A Quantitative Analysis of Sex Determination

Harry Wang[1] (王熙)

I. INTRODUCTION.

Sex is genetically determined. The diploid (2N) chromoromes (one haploid (1N) set contributed by each parent) of the zygote determines the sex of the individual. This article deals with this chromosomal sex.

In this chromosomal determination the outcome of sex is decided by an interplay of three factors. These are (1) the autosomes as a whole (2) the X and (3)Y sex-chromosomes. The autosomes are for maleness, X chromosomes for femaleness. The Y sex-chromosome, on the other hand, exhibits two patterns of operation: in some species it has no effect on sex determination while in others it adds its strength to the autosomes for maleness. Under this setup sex is determined by one of two ways as follows:

Pattern A.

Example: *Drosophila melanogaster*. (male heterogamy)

Autosomes (A) (maleness)	vs.	X (femaleness)

A = 3, therefore,

Male (2A X(Y)[@]) has 6 autosomes + XY

Female (2A XX) has 6 autosomes + XX

@indicating Y chromosome, even when present, playing no role in sex determination.

Pattern B.

Example: *Homo sapiens*(also male heterogamy)

Autosomes + Y (maleness)	vs.	X (femaleness)

A = 22, therefore,

Male (2A XY) has 44 autosomes + XY

Female (2A XX) has 44 autosomes + XX

The above shows how sex is determined normally in these two species. The situation is, however, not that simple. In both these species certain percentage (presumably low) of individuals among the population are neither normal males nor normal females, but present abnormal conditions to various degrees. It is now quite established that what causes these sex abnormalities is nondisjunction. It is an error on the part of a mechanism which normally reduces the chromosome number from the 2N to 1N state during meiosis. This reduction is accomplished through separation or disjunction of paired homologous chromosomes so that the mature eggs and sperms invariably have only one member of each pair.

That is:

All human eggs (1A 1X) contain 22 autosomes + X

Spermatozoa are of two kinds by equal proportion:

either 1A 1X, which contains 22 autosomes + X

or 1A 1Y, which contains 22 autosomes + Y

The mechanism of disjunction is ordinarily highly stable. Occasionally, however, for reasons still incompletely understood, the mechanism fails with the result that two classes of germ cells, one receiving all of the chromosomes, the other, none, are obtained. In other words when nondisjunction happens the mature germ cells get 2N instead of 1N chromosomes. Sometimes nondisjunction is confined to the X and Y

1. Fulbright visiting professor, 1969-1970;
Professor of Anatomy, Stritch School of Medicine Loyola Univestity, Maywood, Illinois, U. S .A.

chromosomes while the autosome pairs disjunct in the usual way. Regardless of whether nondisjunction involves all the chromosome (synaptic) pairs or only the sex-chromosome pair, there are available new kinds of eggs and sperms which upon fertilization contain an unusual chromosome complement.

Years ago Bridges proposed the "theory of genic balance" to explain sex aberrants of this origin in *Drosophila melanogaster*. More recently human cases of comparable though different sex aberrants displaying defintive syndromes have attracted attention from clinicians and biologists alike. These syndromes provide suitable materials for a quantitative appraisal of the relative potency of the three sex-determining factors: the autosomes, and X and Y sex-chromosomes.

The present study is a preliminary attempt to test the validity of this quantitative concept of sex determination. The test consists in assigning a numerical value to each of the sex-determining factors and to apply them to the known sex aberrants according to their respective chromosomal complement. The idea is to see if by the use of such a simple system an index of sex may be thus instituted. For purpose of confirmation the system is subsequently tested on theoretical cases of human sex aberrants assumed to result from nondisjunction of all the chromosome pairs.

II. PRESENTING THE NUMERICAL SYSTEM.

A. The working principle of this system is that the chromosomes in a zygote carry antagonistic or opposing sex-determining factors for maleness and femaleness. The numerical difference of the two determines the sex of the individual. This difference represents a quantitative index of sex. The following criteria must be met:

(1) A differential of 2, in either direction, denotes normal maleness or normal femaleness.

(2) A zero differential (when maleness and femaleness determining forces are equal) leads to an intersex, an individual neither male nor female possessing intermediate characteristics.

(3) A differential above 2 denotes oversexness in either direction.

(4) A differential under 2 denotes undersexness in either direction.

B. The values of the three sex-determining factors are:

(i) when Y chromosome counts,

X=3 for femaleness

A = 2, Y = 1 ......for maleness

(ii) when Y chromosome does not count,

X = 3 for femaleness

A = 2 for maleness

C. Applying these values to normal maleness and normal femaleness:

In human ....
- 2A XY (male)=5 : 3 (♂by2)
- 2A XX (female)=4 : 6 (♀by2)

In *Drosophila* ...
- 2A 1X (male)=4 : 3 (♂by1@)
- 2A XX (female)=4 : 6 (♀by2)

@implies that as a consequcence of the functionless Y chromosome, the male sex with a differential of only 1 could mean a weak male sex in *Drosophila*.

The tests for conditions (2), (3) and (4) will be made at the proper moment.

III. SEX ABERRANTS IN DROSOPHILA AND THE NUMERICAL SYSTEM.

An egg from nondisjunction, 2A 2X, is

fertilized by a sperm, 1A 1X, resulting in a zygote which has 3A 3X chromosomes. This female fly is known as a Tri-X female. It is viable and produces four kinds of viable eggs, (25% each) as follows:

2A 1X
1A 2X ......(from nondisjunction, but all viable)
2A 2X
1A 1X (the only normal kind)

These eggs may be fertilized at random by normal spermatozoa, giving rise to a progeny shown as follows.

Table 1. *Drosophila* flies resulting from crosses between eggs from nondisjunction and normal spermatozoa.

Eggs / Normal sperm	from nondisjunction of a Tri-X female 2A 1X	1A 2X	2A 2X	1A 1X
1A 1X	3A 3X	2A 3X	3A 3X	2A 2X
1A 1(Y)@	3A 1X	2A 2X	3A 2X	2A 1X

@ indicating Y chromosome not functioning, hence excluded in the zygotes that contain it; evidence for this comes from the fact that the phenotypes of XY and XO are the same.

Six varieties of zygotes are formed by chance matings. In the following they will be listed with (a) their frequency (b) the X/A ratio (c) status of sex and (d) application of the present numerical system.

Zygotes	*Frequency*	*X/A ratio*	*Status of sex*	*Sex differential based on the numerical system*
2A 3X	1/8	1.5	Super-female	(4 : 9) ♀ by 5
3A 3X	1/8	1.0	Tri-X female	(6 : 9) ♀ by 3
2A 2X	2/8	1.0	Normal female	(4 : 6) ♀ by 2
3A 2X	2/8	0.67	Intersex	(6 : 6) 0
2A 1X	1/8	0.5	Normal male	(4 : 3) ♂ by 1
3A 1X	1/8	0.33	Super-male	(6 : 3) ♂ by 3

It is to be noted that the numerical system when applied to all the six varieties of zygotes indeed satisfactorily meets the criteria set under II. Not only that, but the system seems capable of expressing the sex status more precisely than could the X/A ratio used by Bridges. For whereas the Tri-X female and normal female both have a X/A ratio of 1, under the numerical system the two show a definite difference in these two female conditions. This implies that the 3A 3X tri-X female is more female than normal female of the 2A 2X complement. The intersex (3A 2X) affords a crucial test for the numerical system; it gives a zero differential exactly as required by one of the conditions set by the working principle of the system. Finally, a differential of 5 for fhe super-female and 3 for the super-male, while both amply displaying a tremendous over sexness of the respective sex, substantially reinforces the notion that in *Drosophila* perhaps a rather unique situation exists, namely that femaleness is the dominant or stronger sex. This is possibly due to the fact that its Y chromosomes does not assume any role in sex determination.

IV. SEX ABNORMALITIES DUE TO SEX-CHROMOSOME ABERRANTS IN THE HUMAN AND THE NUMERICAL SYSTEM.

Assuming that nondisjunction happens in both sexes, two new varieties of spermatozoa (XY) and (0) (the latter kind containing no sex chromosome) in addition to the two normal kinds, (X) and (Y), will result. Similarly, there will be two varieties of eggs available: (XX) and (0) in addition to the normal kind (X). The frequency of sex chromosome nondisjunction is not known, nevertheless these abnromal human gametes are present in the population. By chance mating some very interesting sex abnormalities have been obtained as follows:

Table 2. Human matings involving union of normal and abnormal gametes resulting from nondisjunction of sex chrosomes.

Eggs \ Sperm		(normal) X	(normal) Y	(from nondisjunction) XY	(from nondisjunction) O
(normal)	X	XX	XY	XXY	XO
(from nondisjunction)	XX	XXX	XXY	XXXY	XX
(from nondisjunction)	O	XO	OY@	XY	OO@

@nonviable

The viable zygotes with their full chromosome complement are listed below showing their frequency, status of sex and application of present numerical system as done with the *Drosophila* cases.

Zygotes	*Frequency*@	*Status of sex*	*Sex differential based on the numerical system*
2A 2X	2/12	Normal female	(4 : 6) ♀ by 2
2A XY	2/12	Normal male	(5 : 3) ♂ by 2
2A XXY	2/12	Klinefelter's syndrome	(5 : 6) ♀ by 1
2A XO	2/12	Turner's syndrome	(4 : 3) ♂ by 1
2A XXX	1/12	Tri-X female	(4 : 9) ♀ by 5
2A XXXY	1/12	Super-Klinefelter	(5 : 9) ♀ by 4

@not real frequency, pertaining only to results of chance matings assuming the 3 kinds of eggs and 4 kinds of spermatozoa being present to an equal extent

Explanation and

Possible significance of the data analysis:

1. Evidence that the Y chromosome in *Homo sapiens*, unlike that in *Drosophila melanogaster*, carries maleness determiners has come from the fact that individuals having XY and XO sex chromosome complements are not alike, In fact, they are drastically differerent in appearance: an individual with 2A XY is a normal male whereas an

individual with 2A XO is an abnormal female, Turner's syndrome. Thus, the effect of the absence of the Y chromrsome is remarkable.

2. It is interesting to note that aside from sex the X chromome has two striking side effects: (a) its absence in a zygote causes death, i. e., any individual must have at least one X chromosme. (b) But, persons having more than two X chromosomes, e.g., Tri-X females, are infantile and mentally retarded. The more X chromosomes a person has, least intelligent will she be!
3. Of the sex aberrantes due to additional X chromosomes or loss of the Y chromosome, the two that have commanded greatest attention are Turner's syndrome (2A XO) and Klinefelter's syndrome (2A XXY). The former has female features, but with gonadal dysgenesis, hence sterile. It is believed to have resulted from the union of a nondisjunctioned sperm (O) with no sex chromosome at all and a normal egg with an X chromosome. (Although the other posssibility (Table 2) of union between a nondisjunctioned egg (O) with a normal sperm carrying an X chromosome is there.) The Klinefelter's syndrome (2A XXY) is a sterile male characterized by testicular atrophy and hyalinization of the seminiferous tubules. Medical geneticists have shown it to have come from a nondisjunctioned egg (XX) fertilized by a normal sperm with a Y chromosome. (The other alternative is the union of a normal egg (X) with a nondisjunctioned sperm with XY sex chromosomes.)

   What appears significant with respect to the present numerical system is that the two cases both denote a decrease in sex differential from 2 to 1, in favor of the opposite sex. In other words, quantitatively a Turner patient is actually a male by a differential of 1 while a Klinefelter patient, actually, a female by the same amount of differential (that is, 1 in the female direction). The apparent sex reversal so manifested can be interpreted as due to the loss of a Y chromosome and the gain of an extra X chromosome, respectively, for the two cases. The analysis, therefore, substantiates the workability (if not validity) of the numerical system.
4. Furthermore. the case of Super-Klinefelter (2A XXXY), which can only be the result of a union between nondisjunctioned egg and sperm, shows a differential of 4 in the female direction. It illustrates the enhanced potency of an additional X chromosome over that of a regular Klinefelter.
5. The Tri-X female has highest female differential (5) because of its 3 X chromosomes coupled with the absence of Y chromosome. It again speaks well for the numerical system.

V. FURTHER TESTING OF THE SYSTEM ON THEORETICAL CASES OF HUMAN SEX ABNORMALITIES.

It is assumed that a human Tri-X female may nondisjunct in the way as a *Drosophila* Tri-X female, thereby producing four kinds of eggs. Similarly, the male also nondisjuncts and forms four kinds of spermatozoa. The progeny resulting from chance matings of these gametes of nondisjunction origin provide an array of sex aberrants. Some of them are possibly new varieties, hitherto unknown.

Table 3. Human matings between eggs resultning from nondisjunction of a Tri-X female and sperm from nondisjunctioned males.

Sperm \ Eggs		From nondisjunction of a Tri-X female 2A 1X	1A 2X	2A 2X	1A 1X
Normal Kind ……	1A 1X	3A 2X	2X 3X	3A 3X	2A 2X
	1A 1Y	3A XY(1)	2A 2XY	3A 2XY(2)	2A XY
from nondisjunction …	1A	3A X(3)	2A 2X	3A 2X	2A X
	1A XY	3A 2XY(2)	2A 3XY	3A 3XY(4)	2A 2XY

These data are treated below in the same manner as before.

Zygotes	*Frequency*	*Status of sex*	Sex differential based on the *numerical system*
(A) *New varieties*			
(1) 3A XY	1/16	Neo-supermale	(7 : 3) ♂ by 4
(2) 3A 2XY	2/16	?	(7 : 6) ♂ by 1
(3) 3A X	1/16	Super-male	(6 : 3) ♂ by 3
(4) 3A 3XY	1/16	Neo-Klinefelter	(7 : 9) ♀ by 2
(B) *Old forms* (Tables 1 and 2)			
2A X	1/16	Turner's	(4 : 3) ♂ by 1
2A 2X	2/16	Normal female	(4 : 6) ♀ by 2
2A XY	1/16	Normal male	(5 : 3) ♂ by 2
2A 2XY	2/16	Klinefelter's	(5 : 6) ♀ by 1
2A 3X	1/16	Super-female	(4 : 9) ♀ by 5
2A 3XY	1/16	Super-Klinefelter	(5 : 9) ♀ by 4
3A 3X	1/16	Tri-X female	(6 : 9) ♀ by 3
3A 2X	2/16	Intersex	(6 : 6) 0

Possible significance of these data.

1. The four new varieties (theoretical) of zygotes have one thing in common, namely, triploid (3X) autosomes. Two of these are super males, which fall into line with the super-male *Drosophila* (Table 1). In fact, they have a differential of 1 above and 1 below that of the *Drosophila* supermale. That the Neo-Klinefelter case (3A 3XY) occupies a position between the Klinefelter's and Super-Klinefelter's (Table 2) makes good sense. The only problematic case is the new variety No. 2 because it has the same differential as regular Turner's syndrome, i.e., with a differential of 1 in the male direction. Yet, the sex chromosome complement pattern is distinctly that of a Klinefelter. For this reason, this case (unnamed) actually offers some challenge to the validity of the system under test. There is no explanation for it at present.
2. The remaining eight varieties all have diploid

(2N) autosomes: these are the same as previously analyzed (Tables 1 and 2). Their recurrence in this theoretical series lends support to the numerical system. More specifically, the Tri-X female (3A 3X) with a differential of 3 in the female direction is reassuring; it is present in *Drosophila*, and now among the human sex aberrants. Also, the appearance, in this series. of intersex (3A 2X) repeating that in the *Drosophila* speaks favorably for the system.

VI. DISCUSSION AND CONCLUSION.

1. The general workability of the system may be comprehended from a continuous scale of decreasing femaleness and increasing maleness (arrow, Table 4) with the intersex occupying the center of the scale. Earlier treated data are regrouped in this way in Table 4. The significance of this regrouping seems evident: it is to bring out much more effectively the thesis that sex is relative, hence representable numerically.

Table 4. Regrouping of data to show a continuous scale of sex status, normal or abnormal.

Human sex aberrants (theoretical)		*Human sex aberrants (known)*			Sex aberrants in *Drosophila*
(Super female)	5	(Tri—X female)	5		5 (Super female)
	4	(Super—Klinefelter)	4		
(Tri—X female)	3				3 (Tri—X female)
(Neo—Klinefelter)	2	(Neo-female)	2	♀	2 (Normal female)
	1	(Klinefelter)	1		
....	0	....			0 (Intersex)
(?)	1	(Turner)	1		1 (Normal male)
		(Normal male)	2	♂	
(Super male)	3				3 (Super male)
(Noe—supermale)	4				↓

2. There in no discrepancy anywhere.
3. The only questionable case is that presented by No. 2 (Table 3); also listed above with a question mark. The case, already commented on above, apparently is a test case for the future. For should such an individual with a 3A 2XY complement become a reality, would it more resemble a Klinefelter or a Turner? The writer wishes it to be the latter.
4. Elucidating comments and criticism on this proposed system are respectfully invited.