ON THE POSSIBILITY THAT SEX-CHROMOSOMES HAVE A GREATER EFFECT THAN AUTOSOMES ON INHERITANCE

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Introduction

Pahnish, Stanley, Bogart and Roubisek (1961) drew attention to several reports in different traits in cattle of a greater influence of sires in female than male progeny. They stated their belief that something other than chance was involved. Then they added, "The possibility that sex-linked genes had an appreciable impact on each of the several traits considered in the four studies seems remote."

They gave no reasons for the last statement. They obviously felt justified in the belief, shared by most workers in the subject, that, as sex-linkage has for so long been accepted as unimportant in quantitative inheritance, it was unlikely to appear suddenly in several traits at once.

Beilharz (1961) has advanced the hypothesis that sex-chromosomes (at least in mammals and birds, although probably in all animals) have an effect on the organism that is greater than that of normal autosomes. The effect need not necessarily be obtained by greater gene number. Each unit of chromosome material may exert a greater effect than a corresponding unit on the autosomes. In that case more than negligible sex-linkage in many quantitative traits would be the only manifestation. Qualitative mutations cannot be evaluated in terms of overall effect on the organism.

This hypothesis would seem to give a perfect explanation for the results cited by Pahnish *et al.* (above). Were this hypothesis correct, far-reaching implications can be seen in breeding. This review discusses the conditions necessary for testing it in mammals. In this review "sex-linkage" is used to mean X-chromosome linkage.

Definition of the Problem

We must not be blinded by the fact that sex-linkage has for so long been ignored in quantitative traits. It will be shown that this belief is to a large extent not based on evidence. We have assumed, for instance, that because the sex-chromosomes are only one pair in a large number of pairs, their influence must be small. This implies the underlying assumption that the effect of the sex-chromosomes is about equal in magnitude to that of a pair of autosomes. We have used this assumption in quantitative inheritance when we have consistently ignored sex-linkage. We seem to have evidence of its correctness in the fact that in over 50 years of genetics very few studies have shown sex-linkage present in quantitative inheritance. If we were only trying to defend unimportance of sex-linkage, as a workable hypothesis, this sort of evidence might be admissible. To distinguish between two alternatives however, this sort of evidence

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is completely unsatisfactory as most of the studies were unable to discriminate between the alternatives.

The alternatives are simply these. (a) Have the sex-chromosomes approximately equal effects to that of a pair of autosomes ? or (b) Have the sex-chromosomes a substantially greater influence than a pair of autosomes ? If (a) is correct, then in most species, because there are more than a few pairs of chromosomes, the resultant sex-linkage effect in quantitative traits can be ignored. If (b) is correct, sex-linkage in all quantitative traits may not be automatically ignored. It may be important enough to suggest alterations in present breeding programs.

There seems to be no direct evidence to decide between the alternatives. Recent cytological evidence is illuminating. For instance Ohno and Weiler (1961) and others, have found that in the mammalian female one of the X-chromosomes in each cell becomes heteropyknotic and condenses in size. Lyon (1961) and Beutler, Yeh and Fairbanks (1962) independently suggested the hypothesis that mammalian females are mosaic at the cellular level for sex-linked genes as a result of the genetic inactivation of one of the X-chromosomes at an early stage of embryonic development. Inactivation is thought to be random with regard to parental origin of the chromosomes. However once a chromosome has become inactive in a cell it is thought that all the descendants of the cell will have the same chromosome inactive.

It seems that in both sexes one X-chromosome is sufficient to exert genetic effects. This suggests that X-chromosomes should have a greater effect than autosomes on the organism. However, we still have no direct measure of the relative effects of the various chromosomes.

Thus we must look to the indirect evidence about sex-linkage in quantitative inheritance. It becomes necessary to critically evaluate which alternative is favoured by this indirect evidence. It is faulty logic to expect one alternative (i.e. the presence of sex-linkage) to be demonstrated significantly merely because the other has been hallowed by time, though based only on assumptions. If the evidence is not significantly one way or the other we cannot arbitrarily discard either.

Requirements for Discriminating between Alternatives

As indirect evidence must be used, we must discriminate between presence or absence of more than negligible sex-linkage. To do this except in two cases cited below, both sexes of progeny must be analysed separately and the relative influence of at least the heterogametic (XY) parent sex determined. It should be easier to find sex-linkage if the relative influences of both parent sexes are compared in both sexes of progeny. The homogametic (XX) parent affects the two sexes of progeny in exactly the same way. Although this effect is more important when no other X chromosome is present (in sons) one cannot distinguish between sexes if regression methods are used.

This follows from the X-chromosome relationships between parents and progeny. Sex-linked additive variation in the XX progeny arises from the XX parent $\frac{1}{4}$, the XY parent $\frac{1}{2}$ (there is no segregation in XY parent), and chance at meiosis $\frac{1}{4}$. Sex-linked

additive variation in the XY sex arises from XX parent ½, XY parent 0 (there is no X chromosome relationship) and chance ½.

If the range of possible phenotypes (adjusted for sex dimorphism) in the XY sex is somewhere near the range of possible phenotypes in the XX sex, then the total additive sex-linked variation in the XY sex must be no less than that of the XX sex. Whatever the relative ranges of possible phenotypes in the two sexes it seems very likely that the total additive sex-linked variation in the XY sex is at least greater than ½ of the total additive sex-linked variation in the XX sex. It follows that if the sexes are combined (unsexed progeny) the XX parent must have a greater sex-linkage influence on variation in the progeny than the XY parent.

Non-genetic maternal effect (to the extent that it occurs similarly in both sexes, and adjusted for sex-dimorphism) can be allowed for by removing equal portions of influence from the dam's effect in both sexes. Where sexes are combined or where only one sex is available sex-linkage is confounded with maternal effect and it is impossible to assess how much of the influence is due to maternal effect. The two exceptions mentioned above are (1) when the dam's influence in sons is no more than that of sire's influence in sons (this also applies in birds) and (2) when the dam's influence in combined progeny is no more than sire's (this does not apply in birds). In these cases it may be argued that both maternal effect and sex-linkage are negligible. In all other cases supposed maternal effect may completely hide sex-linkage.

It is obvious that many inheritance studies could not discriminate between the two alternatives. They must thus be eliminated from the discussion. It is now obvious why the fact that sex-linkage has rarely been found in the past cannot be used as evidence against the sex-linkage alternative.

LITERATURE SURVEY

Of 36 studies of quantitative inheritance located in
Journal of Genetics **56** (1958-59)
Journal of Agricultural Science **50** (1958), **51** (1958), 52 (1959)
Journal of Dairy Science **41** (1958)
Animal Production **1** (1959), **2** (1960)
Journal of Animal Science **17** (1958), **18** (1959), **19** (1960), **20** (1961)
thirty were judged as incapable by virtue of experimental design of differentiating between the alternatives. The remainder were as follows.

Kincaid and Carter (1958). The response of both sexes to selection in sires for fast and slow growth is given. There seems to be no greater response in females than in males. However, the trait is not quite identical in both sexes. Steers were full-fed in feed-lots, heifers were wintered largely on roughage and the gains on pasture in their yearling summer were measured.

Tallis, Klostermann and Cahill (1959). Data are given for both sexes. There is no apparent difference in trends in the two sexes.

Bradford, Weir and Torell (1960). A sire by sex of lamb interaction would have shown sex-linkage. This was apparently not significant.

Table 1

Heritability estimates of various beef characters from data of Carter and Kincaid (1959)

Type of Estimate	Paternal half-sib correlation		Regression of Progeny average on sire		Intra-sire regression of progeny on dam	
Sex of Progeny	M	F	M	F	M	F
Character						
Wt. at 6 months	0·08	0·69				
Feeder grade	0·41	0·51	0·16	0·63	0·07	0·00
Daily gain	0·38	0·54	0·21	0·20	0·40	0·57

Carter and Kincaid (1959). The influence of 38 sires was shown to be greater in heifers than in steers. Heritability estimates for the sexes are given in Table 1 for the traits measured in both sexes. Weight at six months and feeder grade are the two traits identical in steers and heifers. In each of the four cases the difference in the heritability estimate between the two sexes is as one would expect from the operation of sex-linkage. Daily gain is not identical in that steers were full-fed in feed-lots while heifers were pasture fed. In this character one set of estimates shows the trend expected with sex-linkage, one shows no trend and the other (the one in which sex-linkage is most difficult to demonstrate) shows an opposite trend. As the various estimates are not consistent for any character one might say the data are insufficient to be conclusive. Agreed, but don't they favour the sex-linkage alternative rather than the other ?

The unquestioning faith in the assumption that sex-linkage is unimportant is clearly demonstrated in this study. The authors give a possible explanation for the enormous difference in heritability estimates between the sexes in six-month bodyweight in terms of "slower growth rate, and presumably lower nutritive requirements for optimum growth, of heifers compared to steers." This explanation assumes without evidence (1) that heifers have a lower nutritive requirement for optimum growth and (2) that nutrition was limiting growth. How much simpler is the sex-linkage hypothesis ?

The authors do state however that if the given explanation were correct "The performance of heifers may give a better guide to the genetic potential of a bull than the performance of steers." This obviously is also a consequence of the hypothesis of important sex-linkage.

McDowell, Fletcher and Johnson (1959). This study showed significant sire by sex of calf interaction in both gestation length and birthweight. These traits, both quantitative, are probably related, as size of foetus does seem to affect gestation length (Joubert and Hammond, 1958). One needs to know more about the exact nature of the sire by sex interaction to make dogmatic statements. However, as a consequence of sex-linkage, one would expect a sire by sex of calf interaction. The sire can affect only females through his X-chromosome. The male progeny on the other hand would tend to reflect more the genotypes of the dams mated to each sire.

Pahnish, Stanley, Bogart and Roubisek (1961). The heritability estimate of weaning weight in heifers was twice as great as that in steers. This result is expected from important sex-linkage.

The first three studies do not show sex-linkage, although they cannot demonstrate the unimportance of it. As it is difficult to get sufficient numbers to demonstrate a difference, lack of difference may be merely due to insufficient numbers.

The last three may quite readily be interpreted as demonstrating the effect of sex-linkage. On the other hand there is in this probably typical sample of inheritance studies no conclusive evidence for absence of sex-linkage in quantitative inheritance.

One point arises from the literature survey. Even if the experimental design could discriminate between alternatives it is extremely difficult to do so significantly. Heritability estimates have large sampling errors. (Hale, 1961; Tallis and Klostermann, 1959; Van Vleck, Searle and Henderson, 1960.) This does not mean that the difference between alternatives is unreal or unimportant or that we need not worry about different consequences. It means that experiments have to be done on a much more critical scale. In the meantime we have to try to evaluate the usually non-significant evidence at present available.

Evidence Advanced to Support Absence of Sex-Linkage

Several studies e.g., Kidwell, Weeth, Harvey, Haverland, Shelby and Clark (1960) and Damon, Harvey, Singletary, McCrain and Crown (1961) have used the method of Henderson (1948) to estimate the relative importance of additive, non additive, maternal and sex-linkage effects in inheritance. Those studies seen by the author have found sex-linkage negligible. It can be sown that this method, by not separating the sexes, confounds true sex-linkage with maternal effect.

Brumby (1960) in a very thorough study of maternal effects in mice concludes that sex-linkage is absent in bodyweight inheritance. This study is based on ovum transplantation and cross-fostering of young. Separate tests on various effects were carried out. It was found that there was a marked difference in the maternal environment provided by a large and small strain of mice to embryos of an unrelated strain. There is thus definite evidence for the importance of maternal effect on bodyweight of mice. It is however, worth examining the tests on which sex-linkage was rejected.

Reciprocal crosses were made between the large (L) and small (S) strains of mice and the resulting fertilised eggs transplanted to unrelated (U) strain females. At birth an appreciable difference in weight was apparent, in favour of the young resulting from the small females and large males. This difference persisted throughout the 12 weeks that bodyweight was recorded, resulting in a difference of weight of the order of 8 per cent at 12 weeks of age. This difference is shown to have occurred both in male and female mice and it is on this criterion that sex-linkage is rejected. Brumby favours the view that the cytoplasm of the small strain enhances body size to a greater degree than does the cytoplasm of the large strain.

Reciprocal crosses between L and S, allowed to develop normally, showed a difference

in birthweight reflecting differences in prenatal environment. This had disappeared by weaning at 3 weeks. Thereafter no apparent difference existed between the two crosses. Brumby states "This apparent anomaly might be explained in terms of the counter-balancing of the poorer maternal environment of the small strain by a greater cytoplasmic contribution of the small strain to growth".

I quote his discussion on these tests. "Though the difference that was established between the reciprocal crosses reared in the same environment provides apparent evidence that cytoplasmic factors are influencing growth, three other possible explanations may be invoked. The first lies in the fact that eggs spent 3½ days post-ovulation in their own dam prior to transplantation. Thus it may be argued that the difference observed in the reciprocal crosses is merely a consequence of this early maternal environment. Some evidence supporting this explanation is provided by the observation that eggs of the small strain appeared slightly further developed at 3½ days post-ovulation than did those of the large strain. On the other hand it was shown that the post-implantation environment of the small strain was poorer than that of the large strain, and it seems unlikely that the reverse would be true of the pre-implantation environment.

"A further possible explanation lies in terms of differential mortality of eggs actually implanted but in view of the success achieved in causing eggs to implant in the U strain females this too seems unlikely. A third possibility is that it is merely a chance result. Obviously further work on this point is required."

There are contradictions in these results. Even the presence of opposed cytoplasmic inheritance in strains of mice that had been selected apart for over twenty generations is a contradiction. The author admits that the result may be due to chance. Under the circumstances even though it is admitted that the single observation on the point shows no sex-linkage, is the author justified in rejecting sex-linkage when every other explanation of these results is open to doubt ? Notice that when one believes that sex-linkage is unimportant anyway, then as it is not demonstrated significantly one may feel justified in rejecting it. However as there is some doubt and as we are trying to choose between two equally possible alternatives, it does not seem to be conclusive evidence for the non-sex-linkage alternative.

This review of evidence against sex-linkage is by no means exhaustive. The two examples show however, how easy it is to reject sex-linkage without necessarily being able to discriminate. This situation can arise of course, only because of the general belief in unimportance of sex-linkage.

Evidence for Sex-Linkage

We have already cited three studies which may be interpreted as sex-linkage. The two other studies cited by Pahnish *et al.* (1961) and not included in this review may be added.

Beilharz (1960, 1961) has presented some evidence of important sex-linkage in bodyweight of poultry, rabbits, mice and sheep. The evidence consists of the observations that the influence of parents was in each species relatively greater in progeny of

the opposite sex. Further he pointed out that heritability estimates calculated under the assumption of complete sex-linkage of additive variation are theoretically somewhat different to those assuming absence of sex-linkage. He found that in all species the heritability estimates assuming complete sex-linkage were more consistent between the sexes and with the expectation of occurring between 0 and 1, than estimates assuming absence of sex-linkage. It seems that in his populations sex-linkage played an important part in bodyweight inheritance. Other evidence, including a suggestion of sex-linkage in ear-length of rabbits, is also given.

His data can be criticised as showing above all an effect of non-genetic maternal effect. This is freely admitted. They are however much more easily reconciled with the sex-linkage alternative than with the other.

The effect does not seem to be confined to any one character. e.g. In milk production of dairy cattle there are reports which could indicate sex-linkage. Lorenz (1960) has calculated correlations and regressions of 223 cows' lifetime records on own first lactation, mothers', each grandmothers', and mothers' and fathers' paternal half-sisters (half-aunts) lifetime performance.

The correlations for fat test were greater in all cases except for that with mothers' performance, where the correlation for milk yield was higher and more significant. I have translated from the author's discussion of this. "An explanation for this result may be found in the fact that mother and daughter were frequently milked on the same farm and were thus subject to the same permanent environmental influences. The likelihood that the daughters in question were milked on the same farm as their grandmothers or half-aunts is much less." The author is making the point that this result is consistent with a higher heritability of fat test than milk yield.

The results show that the correlation with mothers' performance is significant and the greatest of the relationships with relatives. The next highest correlation, significant in the fat test, is that of half-aunts on the maternal side. The correlation with half-aunts on the fathers' side is very low and this regression both in milk yield and fat test is slightly negative. This is a result one would expect with sex-linkage. There is no X-chromosome relationship to half-aunts on the father's side. The relationship is broken by the passage of a Y-chromosome from grandfather to father. On the mother's side one X-chromosome of the mother is the same as one X-chromosome of each of the half-aunts. The X-chromosome relationship is thus quite high.

Lorenz dismisses this discrepancy again in terms of permanent environmental influence, as the likelihood of several daughters of one bull (mother or aunts) milking on one farm is great. This dismissal is not satisfactory. Firstly, the author has earlier used the greater expected environmental correlation between daughter and mother relative to daughter and any other relation to make his results consistent with higher heritability of fat test. Secondly, it is in the fat test, which the author has just stated is less affected by environment, that the half-aunt correlation is greatest.

The only study of the inheritance of breeding worth based on the relation of progeny test results between bulls and their sons (Robertson, 1960) has shown the actual relation to be 25% less than theoretically expected (on autosomal inheritance) in milk yield,

although in fat test the results are close to expectations. One would expect a lower relation between father and son in the presence of important sex-linkage.

Again the review cannot be considered exhaustive. The examples show however, that evidence of possible sex-linkage can be found even in studies where the authors have not considered it.

Conclusion

1. There seems to be no direct evidence discriminating between the alternative hypothesis that sex-chromosomes have an approximately equal, or a substantially greater effect on the organism than a pair of autosomes. To discriminate between them it thus becomes necessary to examine their consequences, the absence or presence respectively, of more than negligible sex-linkage in quantitative traits.

2. Before we can discriminate, it is necessary to eliminate the majority of inheritance studies because of unsuitable experimental design.

3. It seems extremely difficult in a single study to discriminate significantly. At present we can usually only hope to decide which alternative is favoured. It is necessary however, that we be not influenced by the prejudice "that sex-linkage is unimportant merely because it has been accepted in the past".

4. The available evidence is certainly not all in favour of absence of sex-linkage. It is thus quite possible that sex-chromosomes have a substantially greater effect than a pair of autosomes.

5. One can thus strongly recommend that this point be critically studied. It seems unwise to continue ignoring sex-linkage without further critical study.

Summary

The belief that sex-linkage is unimportant in quantitative inheritance is not based on evidence.

The conditions necessary for discriminating between the alternative hypothesis that sex-linkage is, or is not, negligible in quantitative traits, are discussed.

Examples from the literature are cited to show that the evidence is by no means all in favour of the negligible sex-linkage alternative.

It is recommended that this matter be investigated further. It seems unwise to ignore sex-linkage in quantitative inheritance without further testing.

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