POSSIBILITIES FOR GENETIC MANIPULATION
OF SEX RATIO IN LIVESTOCK

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Summary

Reports are reviewed in which genetic differences for sex ratio of offspring were found among breeds, breed crosses, strains, lines, line crosses, families or individuals. Although reports in which genetic variation could not be identified outnumber those in which it could, important genetic variation does exist in at least some populations. The direct or correlated response of sex ratio to selection is reviewed. Again, results are equivocal, but there is ample evidence that sex ratio will respond to selection in at least some populations of laboratory organisms. Segregation distortion in the mouse and in Drosophila is examined. Segregation distortion occurs when a heterozygous male mated to a homozygous female does not produce the two offspring types in equal proportions and the disparity cannot be accounted for by sampling or differential mortality. Although the most well-known systems have no effect (in the mouse) or only a moderate effect (in Drosophila) on sex ratio, systems in which sex ratio is subject to segregation distortion are known to exist in insects and could exist in mammals. Finally, the possibility is discussed that XX/XY chromosome chimaeric bulls, born co-twin to a heifer, might produce a preponderance of heifer progeny. A few reports suggest this might be the case, but other research is not in agreement.

(Key Words: Sex Ratio, Livestock, Laboratory Animals, Genetic Manipulation.)

Introduction

Male mammals are heterogametic. Because of their XY sex chromosome genotype, they produce two kinds of gametes with respect to sex chromosome content. Female mammals, with an XX sex chromosome genotype, are homogametic. All their gametes, barring errors in meiosis, carry a single X chromosome. When male and female gametes unite at random in fertilization, one-half the resulting zygotes should have an XY sex chromosome genotype and differentiate as males; the other half should have an XX sex chromosome genotype and differentiate as females. In birds, the situation is reversed. Males are homogametic (ZZ) and females are heterogametic (ZW), but the segregation of chromosomes at meiosis, the random union of gametes at fertilization and the resultant near equality of sex ratio in the progeny is the same in both classes.

Less well understood than the mechanics of sex determination is the reason that the presence of one or more Y chromosomes in mammals almost invariably causes male differentiation, while the absence of a Y, irrespective of the number of X chromosomes, generally is associated with female development (Beatty, 1970a). Male differentiation currently is thought to be triggered by histocompatibility Y antigen. This antigen is either the product of or under transcriptional control of a Y chromosome-linked gene (Silvers and Wachtel, 1977; Wachtel, 1977; McCarrey and Abbott, 1979). Cases of masculinization in the absence of a Y chromosome (Bennett et al., 1977; Selden et al., 1978; Gileva and Chebotar, 1979) could be due to translocation of a portion of the Y chromosome to an autosome, to an X-Y translocation or to an autosomal locus mimicking the role of the Y chromosome.

Long before the chromosomal mechanism for sex determination was recognized, humans were interested in developing a means to predetermine the sex of offspring, not only in domestic livestock but in our own species as well. Many superstitions evolved (Parkes,
1971), and some have persisted to the present day.

An early attempt at sex ratio manipulation in domestic animals by X versus Y chromosome-bearing sperm separation was reported by Lush (1925). Since that unsuccessful experiment involving centrifugation of bull semen, there have been numerous attempts to process semen and thereby alter sex ratio in subsequent conceptions. Such research was reviewed in an ASAS Symposium (Kiddy and Hafs [Ed.], 1971), by Beatty (1970b, 1974) and by Stranzinger (1977). Physical or chemical techniques that have been attempted include density gradient centrifugation, sedimentation electrophoresis, treatment of semen with chemicals or hormones, alteration of atmospheric pressure, varying of the pH of the dilution medium, electrophoresis in combination with centrifugation and chemical treatment, selective absorption of sperm cells on ion exchange resins, froth flotation and reaction of semen in suspensions of cytotoxic antibodies for histocompatibility antigens on Y chromosome-bearing sperm cells. Techniques based upon the assumption of different physico-chemical properties of X- and Y-bearing sperm cells include insemination timed with respect to initiation of estrus (Deinhardt and Muller, 1978; Gebicke-Harter et al., 1977), alteration of the pH of the female reproductive tract (Roberts, 1940), alteration of the mineral nutrition or blood mineral balance of the female (Lyster, 1972; Stolkowski, 1977) and immunization of females to Y chromosome histocompatibility antigen (Beer and Billingham, 1976).

Most of the techniques cited above have not been successful in altering sex ratio. For others, reported successes have not been consistently repeatable. Results with several techniques, however, have been encouraging enough to stimulate further experimentation. Perusal of any recent volume of Animal Breeding Abstracts will show unequivocally that the race to achieve sex ratio control in livestock through manipulation of semen or of the breeding female is still on.

It is intuitively obvious but difficult to quantify that sex ratio control would be economically advantageous in livestock production. Reports in which genetic and(or) economic benefits have been described include those of Foote and Miller (1971), who discussed dairy and beef cattle, swine, sheep, horses, mink and poultry; Horn et al. (1972); Skjervold (1972); Cunningham (1975, 1977); Van Vleck and Everett (1976), and Adam (1978), all of whom discussed dairy, dual-purpose or dairy plus dairy x beef crossbreeding production systems. Realization of potential benefits involves taking advantage of sexual dimorphism for economic traits (higher growth rate of males than females, for example), allowing greater selection intensity and thereby greater response to selection, as well as lower cost per replacement individual, and(or) facilitating the application of various mating systems (allowing, for example, the production of a high proportion of F₁ female offspring from the crossing of breeds chosen specifically for maternal ability).

In this article, I will examine possible genetic means of manipulating sex ratio. Included will be a review of evidence from the literature on genetic variation in sex ratio, a review of experiments in which sex ratio has been subjected to direct or indirect selection, discussion of a genetic phenomenon providing an exception to Mendel’s laws of segregation and(or) random union of gametes and a description of the possibility that XX/XY chimaeric bulls born co-twin to a heifer might sire a preponderance of heifer progeny. The thesis of my article is that since physical and chemical techniques for manipulating sex ratio have not produced the desired results, it may be time to pursue new courses of research. The rewards to society of success would be so great that no scientifically rational inquiry should be discouraged.

**Evidence for Genetic Variation in Sex Ratio**

Genetic variation in sex ratio (male offspring as a proportion of total births) can be sought at various levels. That is, genetic differences could exist among species (which would not be of particular concern to livestock producers) or among breeds, strains, lines, families or individuals. In addition, crosses or strain or line crosses could differ among themselves or from their straightbred parents in sex ratio of the offspring. This review is limited primarily to investigations in which the search for genetic variation was rewarded with positive results. The number of contemporary investigations in which results were negative would outnumber the positive studies by a considerable margin. My purpose, though, is not to determine whether meaningful genetic variation
usually exists, but whether it ever exists, and if so, to characterize its magnitude and type.

**Variation among Breeds and Breed Crosses.**
Evidence of genetic variation among breeds in sex ratio of the offspring is limited. Two reports (Ilancic, 1968; Ledor and Reif, 1978) indicate that dog breeds differ significantly from one another in sex ratio, with larger breeds producing a preponderance of males. Skjervold (1978) reported statistically significant differences among dairy breeds; the range in percentage of male calves at birth was from 47.7% for Finnish Ayrshire to 51.6% for Swedish Red and White cattle.

Skjervold (1979) also reported significant variation in sex ratio of offspring among breeds of sheep. The range in least-squares means was only 48.4 to 49.2, so the statistical significance was more a function of population size (nearly 500,000 lambs) than the magnitude of differences among breeds. Nishida et al. (1969) reported that sex ratio of offspring for Berkshires was lower (.45) than that for Yorkshires, Hampshires or Landrace (.52 to .53) at a Japanese experiment station. Later work by Nishida and co-workers, however, failed to confirm important differences among breeds (Nishida et al., 1971, 1976). Kennedy and Moxley (1978) reported higher sex ratios for Landrace- and Lacombe- than Yorkshire-sired litters. Merat (1963) found differences among breeds of chickens in sex ratio of the offspring, and Champion (1960) reviewed earlier work in which breed differences for sex ratio in poultry also were reported. Numerous other compilations, however, have failed to expose meaningful differences in sex ratio among breeds of dairy cattle or sheep (see, for example, Foote, 1977; Muramatsu and Kawanishi, 1975; Napier and Mullaney, 1974).

Guha (1972) reported an unusual finding regarding sex ratio of crossbred dairy cattle. Holstein and Jersey bulls imported into India were mated to local Hariana cows to produce F_1 offspring, which were then mated *inter se* to produce Holstein × Hariana and Jersey × Hariana F_2 crosses. In both F_2 groups, the sex ratio was significantly and markedly below the expected value of about .50 (.45 and .44 for Holstein and Jersey crosses, respectively). This could be explained as a weak manifestation of Haldane's (1922) rule that among progeny from wide crosses, the heterogametic sex will be deficient (if there is any departure from normal sex ratios), except that in the F_1 generation Holstein crosses and Jersey crosses had sex ratios of .51 and .50, respectively. Guha speculated that Y-bearing sperm cells produced by the F_1 bulls (the Y having originated from the exotic breed) had poorer motility than did X-bearing cells from the same bulls (the X chromosome having originated from the indigenous breed). He pointed out that the creation of an F_2 from the reciprocal crosses (Hariana males × Holstein and Jersey females in the F_1) and evaluation of sex ratio within that F_2 would allow his hypothesis to be tested. Such an experiment apparently has not been done.

**Variation among Strains, Lines or Strain or Line-Crosses.**
Evidence supporting the existence of genetic differences in sex ratio among lines of laboratory rodents has been reported by a number of investigators. Cook and Vlcek (1961) studied nearly 18,000 mice from 2,873 litters and 11 inbred lines and concluded that three lines had a significant excess of female offspring, while one had a significant excess of males. Sex ratios for the aberrant lines were .45, .45, .47 and .53; the overall sex ratio equaled .49. Ohzu and Sato (1963) reported that in four of nine strains of laboratory rats, sex ratio was sensitive to seasonal influences. In three strains, the proportion of male offspring increased in autumn months, while in the fourth strain, it decreased. This genotype × environment interaction was interpreted as evidence of genetic variation. Schlager and Roderick (1968) studied sex ratio in 30 inbred mouse strains over two time spans at the Jackson Laboratory, Bar Harbor, Maine. There were 1,146 to 10,375 animals per line. Three strains had consistently low proportions of males and seven had consistently high proportions of males. Despite this evidence of interline genetic variation, Schlager and Roderick calculated that only 2% of the variation in sex ratio was attributable to genetic causes. Nishida et al. (1974a) studied sex ratios in 10 inbred mouse strains, with 2,393 to 7,063 offspring per line. Sex ratios for six lines were significantly above expectations;
none was significantly below. Lines ranged from .49 to .54 in proportion of males. In a later study, Nishida and Inaba (1978) reported small but significant differences among four lines descended from the same foundation population. In these lines, the sex ratio ranged from .49 to .53.

Howard et al. (1955) studied sex ratio in litters from all possible matings among four inbred mouse lines. The four parent lines did not differ significantly from one another in sex ratio (overall average .53), nor did the reciprocal crosses differ (average difference .03). The six linecross groups (reciprocals pooled) did, however, differ significantly, with sex ratios ranging from .45 to .59. The authors concluded that the differences among F₁ groups were attributable to genetic effects acting directly on the hybrid offspring rather than on the inbred parents.

Champion (1960) presented evidence that strains of White Leghorns differed significantly but modestly in sex ratio and reviewed literature dating to 1924 which also documented strain differences in sex ratio in the fowl. Merat (1963) reported significant strain differences in sex ratio in chickens at French experiment stations. The range in sex ratio he reported was .47 to .51.

Variations among Families and Individuals. The sex ratio of the progeny of a population of individuals is expected to be distributed binomially, or possibly according to the Poisson distribution, for litter-bearing species (Howard et al., 1955; Krefft, 1972). In either distribution, the variance in sex ratio would be large when the number of offspring was small, so marked deviations from the expected proportion of .50 would be fairly common. It would therefore be most reasonable and potentially most rewarding to seek meaningful evidence of individual variation in sex ratio in species with a large number of progeny per parent. Likely candidates are cattle (for which artificial insemination allows very large paternal half-sib families), swine, poultry and laboratory rodents. A perusal of the literature on these species located considerable evidence of differences among individual males or females in offspring sex ratio. This individual or phenotypic variance does not confirm the existence of genetic variance for the trait, but there cannot be genetic variance unless significant phenotypic variance exists.

Roy et al. (1970) reported no significant difference among cattle or buffalo sires in sex ratio of offspring. Although Brands et al. (1965) identified significant differences among dairy bulls, the authors doubted the practicality of selection based on sex ratio, because the offspring sex ratio for a bull mated to heifers frequently was at variance with the sex ratio observed when the same bull was mated to older cows. Powell et al. (1975) studied sex ratio in the offspring of Holstein bulls used for artificial insemination. Although each sire had a minimum of 80 and an average of 154 offspring, and even though the proportion of male offspring ranged from .39 to .64, sire differences were only about as large as would be expected strictly by chance. The heritability estimate for sex ratio was near zero. Foote (1977) reported that offspring sex ratios for six of 111 sires differed significantly from breed averages. Six of 111 is discouragingly close to the one in 20 "significant" differences readily attributable to chance.

Gray and Hurt (1979) computed the correlation of sex of calf in successive as well as nonsuccessive calvings by the same cow. The correlations were essentially a repeatability and as such would be influenced by total genetic differences (additive and nonadditive) as well as by permanent or transitory environmental differences among cows. The correlations were small and nonsignificant, but they were predominantly positive for successive parities or parities separated by only one calving.

In contrast to these generally negative results, McWhirter (1956) reported that of 32 sires with an average of over 1,150 offspring each, 12 had offspring sex ratios that deviated significantly from the expected ratio. For most of the bulls for which appropriate data were available, sex ratios were fairly consistent across years. Heiman (1968) also reported repeatable deviations in sex ratio for offspring of certain Israeli artificial insemination sires. Muramatsu and Kawanishi (1975) studied sex ratio of offspring of Japanese Black, Japanese Brown and Japanese Shorthorn bulls. Offspring of 13 of 117 sires showed a deviation toward one or the other sex; the most deviant bulls had offspring sex ratios of .40 ± .03 and .31 ± .04.

Bar-Arian and Robertson (1975) analyzed offspring sex ratios of Israeli Friesian sires used for artificial insemination. There were
highly significant differences among sires in sex ratio of the offspring, and there was positive correspondence between a sire’s sex ratio when he was mated to heifers and when he was mated to older females. Offspring sex ratios for sires were positively correlated with sex ratios for sons \((r = .50)\), and there was a positive intraclass correlation among paternal half sibs as well.

Skjervold and James (1979) studied variation in sex ratio in Norwegian dairy cattle populations. They reported that sire differences were important and, further, that heritability of sex ratio estimated from a paternal half-sib analysis was \( .50 \pm .15 \). As in the study by Bar-Anan and Robertson (1975), though, the standard deviation for sex ratio was not large \((.019)\), so large families would be necessary for one to estimate breeding value for sex ratio accurately. Selection differentials would not be large, and predicted response to selection would be slow. Interestingly, the sex ratio of a sire’s progeny had little relationship to sex ratio in progeny of daughters of the sire.

Lopes Seco and Vieites (1971) reported significantly deviant sex ratios for offspring of three of 50 Landrace sows and three of 37 Landrace boars. These are well within the number of "significant" differences readily attributable to chance, but four daughters and six sons of one boar produced excess daughters, as had their sire. In another swine study, Kennedy and Moxley (1978) reported that neither sires nor dams within breeds influenced sex ratio of the offspring. Repeatability of sex ratio measured as a characteristic of the sow was .05. Nishida and his colleagues studied genetic and environmental factors influencing sex ratio in swine at a number of experiment stations in Japan. Nishida et al. (1969) reported that offspring of 16% of boars, but of only 6% of sows, showed statistically significant shifts (deviations from the expected value of .50) in sex ratio. An analysis of sex ratios of ancestors of aberrant individuals did not provide conclusive evidence that the shifts in sex ratio were highly heritable. This report was followed by seven others (Nishida et al., 1971, 1972, 1973, 1974b, 1976, 1977, 1978), each studying large numbers of offspring, sires and dams from different Japanese experimental farms. In each paper, the percentages of boars and sows whose offspring showed a significant shift in sex ratio were tabulated. In no case did this percentage deviate markedly from 5%, that expected strictly from the vagaries of random sampling. Thus, Nishida’s large body of work does not provide encouraging evidence of individual differences in sex ratio of male or female swine.

Nishida has conducted similar research with laboratory rodents. As with swine, the proportions of male and female rats (Nishida and Nakama, 1971) and mice (Nishida and Inaba, 1978) with significantly aberrant sex ratios differed little from the expected 5%.

Individual differences among roosters in sex ratio of offspring were reported by Mussehl (1924), but neither Hazel and Lamoreux (1946) nor Champion (1960) found compelling evidence of family differences in sex ratio. The earlier study examined paternal half-sib, maternal half-sib and full-sib families; the latter study included only full-sib families. Foster and McSherry (1980) reported that White Leghorn hens did not differ in sex ratio of their offspring but that significant variation did exist among sires. The regression of son on sire was only \(.03 \pm .09\), however. Individual and familial differences in sex ratio in poultry also have been examined in a series of papers by Merat. From an extensive experiment involving many strains and 172,000 offspring, Merat (1963) concluded the following: (1) within strains and years, there were highly significant differences among dams and especially among sires in sex ratio of offspring; (2) significantly more sire families than expected had an excessive number of male or female progeny; (3) in some instances, there was heterogeneity in sex ratio of different full-sib families from the same sire; (4) in the most intensively studied strain, familial differences in sex ratio were not attributable to differential mortality of sexes within families, and (5) parental differences in sex ratio did not appear to be transmissible to the progeny.

In another investigation, Merat (1969) reported the existence of sire families in which sex ratio varied from .08 to .68 and dam families in which ratio varied from .06 to .79. Fertility and hatchability in the families were high, eliminating differences in mortality between sexes as a cause of abnormal ratios. Merat (1970) confirmed the existence of important variation among sire families but added the disturbing observation that differences in sex ratio often existed between suc-
cessive hatches from the same sire. Moreover, the timing, direction and magnitude of these differences did not coincide from sire to sire. They did not appear to be synchronized by some unidentified environmental change.

The general conclusion justified from the foregoing review of research on genetic variation in sex ratio is that such variation probably exists, at least in some populations, but that identification, characterization and effective utilization of such variation in selection and mating schemes will not be an easy matter.

**Direct and Indirect Selection for Altered Sex Ratio**

If genetic variation exists for sex ratio of the offspring, and if a portion of that genetic variation is additive, then directional selection should be successful in altering the sex ratio in a population. If genes influencing sex ratio have pleiotropic effects on other traits (or if such loci are closely linked to genes affecting other traits), then there occasionally should be correlated response in sex ratio to selection applied to another characteristic.

Results of experiments in which directional selection was attempted have been variable. King (1918) founded two inbred lines from brother-sister pairs from the same litter of random-bred albino rats. After six generations of brother x sister mating, during which there was no selection, she began selecting for increased versus decreased sex ratio in the two lines. Response was immediate in both and lasted for about six generations. Through an additional 13 generations of selection, sex ratios in the two lines remained at approximately .55 and .44. Selection line females mated to unrelated, outbred males produced litters in which the sex ratio deviated from the norm in the same direction as it did in the line from which the dams originated. Selection line males, however, had only a minor influence on sex ratio of the progeny when mated to unrelated, outbred females. King attributed this difference to differential chemotactic responses of ova from selected females to male- versus female-determining sperm cells.

Falconer (1954) attempted without success to alter sex ratio by directional selection in both mice and Drosophila. In mice, the heterogeneity among families in sex ratio of offspring was not statistically significant, and heritability estimated from resemblance among relatives was about .05. Falconer acknowledged the existence of major genes capable of modifying sex ratio (and attributed King's success to the existence of one or a few such loci in the lines she founded). He pointed out, though, that variation in sex ratio attributable to binomial sampling would be large and generally would render additive polygenic variation in sex ratio difficult to identify and difficult to exploit through selection.

Probably the most well-known case of correlated response in sex ratio to selection for another trait was that reported by Weir (1972) in a study involving blood pH in the mouse. After a single generation of selection, lines from a common base population had become differentiated for increased (H) versus decreased (L) blood pH. After two additional generations of selection with no response, selection was terminated, and the lines were propagated thereafter by brother x sister matings. After some time, Weir discovered that the blood pH lines also differed in sex ratio of offspring. Sex ratio in the pHH and pHL lines averaged about .54 and .44, in contrast to .49 in the base population before selection began. Sex ratio was never a conscious selection criterion. In fact, inadvertent selection would have been counter to selection response (since unisexual litters contributed no parents to the next generation) or could have had a stabilizing effect (since litters in which sex ratio was near .50 contributed more mating pairs to the next generation than did litters with an excess of one sex or the other).

Blood pH per se apparently was not the cause of variation in sex ratio, since altering the pH by diet did not cause a corresponding shift in sex ratio (Weir and Haubenstock, 1964). Also, in an experiment patterned closely after Weir's original work, pH again responded quickly to selection and then plateaued, and again there was a correlated response in sex ratio but, contrary to Weir's results, the low pH line had an excess of male offspring (Wolfe, 1961).

Weir has shown in a series of carefully designed and replicated experiments that the alteration in sex ratio is attributable to the male rather than the female parent. In reciprocal crosses of the pH-selected lines, pHH male x pHL female matings produced a preponderance of male offspring, while pHL males x pHH females produced a preponderance of females (Weir, 1955). When pHH and
pHL males were mated to females from four inbred lines, sex ratios in the resulting progeny averaged .56 and .39, respectively (Weir, 1960). Also, pHH and pHL males crossed to outbred females derived from crosses among five inbred lines produced progeny in which sex ratios averaged .53 and .39, respectively (Weir, 1962). When reciprocal F₁ cross males were backcrossed to the line of their dam, outcrossed to females of other lines or mated to an F₁ female of the same reciprocal cross, sex ratios in the litters averaged .51 when the F₁ male derived his Y chromosome from the pHH parent and .47 when the Y chromosome originated from the pHL parent (Weir, 1976). Analysis of F₂ and backcross data indicated that the Y chromosome was partly but not wholly responsible for the effect on progeny sex ratio (Chi, 1975; Weir, 1976). An effect on male mating behavior wholly attributable to the Y chromosome also was reported (Weir, 1976).

Wilson et al. (1971) reported another case in which sex ratio exhibited apparent correlated response to selection. They described response to long-term selection for body weight in the mouse and noted that over time, the sex ratio shifted from an excess of females (sex ratio of approximately .45) to an excess of males (sex ratio of approximately .55). Selection had been based on a combination of individual and family data and upon progeny testing. It is possible that there had been unconscious selection for increased sex ratio.

Robins (1959) reported that mice afflicted by congenital clubfoot, a condition caused by an autosomal recessive gene with complete penetrance, had an altered sex ratio of .60. He attributed this result to differences in embryonic mortality between the sexes, however, rather than to genetic correlation between the defect and sex ratio. Meyer and Plonait (1968) found that approximately two-thirds of the offspring produced by boars homozygous for congenital rickets were male, and speculated that the effect might be due to gametic selection. Even if this system proved to be consistently effective, selection for a hereditary defect would not be a suitable or cost-effective means of manipulating sex ratio.

**Segregation Distortion in Drosophila and Mice**

Considerable research effort has been expended over the last 80 years to verify the general applicability of Mendel’s laws. It is dogma that a heterozygote will produce gametes with equal proportions of each allele and that, at fertilization, male and female gametes will unite at random. When the expectation that a heterozygote × homozygous recessive mating should result in heterozygous and homozygous recessive offspring in equal proportions has not been met, it generally has been possible to explain observed results in terms of differential embryonic mortality. There are, however, two well-documented exceptions, one in mice and the other in Drosophila.

Braden (1972) has reviewed the T (tailless) locus in mice. An allele T, probably a point mutation, causes embryonic mortality of homozygotes and taillessness in heterozygotes. A large series of t alleles, shown to involve a considerable length of chromosome rather than a single point, decreases tail length in a characteristic fashion in Tt heterozygotes but generally results in normal tail length in wild type heterozygotes (t+). The most interesting property of the t alleles is that Tt males mated to ++ females generally do not produce T+ and t+ offspring in equal proportions. The altered “transmission ratio” of t can be as high as 20 to 1. Heterozygous t+ males mated to ++ females also generally do not produce the two offspring types in equal proportions. Differential embryonic mortality has been ruled out as the cause of the “segregation distortion,” as the phenomenon has come to be called. Also, the altered offspring ratios are a property of heterozygous males; mating heterozygous females to ++ males results in normal ratios in the offspring and no segregation distortion. Differences in fertility between t- and T- or + -bearing sperm (rather than production of different numbers of t versus T or + sperm) probably account for the segregation distortion, since the transmission ratio for a t allele is influenced by the time of mating with respect to ovulation and by other factors that could not influence the number of mature sperm of each type in an ejaculate.

Segregation distortion also occurs in Drosophila, as reviewed by Hartl and Hiraizumi (1976). In the most well-known system, the amount of segregation distortion in a particular population is influenced by an Sd locus, from which the gene product causing altered Mendelian ratios is thought to originate; a
responder locus (Rsp), situated on the same chromosome and thought to be the site of action of the Sd gene product; and various modifier genes, located throughout the genome and able to moderate the effect of specific Sd and Rsp genotypes. As in mice, differential mortality cannot account for the altered phenotypic ratios in progeny of heterozygote male × homozygous wild type female matings. Also as in mice, the reciprocal mating of wild type males to heterozygous females results in normal offspring ratios.

Neither the T locus nor the Sd and Rsp genes are sex linked, and in neither system is there a marked influence on sex ratio of the offspring (though Hiraizumi and Nakazima [1967] reported small but consistent deviations from a normal sex ratio in segregation distortion systems in Drosophila). Instances of segregation distortion from sex-linked loci in Drosophila are known, however (Zimmering et al., 1970; Peacock and Miklos, 1973; Policansky, 1974). Such systems cause heterozygous males to produce progenies that are predominantly female. In mosquitoes, a segregation distorter closely linked to the sex determination locus causes the opposite result, predominantly male families from the mating of heterozygous males to homozygous females (Hickey and Craig, 1966).

By X-irradiating males from a stock segregating for Sd, then introducing into population cages males in which the Y chromosome had become linked to Sd through translocation, Lyttle (1977) succeeded in achieving sex ratio control in cage populations of Drosophila. Such males produced only male offspring, driving populations to extinction in about seven generations. Unfortunately, the potential use of this method for biological control of insects is limited by the existence and segregation in wild populations of modifier genes that lessen effects of known segregation distortion systems.

Braden et al. (1972) summarized the remarkable similarities between properties of the T locus and the Sd systems. Notably, these segregation distorting systems, though they impose a genetic load upon any population in which they exist, are distributed ubiquitously in natural populations of mice and Drosophila, respectively. The existence of sex ratio distortion systems in Drosophila suggests the possibility that they exist in mammals, although none has been reported. (The observation of Moriwaki and Sakakibara [1976] that a deletion on the Y chromosome caused an increased frequency of malformed spermatozoa and a slight decrease in the sex ratio of offspring in mice could be a case of Y-linked segregation distortion.) If such systems do exist, they could be used to manipulate sex ratio, as discussed by Beatty (1971).

**XX/XY Chimaeric Bulls**

The bovine freemartin is a masculinized heifer born co-twin to a bull. This condition has been known since ancient times (Belloni, 1952), but recognition of anatomical causes of the phenomenon emerged only in the early 1900's (Tandler and Keller, 1911; Keller and Tandler, 1916). Early in gestation, chorionic membranes of the majority of twin fetuses fuse, and vascular anastomoses develop, allowing common blood circulation to both of the twins. Certain types of fetal cells enter this common blood stream (Owen, 1945; Ohno et al., 1962), then migrate to and become established in the appropriate tissues of the co-twin. Donor and recipient cells can exist in each co-twin through maturity (Ohno, 1969), and the dizygous twins become partially immunologically tolerant of one another (Stone et al., 1965). Because of (1) circulation in the female's blood stream of testicular hormones produced by the male co-twin, (2) influences from XY chromosome-bearing cells in the female's undifferentiated gonads, (3) a combination of effects or (4) undetermined factors, the freemartin heifer undergoes prenatal masculinization (Short, 1969; Marcum, 1974), generally with accompanying infertility.

Male twins from a heterosexual (male/female) birth have piqued less scientific curiosity than have their freemartin sisters. They generally are phenotypically normal but may be subnormal in fertility (Dunn et al., 1968, 1979; Stafford, 1972; Long, 1979). The male twins are of interest in this discussion of sex ratio control because the existence of XX chromosome-bearing cells in their germinal epithelium could lead to a higher proportion of daughters among their progeny.

Many bull calves born co-twin to a heifer are chimaeric for XX and XY chromosome-bearing cells. This chimaerism is easiest to locate and has been reported most commonly for leucocytes (see Marcum, 1974, for a review), but it exists in other tissues as well (bone...
marrow: Teplitz et al., 1967; Dunn et al., 1968; Short, 1969; Lodja, 1972; kidney: Lodja, 1972; spleen: Teplitz et al., 1967; lymphatic system: Short et al., 1969). There is some tendency for a positive association of ratio of XX to XY cells across tissues (Ohno et al., 1962; Teplitz et al., 1967; Dunn et al., 1968). For leucocytes and lymphocytes, the ratio of XX to XY cells also is repeatable across time (Teplitz et al., 1967; Weiss and Hoffmann, 1969).

Ohno et al. (1962) reported XX as well as XY chromosome-bearing cells in the testes of 1-day-old Holstein heterosexual twin bull calves. The presence of XX cells in testes of older affected bulls was reported by Teplitz et al. (1967), Weiss and Hoffmann (1969) and Lodja (1972), but Weiss and Hoffmann (1969) reported that the ratio of XX to XY cells declined with advancing age. Whether XX cells are capable of meiotic division in the testicular environment of the heterosexual twin bull is a subject of controversy. Teplitz et al. (1967) presented photomicrographs of meiosis of XX germ cells through diakinesis, but the authors’ interpretations of the photographs have been questioned by Ohno (1969) and Ford and Evans (1977). Ford and Evans (1977) examined 87 spermatogonia and 1,052 primary spermatocytes from seven heterosexual twin bulls and found no XX cells. Dunn et al. (1979) also failed to detect XX germ cells in testes of 11 postpubertal chimaeric bulls.

Direct evidence that XX cells could undergo successful gametogenesis in the bull would be furnished by documentation that a calf inherits traits from its sire’s freemartin sister. Evidence of this type is lacking. Ohno et al. (1962) cited a personal communication from R. D. Owen indicating that in the course of Owen’s studies of blood group chimaerism of dizygotic cattle twins, no evidence was found of a bull transmitting to his offspring the traits of his freemartin sister. Dunn et al. (1968) also reported no evidence of inheritance from the bull’s sister in 23 offspring of a heterosexual twin bull. Stone et al. (1960) examined seven and 19 progeny of dizygous twin bulls. In each case, the offspring’s phenotype for various blood antigenic markers was consistent with the genotype of the sire rather than that of the uncle. This experiment did not, of course, examine the ability of immigrant XX cells to undergo spermatogenesis, but it suggested that immigrant XY cells did not do so.

Tucker et al. (1978) created tetraparental rams by transplanting blastomeres from a donor zygote into intact four- or eight-cell embryos which subsequently were transferred to recipient ewes. Two of the rams were XX/XY chimaeras. Of 27 lambs produced by those rams, 18 were male and nine were female. Two of the 27 lambs could not be assigned to blastomere or embryo cell line parentage of their sire, but the remaining 25 resulted from a male gamete whose cellular ancestor was a transplanted blastomere. In other words, the XX/XY chimaeric rams apparently were not producing functional gametes from their XX cells. In the same study, an XY/XY chimaeric ram did produce offspring from both blastomere and embryo cell lines, in contrast to the results of Stone et al. (1960) with cattle.

Indirect evidence that XX cells can undergo successful gametogenesis in a testicular environment would be furnished by a lowered sex ratio in the offspring of heterosexual twin bulls. Such evidence has not been consistent, but there have been some tantalizing suggestions that some such bulls do sire a preponderance of daughters. Dunn et al. (1968) studied three heterosexual twin bulls. For the progeny of two, the sex ratio did not deviate from the norm, but among progeny of the third, daughters outnumbered sons by 38 to 14. Lodja (1972) reported a sex ratio of .40 for a heterosexual twin bull, but the remaining 25 resulted from a male gamete whose cellular ancestor was a transplanted blastomere. In other words, the XX/XY chimaeric rams apparently were not producing functional gametes from their XX cells. In the same study, an XY/XY chimaeric ram did produce offspring from both blastomere and embryo cell lines, in contrast to the results of Stone et al. (1960) with cattle.

Thus, it is evident that it will not be possible to lower, at will, the sex ratio in cattle by the
indiscriminate use of XX/XY chimaeric bulls (which currently would be relatively easy to produce by embryo transfer techniques; one-half of all successfully induced twin pregnancies should yield a heterosexual twin bull). The evidence does not exclude, however, the occurrence of chimaeric bulls with functional XX spermatogonia, normal fertility, a preponderance of X-bearing sperm cells and a preponderance of heifer offspring. A judicious search for such bulls, by means of modern immunological and cytogenetic techniques, might well be warranted.

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