Where does this bring you with regard to this 5 per cent value?

CROW: I made it 5 per cent instead of 20 per cent.

ROBINSON: All right. We've gone ahead with these random lines I was talking about, and recently have done extensive studies on making the intercross between these lines. That is a type of evidence which bears very directly on this.

CROW: Good! Can you describe it briefly?

ROBINSON: In Dr. Cross's discussion on his 1948 and 1952 work, when he visited us, that was one of the reasons we went into making these random lines, because of his hypothesis and his theory that he had come out with, of the best possible combination, if we can assume that these are equilibrium populations, of course, which he indicated we could do. Well, then, in a recent study from lines with these populations, from a very high number of intercrossings with these lines, we were looking to see what would be the range of the yield, the distribution of the yield, when you intercrossed these random lines of seven or ten generations of inbreeding.

All we came up with was on the high side. Some were 32 to 33 per cent above the average of the open pollination or this equilibrium population itself, which is far beyond even your adjusted figure here, which seems to me another line of evidence, and a very important line.

CROW: In favor of the hypothesis, say, D instead of B?

ROBINSON: Right. In both cases, with the various interline crosses and with the Indian Chief, they are running from 30 to 35 per cent; that is, the best possible combination
of lines, again, just a cyclic production of a whole series
of intercrosses among these random lines. The objection to
it is the fact that there has been some selection. We went
into this on Monday.

CROSS: Yes. I'm still caught between what you
are saying and what Kim was saying. What I really wanted to
say, or should have said, was not to dismiss the suggestion
of the molecular geneticists as irrelevant, because it obvi-
ously is relevant, but to say, on my own views, the physio-
logic genes, which I thought were pretty universally accepted
views, are "yes" as the answer to question 1. This was pretty
much a priori before anyone did any experiment. It was only
the fact that the question was raised by some people that I
thought it worth discussing. I think the general reluctance
to accept Bruce's results has nothing to do with the goodness
or badness of the experiment; in fact, I think it is pretty
good. Its a priori plausibility or likelihood of results in
terms of the conventional notion one has of gene action--

WALLACE: You're talking about a class of genes
charged with responsibility for making the proteins, and it
seems to me that you're forgetting the controlling elements
and lots of other things of the genome.

LEWONTIN: You see, the point Kim has made, perfect-
ly correctly, is that if we could find out that there was very
little difference in protein, then we would know the structural
genes, at least, are not very heterozygous in the populations.
That would be a direct answer to question 2, but it is not an
answer to question 1, for this reason, which I did not dismiss
cavalierly; namely, that the question of the possibility of
heterotic mutations and whether new mutations can be heterotic
and in what proportion is a question of a terminal point in
the developmental sequence, not an initial point.

BODMER: But if every new mutant were heterotic,
then, every locus would be polymorphic, and the species would
lose its identity.
LEWONTIN: That is not true, as Jim has pointed out. In a finite population, even if most new mutants were heterotic, you still could not maintain an awful lot of them, because of the fact that the population is finite.

BODMER: But you would have up to twenty or thirty alleles polymorphic in every single locus.

LEWONTIN: In a population size of 10,000?

MILLER: You would have two or three, anyway, wouldn't you, very commonly?

BODMER: Yes, and, even if it is one, it would be inconsistent.

LEWONTIN: This is another way to knowing the answer to 2 may give you the answer to 1, but knowing the answer to 1 doesn't necessarily give you an answer to 2. That's all we're saying. A priori information about the mutations and the nature of developmental processes can tell you something about whether mutations can be heterotic. That is absolutely true, but they are two different questions.

GLASS: It seems to me there is one other bit of evidence on the biochemical side that makes the considerations that have been mentioned a little less certain; that is, the increasing evidence that most enzymes, or at least a great many, exist in the form of varieties, which have been called isozymes, and that in at least the best analyzed case, these are various combinations, all possible tetrameric combinations of two essential polypeptide components; so we don't know what the genetic background of these is.

We know fairly well what the relation of certain genes to certain polypeptide structures is, but we don't know as yet, or we don't have very much knowledge, how these polypeptides are controlled genetically in their assemblage into various tetrameric or other kinds of combinations, which are often the functional developmental units.

CROW: I wonder if I could suggest procedure for a moment? There are two or three people who have specifically
said they would like to have the floor briefly this morning, and I think, perhaps, I should call on them first, and then have a general discussion. Dr. Li has written three articles critical of the third concept here and would like to discuss this. Let me say something about it in advance: that if it turns out that 3 is an idea which may or may not be good, but on which the data are likely to be so poor that we can't use them, this means, perhaps, there is not too much point in discussing it. However, this is as Dr. Li and the rest of the group wish. I'm perfectly willing to go on with it.

LI: The discussion in the last few minutes has spoiled my wish, because this meeting has reminded me of the genetic meetings I used to attend twenty years ago, when we just talked about crosses and offspring and no DNA in the molecule and so forth. I was saying that this is the kind of genetic meeting I haven't attended for years. But, in the last few minutes, DNA has come up. [Laughter]

Before I talk about the main topic of load or issue and so forth, I have several other unrelated points, which I wanted to state but didn't have a chance. I was sitting behind the projector all the time.

This is Dr. Sewall Wright's correlation coefficient—well, there are two approaches to this problem. One is the classical approach. This is the thing I learned early in the thirties. Now, we have the probability approach. I personally have used this correlation all the time. I admit it is not the simplest. Sometimes, this probability approach is simpler. But I stick with the correlation method. I have heard two explanations for it. Both of them are true. One is, I'm old-fashioned. That is very true. The second explanation is that I don't speak French, but I did get an English translation from Jim, ten years ago, when you made a rough translation and I got hold of a copy. A recent addition to this is the reason Dr. Wright brought up yesterday. But I have a personal reason, as to why I would rather use correlation than probability.
In developing a genetic method, you have two acid
tests. One is to generalize the multiple alleles and see
how it works, and the other acid test is to generalize it
with sex-linked genes. With respect to sex-linked genes, I
could get the right correlation coefficient simply by a proba-
bility argument, because, conceptually, these are really two
different things. Correlation ordinarily has no direct physi-
cal meaning. It is an index of associations. For sex-linked,
we have a correlation like this [indicating on board]. You see,
I can obtain this correlation coefficient very easily by the
correlation method, but I couldn't reach probability with this.

Another example is this [2 over the square of 2].
When you read Monteil's book, therefore, what is in there is
elegant, but what is not in there is also significant. He
never mentions this business of bringing it to sex-linked
genics, you see. I think I'm going to stay old-fashioned.

CROW: What is this 2 over the square of 2 the
correlation of?

LEWONTIN: For sex-linked genes.

LI: Yes, sex-linked genes, simply because we don't
have a symmetrical correlation table. For autosomal genes,
it works so well because it is always on 3 x 3 or 6 x 5, but
for a correlation table of this kind, on a 2 x 3--well, we
have no trouble in calculating the correlation, but I couldn't
argue on the basis of probability any more. But let me go on.

CROW: Is it fair to interpose a remark? I think
it is proper to say that if you are computing a correlation co-
efficient, the correlation is the direct way to do it. If the
question is one of inbreeding, it seems to me that to argue
that one is better than the other, when there are two ways of
solving problems, doesn't really answer it.

LI: No, I hate to use the word "better" or "worse."

CROW: I'm sure you could arrive at almost any
answer either way, so this is a matter of personal preference.

LI: If you don't talk about any particular case,
if you review the entire field of population genetics, you will find the correlation method is more versatile. You can use it from the beginning to the very end. But the probability method is very powerful with respect to one particular problem.

For the second point, it is more interesting. It is this: I used to see Jim Crow every year but for the last three years, I haven't seen him. The very first day, when we saw each other, as long-lost friends, he said, "We should have seen each other more often than we did." While this is a sort of isolation, I said, "Good"—you know, Dr. Crow and I, both of us together, have managed to prove one of the basic theories in evolution; that is, evolution by isolation. When you are isolated from each other, you are bound to divert. That is a law of nature. [Laughter] At least, I think, Jim and I have proved this. If nothing else, that one point is already worth while. In view of this, I think that the Macy Foundation probably should promote more isolation rather than more conferences. [Laughter]

SLATIS: But this gives us the chance for competition, so you can get selection and survival of the fittest.

LI: The next point is to argue about an issue. I made a statement like this: [Writing on board, "The light is green."] Or you ask me about the color of the light, and I say, "The light is green." You immediately say, "You didn't spell it right." From now on, the discussion is all about spelling, how it is spelled in Webster, how it was spelled in the sixteenth century, and nobody bothers about the original statement any more. [Laughter] This bothers me quite a lot.

My original statement is about the inbreeding method, to distinguish two types of equilibrium. This was my original statement, and Jim and I agreed not to bring up any published results, to which I agreed.

CROW: Incidentally, I don't object to this.

LI: Yes, I think it's a good rule; otherwise, we could go on to next week. I wouldn't want to mention old things, but I do want to mention a few things. These are the points
that I would like to list, in the fashion of Dr. Crow, 1, 2, 3, 4, 5, and 6. Of the six points, I will probably talk only about No. 5, and just mention the title of No. 6.

No. 1 is the classification of types of equilibrium. This is different from what Dr. Crow has on the other side of this board. He is talking about the alleles, the effect on the heterozygous, and so forth. I'm talking about the type of equilibrium.

Usually, we classify these as the mutational type, and then we try to distinguish them. In order to distinguish them, we apply a kind of test. You can take any kind of test you can think of, but the purpose is to distinguish between the two types of equilibrium. This is the main purpose. I personally thought that this very premise is not satisfying to me, from the very beginning, because this is like going to a fruit stand. You will see a hundred kinds of fruits there, and you try to classify them. Before you see the fruit, you have already agreed to classify them into two types. One is an apple and one is a banana. There are only two kinds of fruit, to begin with. In your own mind, then, you pick up a pear. Then, I couldn't call it a pear because, on the blackboard, there are only two types of equilibrium. When I see the pear, then, I am forced to call it an apple. From the very beginning, there are two types of equilibrium specified, and, from then on, I am going to classify this into this or that.

This point is not very satisfying to me, because I thought this is the attitude of a lawyer rather than a naturalist. You see, a lawyer has a printed book. If you do something wrong, he has to fit you into one of the charges in the book. He cannot charge you with something which is not in the law books. The naturalist is doing the opposite. He goes off to nature and tries to find out what there is, and then comes back and classifies it. I thought of the concept of classifying equilibrium into two types; yet, this very approach is somehow not satisfying enough for me.
The basic reason is that I must say there are hundreds of kinds of equilibrium in nature. We don't know them, simply because of our own ignorance, not because of the diversity of nature. We have no right to classify them into apple and banana and nothing else. This is the first point.

The second point is to describe a difference. In describing a difference, there are many ways, but this is the question Jim Neel kept on asking, and Dr. Crow didn't have a chance to answer. There are so many other questions involved. What Dr. Neel actually was asking was this: Suppose I have this height and this one; ordinarily, I would compare these two. I would say this is five inches taller, or I can take the ratio and say this is 100 per cent higher than this, and that's all. The load ratio, he has defined now, as being like this: We don't measure things from the bottom. We measure the height from the ceiling down. We assume that there is a ceiling and we measure this space between the ceiling and the height. Here, we assume a ceiling and we measure this, and then we compare the two. This, essentially, is the load-ratio method.

If you identify this with the mean, then, this is the deviation of the mean from the highest possible point. The ceilings are not at the same level. I can modify the load ratio in a number of ways such as this [lowering ceiling]. Then, these two ratios would be enormous. If I am not satisfied with this, I will put this ceiling up here, and then the load would be even more tremendous. Actually, this [ceiling height] is unknown. There is no way to determine the maximum fitness of an unknown genotype. That is the second point.

These points are all controversial, but I will go over them very quickly.

The third point is inbreeding is a diagnostic tool. Well, since we don't know which type of equilibrium it is, this is just like the interpretation of urine sugar or blood count. We apply a test here. We subject the population to
inbreeding without determining gene frequency. By that method, we hope we compare the difference between the two types. Then, essentially, the controversy is, somebody says we can, and somebody else says we cannot. I'm not going to go into that controversy again, but this is the main point of my theory. I say, when you subject a population to inbreeding, there are a lot of hidden recessives to get out, and this would be true regardless of the type of equilibrium. Whether it is one type of equilibrium or another, upon inbreeding, you get the same segregation phenomena. But they do have a very strong argument in favor of this method. By the way, this is the only major point here in the whole thing.

No. 4 is the mortality data. One of the strongest arguments of the load-ratio people is that we don't claim very much. We admit that load ratio doesn't work all the time. But, surely, it can be applied in a very straightforward manner with mortality data, because mortality data give you a measurement of fitness from zero to 1. You see, mortality is zero, so your fitness is 1. So in such a clearcut case, your load-ratio method would work. Most of the examples are with mortality data. My impression is, again, exactly the opposite. Of all the human data we can collect, mortality data are the least usable, and I'll tell you why.

Here is a type of family, and this is the number of births and the number of deaths [two births and zero deaths], number alive, two. Mortality is zero. You have two children. Everybody survived. The mortality is zero. In another type of family, the births are 8, 3 died, and 5 survived. The mortality is .375; 37 per cent mortality.

This is fine. When you talk about fitness, what can you say here? The mortality people would say that the mortality of the first family is zero. This is the highest frequency. I call it 1. This mortality is 37 per cent, so it should be less fit. This is not the case at all. These mortality data
do not tell us the fitness, because, if you take the number of live children, this contributed only two children, and the second family contributed five. While these mortality data are useful, the usual impression of people who are not dealing with mortality data is that the higher the mortality, the less children you have. This is assuming that the number of births remain constant. The more who died, of course, the less are left. But this is not true in human populations at all. The opposite is true. The higher the mortality, the larger the size of the family. Mortality is positively associated with size. The larger family has mortality, and the smaller family does not.

How are we going to assume the fitness value in order to calculate the load?

LEWONTIN: May I ask, Dr. Li, whether the observed positive correlation between mortality and fertility, which is obvious from what you are saying—do you assume this is a genetic correlation or a socioeconomic correlation?

LI: Whatever it is, it is there.

LEWONTIN: But suppose the correlation were the opposite, genetically; would you not take this out by your socioeconomic regressions, which we talked about on the first day? I don't know. Would you or wouldn't you?

NEEL: No, you would not.

LEWONTIN: All right.

NEEL: At least, the kinds we talked about would not get at that.

DEMPSTER: Yes, but it seems to me that the question arises, in negative correlation, if that should be recent, say, in terms of two or three thousand years in human experience, due to socioeconomic factors, then, the size of the family is now a useless measurement for us, but the mortality remains, and it may still represent a genotype having the same impact as it did many years ago. That is a possibility.
NEEL: I agree, and I can only say we're doing our best to get data of that nature on very primitive populations right now.

DEMPSTER: So I don't think we can just throw mortality away because of this correlation.

NEEL: No, but we can raise some serious questions about it.

LI: All I can do is raise a question. I don't claim that every family is like this.

MORTON: Is it generally true that people agree that the number of sternopleural bristles is something in which we should all be interested, but mortality is something we shouldn't be?

DICKERSON: I won't buy that.

DOBZHANSKY: Absolutely. Since Professor Dempster ascribed to me an opinion that lethals were what kept man going, I think that I can ascribe that opinion to Dr. Lewontin.

LI: Well, the last point is correspondence. The correspondence always bothers me a good deal. This means, when you get a body of human data, you can calculate all kinds of things. This, I will call the statistical or observed effects. On the other side, we have a set of genetic parameters which are specified by our selection, the load ratio, the definition of the load, and so on. We have one set of observed things, and, on the other side, we have one set of abstract thinking. How are we to establish the correspondence between the two?

I think, in one paper, the distribution of number of children in families was mentioned as an index of natural selection, and so on and so forth. But, on the other hand, if you say that the distribution of the number of size has nothing to do with natural selection, it would be equally true, at this moment of ignorance, because, if we are all of the same genotype, we still have a distribution of number of children in the population. In going through these papers, I think,
therefore, some of us have taken for granted that each statistical observation has a genetic core; so this parameter corresponded to that, and this with that. This, I have grave doubts about.

Before we can apply this method, we have to be clear about all these five points. Any one of the five would cast doubt on the meaning of the ratio. What I have been talking about, then, is really a set of preliminary and elementary considerations behind the things that Dr. Crow talked about, on the other side of the board. If we could not get any agreement on any of these five points first, then, I don't see any concrete physical meaning of this ratio at all.

No. 6, and I promised you I wouldn't talk about this, so I'll just put the title down and leave it [Social Effects.]

Well, I am privileged to have a front row, so I can watch my various friends react. I know you are all experimental scientists, but if you devote a small fraction of your time to studying sociology, I think, you will agree with me that human beings are more interesting than corn, mice, or Drosophila.

NEEL: Dr. Li, before you sit down, under your No. 1 classification, you pointed out other models which should be brought into the picture. Would you care to elaborate on that a little bit?

LI: Well, as I said, I would be the first one to admit my ignorance, but our ignorance has nothing to do with the true state of nature. Just to give you one example of the kind we have been talking about, mitotic drive, my philosophy is that each type of equilibrium has a story behind it; each type of equilibrium has to be studied per se. You see, if we keep out the pear, we have to call it a pear. If we pick it out, we cannot force it to be either an apple or a banana.

I can give you a third kind. A certain gene
frequency may not be able to be maintained by heterozygous advantage alone. Maybe, the advantage is only slightly advantageous, but the gene, for instance, is higher than that that can be explained by this. On the other hand, it cannot be explained by mutation rate alone. It could very well and easily be that we have a low mutation rate and a low heterosis. These two factors coincide.

Then, finally, we get an equilibrium. This is the point; this heterosis and the mutation are not mutually exclusive. Why do we have to divide them so clearcut? Mutations occur all the time, in all populations, in all loci, and, in some of the heterozygous, the heterozygous are better, and in other cases, they are worse than the normal heterozygotes. With both of the forces, shall we say, existing in the population, why should we force this population into one category or the other?

DICKERSON: Are you simply saying that it could be a continuous distribution, more or less, in degree of dominance or something of that sort, and that you are objecting to a sharp line of demarcation?

LI: Well, that's too strong a statement. I am not objecting. I thought we sort of imposed our arbitrary standard on nature instead of treating nature as it is.

NEEL: I wonder, C.C., if he isn't bringing out a point that should be brought out; namely, that you do have mixed loci. Most certainly, you have mixed loci, the mathematics of which are scarcely touched up to now, and which may do some very strange things.

LI: Yes, this is a good word. I usually talk about mixed loci, and we can talk about mixed forces in nature.

FALCONER: Is there, possibly, a third type of force that we have--

CROW: We haven't even heard the first yet.

FALCONER: --where mutation rate is not negligible in relation to selection pressure, where selection pressure
is smaller than mutation rate, and we have a balanced polymorphism, maintained by mutation in opposite directions? Now, I don't know, this may not be realistic, but can we completely neglect it as a possibility?

CROW: We can neglect a lot of things as first approximations, but it is true that in such a locus, where both factors are involved, the segregational component and the mutational component are not strictly compartmentalizable and additive, but this doesn't mean you can't deal with a situation like this. Theoretically, I choose not to do it in this discussion, but--

NEEL: But this may be the most meaningful.

CROW: No, I don't think it is.

NEEL: It certainly is the most common situation.

CROW: Not, not unless heterotic loci are very frequent, which I am inclined to think they are not.

NEEL: Let me restate it: that where we discuss heterotic loci, this is the most common.

CROW: But then, I think, I can say fairly, for most heterotic loci, the segregational component is not important.

NEEL: But the inbreeding effects you get from such loci are what I'm talking about.

CROW: I think they are clearly due mainly to the segregational component, too. I don't think you are neglecting very much of significance when you neglect segregation rates at a segregational locus. This can be worked out. It isn't that you just neglect something. You work it out and see that it is small.

BODMER: Isn't what you're saying, in a way, Jim, that there is a very narrow range of selection coefficients where you have a heterotic locus, where both the mutation and the heterotic component contribute more or less comparable amounts?

CROW: Yes.

BODMER: That, over most values of selection
coefficients, one or the other is predominant.

CROW: Yes. If the heterotic effect is of the
order of $10^{-4}$ or so, that is, the same order of mutation,
there are a number of complications, but these aren't contributing very much.

DICKERSON: It is a strongly bimodal population; is that right?

WRIGHT: There is another kind of balance that, it seems to me, is important, or I have considered it as most important. In my 1931 paper, which was to quite an extent concerned with modes of balance, the kind that I stressed most was one that would give rise to what you might call immigrational load, immigrational acts like mutation, but a tremendously more powerful factor than mutation. If you have a population in a large area, with sufficient isolation in different regions so that selection can operate differently in different regions, many people have criticized me for saying all differentiation was random drift between regions, but that is not the case at all. Those same people usually argue that differentiation was due to difference in the conditions of selection in different regions.

I don't think there would be much disagreement about there being differences in the conditions of selection in different regions, which means that there is a favored-- well, let's just put it on the basis of a single gene: that one allele is favored in one region, and the other allele is favored in the other region. But now, if they are not completely isolated, there would be a leakage there, so that the immigrants would be going from each region to the other, pulling it down from what it would be if they were completely isolated; so that both of these regions will be suffering from an immigrational load that is in balance with adverse selection.

You can't put them on the same basis, because the best genotype in the two regions is different. They are simply not comparable. They are qualitatively different. But each
region will be in balance between immigrations, tending to pull it down. As far as it is concerned, it is a good gene in the other region, but pulling it down as far as that region is concerned.

Selection is operating against that in precisely the same way as your mutational load operates, but, in that case, the gene frequencies may very well be high, in the neighborhood of .30, .40 or .50 and so on, because immigration is such an important, powerful factor, more so than mutation. You have something, therefore, that is very much like mutational load, except that the characteristic gene frequencies or the equilibrium frequencies are not of the order of, perhaps, one in ten thousand but may be in the neighborhood of one half, like the segregational load.

CROW: I thought about this quite a bit, Dr. Wright, but--

WRIGHT: So it seems to me that it would ordinarily be the case that you would have polymorphism in each of these regions, due not at all to heterotic advantage of the heterozygote, but due to the balance between immigrants that are unfavorable from the standpoint of reaching this equation.

MÜLLER: Could I say something in addition to that? It won't take long. To extend the mechanisms of balance and load still further, all loads existing in an equilibrium correlation are, of course, balanced. I might give an example which I mentioned in my 1945-47 paper as a sample of this, which I think a lot of people have already realized; namely, of genes—and I think Fisher mentioned this sort of thing, too—and it has nothing to do with segregation load in the sense of heterotic, although that might work with it.

Our advantages are advantageous when present in a given population, in a small frequency, and become disadvantageous at a high frequency, like the hypothetical case of near-sightedness in human communities, which would be advantageous as far as producing individuals who were helpful in making
arrowheads or other fine work that was useful, and disad-
vantageous beyond a certain point.

WRIGHT: Yes. Dr.Dobzhansky and I discussed that in a paper a good many years ago, especially as applied to regions in which there is something of division of labor.

MULLER: However, I think that is a very rare sort of thing, compared with this great majority of things we are talking about.

CROW: There is something more important to say, and that is, loci that are maintained this way will not be specially responsive to inbreeding. Therefore, the B/A ratio still argues for a mutational hypothesis.

WRIGHT: The immigrational load is precisely the same as mutation load, because it acts linearly.

CROW: It will have a different inbreeding effect, though, because of the different gene frequencies you are likely to find under these conditions.

WRIGHT: That is essentially the point; that gene frequencies will be one in five, and mutation load will be very low, one in ten thousand.

CROW: I really think you can distinguish between the mutational component and everything else, throwing this in with the rest, which I am trying to do.

WRIGHT: This behaves very differently in the segregational load.

CROW: Not as related to inbreeding.

MORTON: At close range, you wouldn't know in a particular case whether a segregational system at a different frequency would change all the selection coefficients.

LEWONTIN: As a matter of fact, you can show quite simply that if you evaluate the fitness at equilibrium, either the heterozygote must be inferior or superior to get it.

WRIGHT: Irrespective of just how it acts, there is a third type of load, that is possibly very different from either mutational or segregational.
CROW: And it is important to try to isolate it. All I was trying to say for the moment, so far as this discussion is concerned, is that I think we can throw this fairly easily in with the S class without making a serious mistake. I think this will appear in most of the experiments we have talked about in the S class.

I want to say, before Dr. Li's discussion stops, I don't really want to discuss the detailed items, 1 to 5, that he has talked about and which he put in print. My own opinion is that Dr. Li is raising, in some cases, semantic questions and, in some other cases, he has not really understood the problem. I also wish, contrary to his wish, that there were less isolation. I think that most of the points he has raised, two or three hours of discussion would clarify. I don't want to do it in a large group like this, where there seem to be more important issues than the understanding of particular definitions of several years ago. But I don't want to be interpreted as agreeing with most of what he said. I disagree quite profoundly.

NEEL: Jim, is it your plan today to get to the interpretation of B/A ratios?

CROW: Not specifically, no. There are several people who have something to say about it. I would like to be free to comment, but I have said so much on this subject in print that I would hate to repeat it here.

NEEL: Well, to some of us, this problem comes up: The B/A ratios for rare, nice, cleancut recessive traits run of the order of 80 to 100 or 150. Newton has calculated those for fairly recessive diseases. Now, a little bit of a B/A ratio of that magnitude, 150:1, goes a long way in raising the B/A ratio.

LEWONTIN: No, it doesn't. It has the reverse effect.

NEEL: I mean, if you have components in the B/A ratio that are 150:1 or 100:1, how do you interpret an overall
B/A ratio of, let's say, 10, which has been mentioned? This is an issue that, I think, it would be worth discussing here.

LEWONTIN: Well, Jim, I spent the last month reviewing all of the biases I could find in B/A ratios and all the experiments, and I described myself yesterday as being a completely uninterested party rather than a disinterested party. I am uninterested in the sense that, to me, it is not a critical issue in evolutionary theory. But I have become interested in it, and I think, if I could have a few minutes this afternoon, I could probably summarize a good deal of these biases and experimental situations.

CROW: I was going to call on Dick Lewontin this morning. I wonder if this is the time to do it?

NEEL: If you are ready, I think, perhaps, this is the time to do it.

LEWONTIN: All right; because it relates specifically to this point you just raised about specific traits and so on. I think what I will say is completely unexceptionable.

LEVENE: Impossible! [Laughter]

DICKERSON: We'll see.

LEWONTIN: I took a look at this question over the last month in preparation for this conference, and simply asked myself, what is the property of the B/A ratio as a detection system? I am not concerned about the biological meaning of load in this particular context, but simply, say, someone offers me an instrument for a detection problem; what are its detection characteristics, its sensitivities over the various parts of the range, and the way it should be used, and so on? That's all I'm concerned with.

It seems to me that this could be looked at in several ways. First of all, is the B/A ratio to be used as a detection system, in the case of single clearcut recessive traits? My conclusion is that it is not. I would like to document this. I think that it has uses, but this is the wrong
place to use them, for a very simple reason—and I think
that Jim agrees with this—

CROW: Oh, yes.

LEWONTIN: At least, I think, he hasn't made
this point here, but you do agree with this.

CROW: Yes, if I understand what you're saying.

LEWONTIN: It's what I wrote to you in my letter.

LEVENE: Use the yellow chalk so we can see it.

LEWONTIN: By a recessive trait, I mean nothing
about fitness. I do not commit myself on the question of re-
cessivity of fitness, but, rather, recessivity of the defect
which we can measure in a human population.

MULLER: Excuse me, but as soon as you use the
word, "defect," you commit yourself with regard to fitness.

LEWONTIN: All right; a characteristic—no, I
don't. It may be a defect which has no effect on the genetic
fitness. There are lots and lots of defects which, presumably,
have no effect on genetic fitness, Professor Muller.

MULLER: I'm sorry, but I don't use the word, "de-
fect," in that sense.

LEWONTIN: All right; I won't use the word, "de-
fect." I'll say we have a human trait which is recognized by
the medical man as a so-called human disorder, or variant of
some kind. I don't want to get into that.

MCKUSICK: Why don't you say "phenotype"?

MULLER: "Deviant," if you like.

LEWONTIN: The essential point is that, from a
medical standpoint, human genetic standpoint, we classify the
population into affected persons and unaffected persons. If
the affected persons are homozygotes for some gene, then, we
try to calculate the B/A ratio. The point is that we have
confounded, in the unaffected class, two genotypes.

This means that when we take the maximum fitness
in the population, whether we use mortality, fecundity, or
anything else, we are, in fact, taking an average of the
fitness of those two confounded genotypes. You see, we are saying that these individuals have a higher fitness than these. These may represent the maximum fitness, and they are confounded. [Comparing aa to A, and a to AA.]

Now, for a gene which is partially dominant on the fitness scale, that is to say, if this is less fit than that, if this is less fit, in turn, than that, this confounding has absolutely no detectable effect on the B/A ratio, for the obvious reason that there really isn't much confounding here, because nearly all the individuals in the population are AA, anyway, so the mean fitness of these things is so close to the mean fitness of AA that there is no problem. I won't go through that.

But let us ask if, perchance, on the fitness scale, the genes should be heterotic. In that case, if we take the fitness of that class as representing the standard fitness, we have confounded the two fitnesses. The result is that the apparent maximum fitness at equilibrium is as follows: what becomes apparent to us, because of this confounding, is simply \( 1 - \frac{S}{S+2}, T \). That is what it appears to be.

If we then put that into the calculation of load in the outbred population, the apparent load—and this is apparent load in the outbred population—it comes out to be, as a matter of fact, \( ST^2/S + T \). The apparent load in the inbred population, of course, does not suffer from this confounding.

WALLACE: Isn't there a parenthesis around \( S+T \)?

LEWONTIN: Yes, I'm sorry. The apparent load in the inbred population becomes this \( [(T(S+T))/S+T] \)

I calculate the inbred component from the unaffected individuals' fitness. I do not refer myself back to the outbred component to get the maximum fitness. I do this clearly, because an inbred component not only is inbred with respect to this gene, but also with respect to all other genes; so if I want to know the marginal fitness due to this gene, I must compare these strictly within the inbred component.
Having done this, I come out with a load ratio as follows—and, to simplify it, let me say that $S$ is equal to $K \times t$. It turns out, then, that the inbred-to-outbred ratio is $1 - (K) \times t$ twice $K$ over $K$, which, for my small value of $K$, is approximately equal to $1/K$.

What does $K$ mean here? It means the proportional disability of these homozygotes, so-called normal individuals, normal from the point of view of the medical defect, as compared with these; so we would assume generally that these individuals are probably not very badly off in comparison with these. These are most badly off because of their defect, and these are badly off for some other reason [comparing $AA$ to $A$]. $K$, then, is generally a small number. $AA$ might have a fitness of 98 per cent of the heterozygote, and $aa$, 89 per cent—a reasonable value, because $K$ is 10.

You see what this means. It means, for such a specific effect, the apparent load ratio looks like the apparent load ratio for semidominant chain, where the load ratio is proportional to $1/H$.

You remember that the load ratio for a semidominant chain is $1/2$—is that right? $2H$?

DICKERSON: Your $K$ is simply $T$ over $S$.

CROW: Dick, could I say something at this point? This is all apparently correct, but I really ought to say, somewhat defensively, that we have known it all along; that is, Newton and I have known it, and we have not used the load-ratio criterion except for traits where there is an optimum from which you can measure the deviation; so this confounding of the homozygote on heterozygote classes doesn't enter here. When this was used for a trait like deafness, it was used to rule out a very definite hypothesis, namely, that all homozygotes were deaf, and that the deafness trait was due to selection on the character, through the trait itself, not through some other trait. I agree, as I think Newt does, that this is a pretty implausible hypothesis, in the first place, and it is
ruled out with a great deal of rigor.

The only other way in which genetic load principle was used, in questions having to do with individual human traits, was where it had to do not with B/A ratio, as here, but it had to do with my point No. 11, in which I asked what the total segregation load is, contributed by such a locus. That is not biased by this kind of consideration, and let me explain why, because I think you know but not everybody in the room does.

When you measure the segregation load from observation of a single trait such as deafness, you do this by measuring the fitness loss by the deafness trait, and then you have an inequality which says that the minimum number of alleles or the maximum number of alleles, is something or other. Now, if I make a mistake in measuring the fitness of this trait and, instead of measuring it from the optimum heterozygote, but measure it from the homozygote to the heterozygote, I have underestimated it, and my inequality is still here, a priori.

LEWONTIN: But this demonstration is not made in any way to point an accusing finger at anybody, but to draw it to the attention of people who may not have realized this, that they ought not to use the load ratio in this straightforward manner.

CROW: But nobody has.

LEWONTIN: Then, I misunderstood Jim in this case. Did you not ask whether this might not be done?

NEEL: My comment was to imply that it could not be done.

CROW: I think we can agree to that.

LEWONTIN: Then, I'm sorry I wasted your time. I assumed there were some people, and I know there is at least one person, in the room who thought that the best way to use
the B/A ratio was, in fact, to take a single human trait, which was a very clear one, and take the affected persons and the nonaffected persons, and use the nonaffected persons as giving the maximum fitness.

DEMPSTER: How would you ever get a ratio that way? There's no way in which you can get a ratio, so, if the person tried to use it, he wouldn't have a ratio to work on.

LEWONTIN: Of course, he wouldn't.

DEMPSTER: So what ratio do you take, in that case? You have to have three values to get this ratio, and I don't see what three values you take from the population.

LEWONTIN: I'm sorry, but you have cousin matings and you have outbred matings.

CROW: You can take the frequency of the rate.

LEWONTIN: Yes. I don't see any difficulty there.

DEMPSTER: Oh, yes.

CROW: You can do this concept, but I don't think anybody who understood the nature of the theory would ever do it that way.

LEWONTIN: Then, I've wasted a little time. I simply wanted to say, please, never use B/A ratios--

CROW: Unless you know what you're doing. [Laughter]

LEWONTIN: No, wait a minute. Never use B/A ratios for specific human traits where you cannot tell the heterozygote. Do you agree?

CROW: Oh, sure.

LEWONTIN: If you can tell the heterozygote for a specific human trait, you do not need the B/A ratio. Is that correct?

CROW: I'm sorry; I was thinking about your first statement.

LEWONTIN: If you can detect the heterozygote, you do not need the B/A ratio to answer the question involved.

NEEL: Then, would you like to take the next step? Having told us we can never use B/A ratios for specific traits--
CROW: I'm not quite sure this is true. Maybe, we can find a way of doing it.

NEEL: Then, can we use it for data which consist of a mixture of specific traits?

LEWONTIN: No. Let me explain that, or at least let me say what I think you can do when you aren't dealing with a mixture of traits. I think it is a question of averaging out, but I'll get to that.

The question is, you cannot use it for specific traits. Then, it must be used simply as the gross picture of fitness in inbred and outbred components of the population.

The first thing we must observe is that if you want to use it in this way, it must be used in such a way that you estimate the fitnesses of the components, the inbred and outbred components of the population, under the same conditions in which the selection was going on, because Howard has provided us with a manuscript, and I believe it is now in print, showing how the B/A ratio can be very sensitive to departures from equilibrium, or supposed equilibrium, of selection coefficients; that is to say, if the selection measure is not the selection under which the population is at equilibrium, then, the B/A ratio can be very misleading.

Using Howard's argument, then, which I find faultless, I must say that if you want to use the B/A ratio, the second thing you must do is to measure the components of fitness in the same environments. These components of fitness must be the components under which the population has been selected.

MULLER: May I say in that connection that I think it was recognized in our joint paper that this was the case, but that it was recognized to work in a certain direction, namely, to minimize the ratio found.

LEWONTIN: But this is, in fact, not the conclusion Howard has come to. If you look at the graphs of the paper which he has now published, he shows that, in fact, there are
many cases where the B/A ratio for heterotic trait can be badly off in the wrong direction. Is that not correct, Howard, that you can get a very large B/A ratio?

LEVENE: I'm sorry I didn't bring the slide.

LEWONTIN: But is that not correct?

CROW: Is there any reason why they should deviate more often in this direction than in the other? I don't know. If the argument here is that you can contrive situations in which this would be a misleading result, obviously, yes.

LEWONTIN: I'm trying to find a situation under which we all would agree that the B/A ratio is as good as you can make it. O.K?

MULLER: No, I would like to come back to that point. Isn't it true that, in general, the environmental conditions have been improving so as to minimize the ratio as found by the method we used, and making it lower than it would have been if done under the conditions in which the equilibrium had been obtained?

LEWONTIN: Excuse me, Professor Muller, but I think the main point I want to make here, and I haven't finished, is now that it ought to be used in human populations, where, I think, your statement is correct, but it ought not to be applied to Drosophila. I think it is a gross error to take a sample from a Drosophila population, bring it into the laboratory, and measure the fitness of various components under a completely artificial set of conditions, which have no relationship to the conditions which established the equilibrium in the Drosophila population, and expect a necessarily sensible result. When we come to human populations, I'll have something else to say, but I think you have to be very careful.

If you can be sure that the conditions in the laboratory are such that your selection estimates, your estimates of fitness, deviate in a known direction from the selection which has gone on in nature, then, you know the direction
of bias, but unless you do know that, your estimates of fitness bear an unknown relationship to the fitness in a natural population. This is what we usually do in Drosophila, after all. We do know the measure of fitness in the natural population.

If this is true, then how can one use the B/A ratio? Well, man is the obvious place where you use the B/A ratio, for the reason that the estimates of fitness which you take do not in any way disturb the population; that is to say, you do not change the selection coefficients when you take the estimates of fitness. They are the estimates of fitness in the standing population.

Now, since we have the result that one must never take an erroneous, or, say, take the least erroneous possible measures of the selection in order that this lack-of-equilibrium argument not upset us, it follows that we must, where we can, avoid taking partial components of fitness, since any one partial component of fitness is not itself a predictor of the equilibrium.

Man, again, is a situation where we can do this, because we can get the complete age-specific mortality and fecundity schedules for man, unlike for any other organism in the world. This is a difficult thing to do, and I am only trying to set up the kind of data which, I think, would give the best kind of B/A estimate. What I require, then, is the complete age-specific mortality and fecundity schedules for the following three components of the population, because I have to allow maternal effect, unfortunately, for the general random component of the population, the so-called outbred population, for offspring which are themselves inbred to various degrees and offspring which are not necessarily themselves inbred, but which come from inbred mothers. One must examine all three of these. If we're lucky, the inbred mother won't make any difference, in which case our problem is easier, but I do say complete age-specific mortality and fecundity.
ROBERTSON: May I just interrupt? The offspring of the matings are going to be inbred?

LEWONTIN: In some cases, yes, because you have cousin marriage.

ROBERTSON: Are you going to take those on and see what their own fecundity is?

LEWONTIN: That would be nice if you could do it.

ROBERTSON: It seems to me that is essential.

LEWONTIN: Well, you must know the fecundity of an inbred individual and the fecundity of--yes, certainly you have to know the fecundity of inbred individuals; absolutely.

LEVEN**: If you had the data on inbred mothers, you could get it on inbred fathers. These, of course, will be of different ages, probably.

LEWONTIN: This is not an easy data-collecting job, Howard. I don't propose that it is, but I propose that it eliminates many of the objections Professor Li has raised to the B/A ratio. You are depending on the real selection business going on in the population, an age-specific selection, which determines the total selection in the human population.

CROW: I think it is really Howard's point rather than Dr. Li's, but that's all right--just to keep the record straight.

LEWONTIN: If that is the case, I had several other points. We come to the last--

MORTON: I follow you completely up to the point where you are estimating A. Tell me what this means when you use fecundity.

LEWONTIN: No, it is age-specific mortality and fecundity, multiplied in the proper way to give you an estimate of R.

DEMPSTER: How about the question, how do you come to your A?

LEWONTIN: I have two more points to make. One is
the biasing effect of A. What we are doing, in effect, is trying to draw a regression line, and we are trying to get B, B being the slope, and A, the intercept. The point has been raised over and over again that the A is above some unknown level, and, so long as it is above some unknown level, we do not know what the real value of A is.

Now, as has been pointed out repeatedly, and I don't have to go through it again, the effect of such a bias is to lower the ratio; that is to say, if A is measured from 100 per cent, or three children per family, when it should be measured from two children per family, then, the effect is to lower the ratio. If A is really remarkably large, if this deviation from the proper measurement point is really remarkably large, relative to the deviation from your assumed point, then, of course, the lowering will be very large; and so this is where we come to this question of the one-sided detection system that we are talking about.

It is characteristic of this detection system that if the ratio is very large, under the conditions I have specified of age-specific mortality and fecundity, then, this bias cannot be the cause of this inflated B/A ratio. But if the B/A ratio is very small, it may be, indeed, one of the contributing causes, and there is no way you can get around this problem, as far as I can see.

MORTON: It's clear that you are taking fecundity; the B/A ratio is not only small but it is negative; that is, the reasonable model for fitness in terms of our enthusiasm for parameters would be the adaptive value in the right sense, or E to A minus BF, so B/A--

LEWONTIN: Well, now, wait a minute.

MORTON: I don't think it's going to be positive.

CROW: I don't think you can do this kind of experiment meaningfully.

LEWONTIN: We don't do this, anyway.

MORTON: The problem is with fecundity. It's
something like a minus BF, because either A represents the mean fecundity, and the amount of inbreeding will lower it, so the exponential term will be B minus BF on that model. This doesn't mean anything, then.

LEWONTIN: Excuse me, but if you have lowered fecundity, you have an estimated fecundity load, don't you?

MORTON: This is a fecundity which doesn't seem to have a clear meaning. Fecundity [balance inaudible due to the fact that half a dozen people were speaking at once.]

LEWONTIN: I don't use them separately, anyway. What I would call U is nothing but the intrinsic rate of increase of R--knowing nothing about humans but something about Drosophila. I would try to estimate R from the equation summation, either minus R M X equals 1 or L. You see, if there is such a thing as a stable age distribution, which there probably isn't, then, where LX is the mortality schedule, this gives me an estimate of--

MORTON: Suppose you were doing this for a population that wasn't increasing or decreasing; you would estimate your Malthusian parameter as zero. That is your A, apparently, and then you get a B for inbreeding effect. Your B/A ratio is enormous. It seems to me that the failure to define your A allows you to get positive, negative or infinite results.

LEWONTIN: How would you define the A?

MORTON: That's the problem.

LEWONTIN: All right.

MORTON: There are some ways of trying to do it, but--

LEWONTIN: I would be happy to hear them. So there is this unknown bias, fair enough, especially for fecundity, as you point out, since you could make the maximum fecundity 143 if you wanted to.

CROW: Are we discussing an experiment someone has done?
LEWONTIN: No, I am proposing to go out, or that somebody go out and get complete mortality and fecundity schedules.

CROW: But the point is that no Drosophila experiments ever tried to answer this question in this way. I don't think it can be done.

LEWONTIN: I don't think the Drosophila experiments can do it.

NEEL: Let me interject and say that such data can be obtained for man, but I hope we will have a discussion as to whether they will yield critical results.

LEWONTIN: The last point I want to make is the one raised several times already in the discussion—the effect of mixtures of different kinds.

CROW: I'm not sure I really understand the purpose of this discussion. Is it to show, where you are dealing with fertility data, this is a hard criterion to apply?

LEWONTIN: Yes.

CROW: Well, this is certainly agreed.

LEWONTIN: There are all sorts of things that you know and that some other people know which other people don't know; I mean, I'm saying everything which seems so patently obvious to me that I feel a little silly, but when I talk to people about this, there is at least one person in the room who hasn't thought about one of these things, so I don't think I'm wasting time completely. I may be wrong. Of course, you know every one of these things and you agree with them. That's what I'm saying.

ROBERTSON: What do you propose to do with these data when you've got them?

LEWONTIN: What I'm saying is that the only way you can hope to use the B/A ratio is if you had the complete selection distribution of your population.

NEEL: But, Dick, isn't this the question at issue? I think that we could, in man, with a great deal of labor, get
the kind of data you have requested. Let us assume that the B/A ratio, however we correct for the environmental component in A, which is a sliding scale, obviously, came out to 10.

LEWONTIN: Yes; I'm about to deal with that point.
NEEL: Then, will we get a critical interpretation?
NEEL: That's my last point.
CROW: A fertility mean or something.
NEEL: The whole gemisch.

LEWONTIN: That's the point I'm trying to lead up to in the end. This comes to the question of the sensitivity of the detection system. What we are asking is, suppose that a proportion of the loci, K, is maintained segregationally, and that a proportion, 1-K, is maintained mutationally; what happens to the load ratio? That's what we're really asking. It is very simple to demonstrate. Jim has demonstrated it. I won't bother to.

NEEL: Please demonstrate it.

LEWONTIN: All right, I'll demonstrate it. Suppose that I have a hundred genes that are maintained by a mutational load, and one gene that is maintained by a segregational load mechanism; what we are going to ask is, what will the ratio of the outbreeding to the inbreeding load be? Notice, we do not take the average of the ratios. We take the ratio of the averages, because you go in and determine outbred load, \( L_c \), in the population, and this is the result of an average of a hundred mutational genes and one segregational gene. Then, you do the same for inbred load, and so you are taking the ratio of two averages. No? What are you actually doing?

CROW: That's right, except that you want to break the whole thing down.

LEWONTIN: I realize that. This is what you're actually doing in practice. You estimate the load in the outbred population, you estimate the load in the inbred population, and you put one over the other. But when you estimate the load
in the outbred population, it is an average of the two components of the load, and when you estimate the inbred population, it is the average of two components of the load. Therefore, the ratio that you take comes out to be a ratio of averages and not an average of ratios.

If you do that, then, in order for the contribution to this ratio to be equal between mutational and segregational load, for example, you would need--

CROW: Equal in the outbred population?

LEWONTIN: Yes, equal in the outbred population; --you would need many hundreds more times mutational loci than segregational loci, because each segregational locus contributes a much larger amount to the load than each mutational locus for those reasonable values of selection that we have been talking about. Therefore, it takes a hundred mutational loci to equal, in its load effect, one segregational locus.

Therefore, every time you add a single segregational locus, you tend to make this numerator larger, that is, you are adding a large value to this numerator, and you are also adding a large value to the denominator, and the result of that ratio is that the value of the ratio gets closer and closer to 1; in other words, every time you add a single locus, which has a high load effect, you add a big number to both numerator and denominator fraction, and therefore you tend to reduce the size of the fraction.

What I am saying, then, is that without any numerical examples--in fact, I did a little test for myself, in which I allowed an average degree of dominance of deleterious genes of 2.5 per cent, a number I just picked out of the air, of course--

MULLER: No, it is not out of the air. [Laughter]

LEWONTIN: That was a joke intended to be at my own expense, Professor Muller: [Laughter] I assumed a hundred loci, with a 2.5 per cent average dominance and a single
heterotic locus, with an average heterosis of 2.5 per cent, that is to say, the two homozygotes were equal, and when I do that, with a 100:1 ratio of those two kinds of loci, I come out with a load ratio of approximately 4.2 or something. I can't remember what it comes out to, but it is a low load ratio.

What I am saying, then, is that if you asked Jim's question No. 2, which is the proportion of loci which are heterotic as opposed to mutational, this detection system is a one-sided detection system to answer that question, because the load ratio, \( r \), when plotted against the proportion of heterotic loci, looks like this [drawing curve], which means that when the proportion of heterotic loci is indeed very small, the load ratio is high, but this curve drops so rapidly that when you get to about 1 per cent or less heterotic loci, it has already dropped down near its asymptote, which is 2.

That being the case, we can call this a one-sided detection system; namely, if I go to nature and I discover that the load ratio is 25 or 30, I can say that heterotic loci are not very common, but, if I discover a load ratio of 4, I cannot say how common they are. It is one-sided in this respect, but I wanted to say--

NEEL: Then, this means, with the kind of load ratios that are beginning to come in, we are in an indeterminate situation. You are subscribing to that?

LEWONTIN: Except that there are other biases which also tend to lower the load ratio.

NEEL: All right.

LEWONTIN: Now, it is one-sided for this reason, and it is one-sided because it also mis-estimates \( A \) and also tends to make it a one-sided hypothesis, so to speak; in other words, it is a detection system which, if you get an extremely high value and you thought the population was at equilibrium with respect to the selection forces you have estimated--

MULLER: Or out of equilibrium, in the direction in
which it is, probably.

LEWONTIN: Yes, or out of equilibrium in the proper direction. In any one of these cases, then, I would regard the B/A ratio as a good one-sided test. It becomes no test at all if there are biases pushing the ratio in the other direction and, for this reason, I have asked particularly that we get an estimate of coefficient which is relevant to the population or at least in the right direction for the population. But I do think it is a two-sided test of what is to me a more important hypothesis, and that is Jim's question No. 3, where we are not discussing the number of loci, which, in my opinion, is a trivial question except as it bears on more important questions, but where we are asking, what is the proportion of genetic variation in the population which can be ascribed to these two kinds of loci?

In this case, I would like to point out that, ipso facto, a low ratio means that there is a lot of variation from however many loci there may be, being contributed by segregational loci, even if they are very small in number, whereas a high ratio means, ipso facto, that even if they were very large in number, which they couldn't be, but whatever their number, they are not contributing a great deal to the genetic variation.

That is why I disagreed with Jim when he said he thought it was a one-sided test of question 2. I think it is a two-sided test of question 3.

CROW: Yes, I think that's all right.

LEWONTIN: That is what I wanted to say. It is, indeed, a one-sided test of 2, because of biases and because of this ratio of average effect, but it can be a two-sided test for 3.

CROW: Let me put two or three numerical examples on the board.

LEWONTIN: That's what I wanted to say. I don't think everybody knows this.
CROW: This is right along the line of what you talked about. Maybe, one ought to do it. Suppose I consider the examples under which the A or a mutational component and a segregational component for inbred and for random come into it. Now, suppose that the mutational component and the segregational component are equal in the random-mated population—and Jim Neel did practically the same thing once in one of his papers—but suppose each of these is equal to 10, for convenience. This, on inbreeding, will increase by a factor, making it perhaps 40 or 50, to take a convenient round number—no, I want a higher factor than that, don't I?

NEEL: Make it 100.

CROW: Yes, 100, which is pretty low for the usual levels of dominance, but say 100 for convenience. Just say there are only two alleles, so this changes to 20. If I now average the averages, this is going to be, collectively, a ratio of 120/20, which is 6. This tells me that the inbred load is considerably more mutational than segregational, but it has been pretty uninformativen as to what is happening in the general population, despite the fact that this is pretty high. This is really the point I'm trying to make, and it is simply paraphrasing what Dick said, but he expressed it not in terms of number of alleles involved but the total contribution of these alleles.

This one example is probably enough, because I happened to pick just about what I wanted it to do. This means that this value has to be pretty low to offer much evidence on the random population.

NEEL: Yes, but then would you agree, Jim, that if the values do come out that low, they do offer—

CROW: Now, this is what I say: They seem to me to be impossible to interpret unless you can distinguish the genetic from the environmental components of A.

NEEL: Well, can we talk about that a little bit?

CROW: Let me say this, that it is undoubtedly
true, if this value turns out to be 2, and you can rule out any environmental component to either the numerator or denominator, that is not inconsistent, you see, with your segregational hypothesis.

LEWONTIN: It is consistent with a fair number of mutational loci. Again, it is the number and not the effect.

CROW: If it is exactly 2.
LEWONTIN: Oh, well, if it's exactly 2---
CROW: But even if it's 2, 5 or 2.3.
LEWONTIN: I think you could get an equal number of segregational and mutational loci giving you a 2.5.
CROW: You don't mean equal numbers of loci; you mean equal contributions to the random load.
LEWONTIN: No. Suppose there were equal numbers of loci, what would the load ratio be? Pretty close to 2?
CROW: Yes, pretty close to 2. But I agree with you, that is not the interesting question. One wants to know more.

MORTON: I believe, if you have a mutational load of the type of extremely small homozygous effect, such that mutations are retarded in both directions to keep it going in the population, then, you could get a low ratio. But if the gene frequency is close to 50 per cent---
CROW: Yes, there is that possibility.
NEEL: One question. We keep talking hopefully about distinguishing the two components of A, the genetic and nongenetic. Actually, I think, one of the facts that shakes us most about the Japanese data that we have is that we have just as nice a consanguinity effect on the frequency of diseases that you would classify as being of an infectious etiology as we do on congenital or idiopathic diseases. Now, this raises in my mind the question of whether you don't have two wedges here in terms of genetic and nongenetic contribution to any particular death, and is this a will-of-the-wisp, to think that
we can ever break $A$ into two components?

LEWONTIN: I believe you can put a maximum value on $A$ for human populations. I would like to know, if you do put this maximum ratio, what the expected bias is. I think you can put it on in the following way: If you look at it as the intrinsic rate of increase of $R$, or as a Malthusian parameter -- let's not forget, in an overlapping population or a population of overlapping generations, it is the early births that count. This is the most important thing from the standpoint of the spread of a genotype in a population, to get those first kids in early, and we don't care about the few that you have at the much later ages.

This being the case, I think that one can make from what one knows about how long it takes to terminate a pregnancy successfully -- first of all, as far as mortality is concerned, the absolute maximum mortality is zero, all right? We can therefore agree that the minimum mortality or maximum liveability, if you like --

SLATIS: Make it minimum.

LEWONTIN: Well, when it comes to maximum fertility, you can certainly assign a maximum reasonable human fertility, a specific fertility schedule. For example, you can say that a woman might have twenty-five children if she conceived every year and brought them successfully to term, but the last fifteen children make relatively little contribution to the Malthusian parameter as compared to the first ten.

I can draw out a maximum human age-specific fecundity schedule; I can just write it down on the board, and, using that maximum human age-specific fecundity table and the optimal mortality table, which is essentially zero, I can calculate what the absolutely largest rate of increase of such a population would be.

Now, I should ask myself, given this value, how seriously does it bias the results which we get? If it turns out to bias them immensely, then, we're in real trouble.
Suppose, however, that it doesn't bias them immensely--

CROW: I think the proper question to ask is, this defines the load space, as Jim Neel calls it, and how many polymorphisms can be maintained within this superman, or whatever you call him, and the average of the population?

LEWONTIN: No, not how many polymorphisms, because I think, again, we agree we don't care. We know the answer to load space--period.

MORTON: Don't you have to take a supremely important point, that if you ask what is the optimum phenotype for man over a long period of time, it is not a woman having two hundred children, because this is just inconceivable--she couldn't raise them--but, under primitive conditions, a child born once every three years, viable, is about as much as the woman can maintain, as you point out, over a rather short interval of time. The optimal fecundity, under these primitive conditions, therefore, is probably not much greater than the mean fecundity now. It is not an enormous thing.

DOBZHANSKY: Is that your definition of optimum genotype? I would like very much to have it spelled out.

MORTON: I think optimum phenotype is the thing that causes the confusion here. The optimum is something inconceivable. It is a man the size of a dinosaur, reproducing every half hour by binary fusion.

DOBZHANSKY: And doing a very good job at that.

[Laughter]

MORTON: The phenotype has to be more or less what we recognize as the species characteristic, under the conditions that evolved him. This means that there are real limits on what the optimum fertility would be.

DOBZHANSKY: I would like you very much to spell out this optimum phenotype limit; just make specifications.

MORTON: All we need is the optimum phenotype for this.

LEWONTIN: I proposed a specification already.
Please sit down with a reproductive physiologist and a sociologist and draw up the best possible fecundity schedule you can make.

DOBZHANSKY: O.K. Then, make a committee consisting of Lewontin, Morton and, I assume, Jim Crow, and let them draw up specifications for an optimum human genotype. It would be very interesting.

LEWONTIN: Not an optimum genotype, but an optimum fecundity schedule.

DOBZHANSKY: O.K., but draw it up, please.

MORTON: There is one other way to do what Dick wants to do--

CROW: Then, what do you want to do with it?

MORTON: Jim's theory about the phenotypic selection, which suggests something about the relative magnitude of the phenotypic selection as it operates on mortality and fecundity, also can be used to get some idea of how large the concept of A is, at least at the present time and for any defined population, relative to what it is for mortality. I think these two methods could be used, and we ought to get reasonable agreement.

LEWONTIN: I would suggest, to refine the problem a little bit, we would have to make the following two assumptions: that over a short range of human evolution, the gestation period does not have considerable genetic variation, let's say. Of course, you can always make a gestation period of two months, but let's hold gestation at nine months, and let's hold the age of puberty at some reasonably early age. If we hold those two constant, then, I think, we can--

DOBZHANSKY: But why should we? Why shouldn't we make a gestation of two months and age of puberty at five years? Wouldn't that be even more optimum? Why not?

LEWONTIN: Why not make man into a Drosophila?

DOBZHANSKY: Well, if you measure the optimum genotype at maximum power, surely, this produces children--
CROW: I think this is not a fruitful argument at this stage.

NEEL: Let's have lunch!

[The session adjourned at twelve-fifty o'clock.]