Sex determination and sexual differentiation are processes that are almost universal in the animal kingdom. There is a bewildering variety of sex determining mechanisms in worms, insects, reptiles, birds and mammals. Even among insects, the phenomenon is confusing. To determine sex, *Drosophila* and *Sciara* use the ratio of X chromosomes to autosomes; in *Musca* or *Anopheles*, the Y chromosome can determine maleness; in some strains of *Chironomus*, dominant male determiners are found and in other strains, dominant female determining genes are known. *Chrysomya* uses a maternal factor. In the *Hymenoptera*, a haplo-diplo mechanism is involved and in *Heteropeza* the haemolymph of the mother determines the sex of the offspring.

However, this apparent multitude of mechanisms probably arise from minor variations of a common principle: a hierarchically built control system with a primary signal, present or absent, that is read by a key gene whose state of activity (OFF or ON) is used to control the sex differentiation genes through the action of a genetic double switch.

In *Drosophila* the ratio of X chromosomes to the sets of autosomes (X:A) provides the primary genetic signal for sex determination. Flies with one X chromosome and two sets of autosomes are males (X/A = 0.5), whereas individuals with equal number of X chromosomes and sets of autosomes are females (X/A = 1.0). The Y chromosome plays no role in sex determination (Cline, 1993).

**Overview of regulation of sex determination and dosage compensation in *Drosophila***

The signal of the X/A ratio is transmitted through genetic elements that are distributed in a hierarchically built cascade leading to terminal differentiation. These elements can be divided into three categories based on the position they occupy in the regulatory hierarchy.

In this hierarchy, *Sex-lethal* (Sxl) is a key pivotal gene that controls sex determination in the soma and germ line as well as dosage compensation. In 1X2A flies, Sxl is OFF and in 2X2A flies, Sxl is ON (Cline, 1978; 1984; 1988; Fig. A).
The first set of the genetic elements are the ones that actually sense the X/A ratio, and consequently regulate Sxl. **Daughterless** (da+) is a maternally acting positive regulator of Sxl (Cline, 1976). Zygotic elements like **sisterless-a** and **sisterless-b** (sis-a+ and sis-b+) are also positive regulators of Sxl. The latter (zygotic elements) are postulated to be the **numerator elements** which contribute additively to the X component of the X/A ratio. Proteins derived from da+ and sis-b+ belong to the helix-loop-helix (HLH) family (Parkhurst et al., 1990). The HLH motif denotes a hypothetical structure of two amphipathic helices connected by a flexible loop. HLH proteins bind DNA as heteromers and function as transcriptional regulators (Murre et al., 1989b). sis-a+ encodes a bZIP protein homolog that functions to activate Sxl (Erickson and Cline, 1993). Sxl initiation in females depends on its transcriptional activation by HLH protein heterodimers of da+ and sis+ proteins. The da+ product is contributed maternally and is present in excess. The counting elements, sis-b+ and sis-a+ are transiently expressed in all cells and are quantitatively limiting. As sisterless expression proceeds dosage compensation, females should make twice as much of each X linked counting proteins as males. Thus, only females would make sufficient da-sis heterodimers to activate the Sxl autoregulatory feedback loop which brings about female specific autocatalytic splicing of Sxl pre-mRNA. Ectopic ASC-T4 (sis-b+) expression has been shown to kill males by raising the effective X/A ratio and inappropriately activating Sxl+ (Parkhurst et al., 1990).

**Hairy** (h), a pair rule segmentation gene normally plays no role in sex determination. However, it has been reported that premature ectopic expression of hairy prevents initiation of Sxl expression in females. Hairy encodes an HLH protein suggesting that ectopic hairy expression can interfere with X chromosome counting, a process where other HLH proteins like extramacrochaetae (emc+) are implicated. Ectopic hairy expression is female lethal by binding T4 (encoded by sis-b+) and other HLH counting proteins and preventing these proteins from binding to the da+ product and activating Sxl+ expression (Parkhurst et al., 1990).
Deadpan (dpn+) a pan neural gene, has been shown to interact with sis-b*/sc+. An interaction between dpn+ and sc+ involves zygotic products. The dpn+ gene on the second chromosome is thought to function as a denominator element because an imbalance between the gene dosage of sc+ and dpn+ results in either male or female lethality by inappropriate activation/inactivation of Sxl+. Dpn+ has been shown to act as a negative regulator of Sxl - a function consistent with its role as a denominator element (Younger-Shepherd et al., 1992). Dpn+ encodes an HLH protein which may be the protein mimicked by hairy misexpression.

Another HLH protein encoded by extramacrochaetae, is thought to act maternally to negatively regulate Sxl+ (Younger-Shepherd et al., 1992).

Thus X chromosome counting is sensitive to the expression of HLH transcription factors. However, activation of Sxl is not solely controlled by HLH proteins. Runt, a segmentation gene, interacts with sis-b+ to activate Sxl+ (Duffy and Gergen, 1991). Runt is regarded as a weak numerator element but here the HLH motif is absent. The HLH motif is also absent in sis-a+ expression, which codes for a bZIP protein that is involved in Sxl activation.

Thus maternal da+, along with sis-b*/sc+ and sis-a+, is required for proper activation of Sxl in females (Cline, 1988). Also involved in the process is runt+ (Duffy and Gergen, 1991). On the other hand, maternal emc+ along with dpn+ is required for proper inactivation of Sxl in males (Younger-Shepherd et al., 1992). A fourth numerator element, sis-c has been identified but its properties have not been published as yet (Cline, 1993, cited in Parkhurst and Meenely, 1994). Considered in the context of all recent studies, it can be stated that Sxl activation/inactivation depends on the positive and negative interaction between maternally supplied gene products of genes like da+, emc+, liz+ and products of zygotically expressed genes like sis-a+, sis-b+, runt+ and dpn+ (Parkhurst and Meenely, 1994; Fig. A).

The second cascade of genetic elements include genes that can respond to the X/A ratio and can also regulate other genetic elements further downstream. This set includes the key gene Sxl. Once the state
of activity of $Sxl^+$ is defined which occurs around the blastoderm stage (Sanchez and Nothiger, 1983), the X/A ratio is no longer needed as a genetic signal, although the X/A ratio would continue to function cell autonomously with respect to dosage compensation.

Molecular analysis of the products of the $Sxl$ locus has shown that $Sxl$ produces two temporally distinct sets of transcripts during embryogenesis.

1. The first set is produced by a sex specific early embryonic promoter, $P_E^+$ which directs the synthesis of a special class of $Sxl$ mRNAs in chromosomal female embryos only. The early promoter is active only for a brief interval between nuclear cycle 8 and cellularization (Keyes et al., 1992) and is thought to be directly controlled by gene products known to be involved in communicating the X/A signal.

2. The protein products of these early $Sxl$ mRNAs.
   (a) initiate the autoregulatory feedback loop in female embryos.
   (b) specify female specific splicing of $Sxl$ transcripts from the late promoter $P_L$ or $P_M$ (promoter-maintenance) which is about 5 Kb upstream to $P_E^+$.

$Sxl^+$ function is achieved by splicing of all exons, except exon 3 and production of a complete message. The proteins encoded by such transcripts share sequence homologies with a family of RNA binding proteins and so they are likely to regulate splicing through a direct interaction with the target pre-mRNAs (Bell et al., 1988, 1991).

These proteins:
(a) direct the autoregulatory feedback loop, which maintains $Sxl$ in the active state in females (Bell et al., 1991).
(b) controls the expression of other sex determining regulatory genes through the regulation of activity of the $transformer$ ($tra^+$) gene which occurs at the level of RNA splicing (Stefmann-Zwicky et al., 1990)
(c) prevents hypertranscription of the X chromosomes in females by preventing $maleless$ ($mle^+$) product from binding to the X
chromosome. It has been suggested that Sxl may regulate dosage compensation by regulating the splicing of the pre-mRNA of one of msls (Gorman et al., 1993).

In 1X2A flies, the Sxl+ function is produced by alternative splicing of an additional exon (exon 3) that introduces a stop codon into the open reading frame resulting in a truncated message (Baker, 1989). This would imply that in 1X2A flies the Sxl+ product is absent. The embryonic promoter (P_E) is not active in male embryos. In the absence of the early Sxl proteins, the primary transcripts from P_L are processed in the male non-productive mode, which then persist by default.

However, Bopp et al., 1991, have shown that Sxl proteins are found in adult males. These proteins are smaller than female specific Sxl proteins and are about 33-35 Kd. These small proteins have been found in the head and thorax of adult males but were not observed in any other tissue or stage in the life cycle. Such proteins have also been found in the head and thorax of adult females. Whether these proteins have a different functional role is not clearly understood.

Sxl stands at the apex of several regulatory hierarchies in Drosophila governing somatic sex, dosage compensation and also germline differentiation. The control of sex determination and dosage compensation diverges downstream to Sxl with different sets of genetic elements regulating sex determination and dosage compensation.

Sex-lethal to doublesex and downstream

Sex determining genes form a short regulatory cascade with Sex-lethal at the top and doublesex at the bottom. There is a cascade of RNA splicing reactions through which the initial message of the X/A ratio is transmitted down the hierarchy. An X/A ratio of 1.0 directs Sxl into the active (female) mode. In presence of the specific Sxl+ products, the transformer (tra+) gene produces a 1.0 Kb transcript due to the mechanism of alternative splicing. This, in turn, brings about female specific splicing of the doublesex (dsx+) pre-mRNA leading to the formation of female determining product dsxF. The male specific
product of $\text{d sx}^+$ ($\text{d sx}^M$) is apparently a default state of expression which is adapted whenever one (or more) of the upstream regulatory genes is (are) inactive. Thus the gene order appears to be $\text{S xl}^+ \rightarrow \text{tra}^+ \rightarrow \text{d sx}^+$. Another gene $\text{tra-2}^+$ is placed outside the linear hierarchy since its expression appears to be independent of $\text{S xl}$. However, $\text{tra-2}^+$ product is required for somatic sex determination in females and sperm differentiation in the male germline. The gene $\text{intersex (ix}^+$) helps to render the female specific product of $\text{d sx}$ functional which places it below $\text{d sx}$ in the hierarchy (Steinmann-Zwicky et al., 1990; Fig. A).

The link between genes in the sex determination control pathway and the terminal target genes is not very clear. However, Coschigano and Wensink (1993) have shown the sex specific products of $\text{d sx}^+$ ($\text{d sx}^F$ and $\text{d sx}^M$) to differentially regulate the transcription of two target yolk protein genes ($\text{Ypl}$ and $\text{Yp2}$). Both $\text{d sx}$ proteins bind to the same regulatory sites on the target genes but have opposite effects in the two sexes. In males $\text{d sx}^M$ represses transcription while in females $\text{d sx}^F$ activates transcription of the yolk protein genes.

**DOSAGE COMPENSATION**

In organisms with a chromosomal basis for the initial determination of sex, a frequent concomitant phenomenon is dosage compensation. In heterogametic organisms, dosage compensation is a process whereby total gene expression from the single $X$ chromosome in one sex is made equal to the total gene expression from the two $X$ chromosomes in the other sex. This can be achieved either by increasing activity of the single $X$ in one sex or decreasing activity of the two $X$ chromosomes in the other or by a combination of these mechanisms.

Like the plethora of primary sex-determining mechanisms there is also a diversity in the mechanism of dosage compensation. In *Drosophila*, dosage compensation is mediated by hyperactivation of the single $X$ chromosome in the male (Mukherjee and Beermann, 1965; Mukherjee, 1966). In the nematode *Caenorhabditis*, compensation probably works in the opposite direction - sex linked transcripts are reduced two fold in XX animals although here too sex is determined by
the X/A ratio as in *Drosophila* (Hodgkin, 1990). Mammals, in contrast, achieve compensation by inactivating one of the X chromosomes in the XX set (Lyon, 1961; 1962; 1972). Dosage compensation has also been demonstrated in other organisms like coccids (Berlowitz et al., 1968), fish (Anders and Klinke, 1966) and orthopteran insects like Gryllotalpa (Rao and Bhattacharya, 1984). In *Drosophila* about 20% of the known genes lie on the X chromosome, most of which are genes without sex limited expression. So the two sexes are aneuploid with respect to each other for an entire chromosome. Since aneuploidy is not well tolerated in most organisms it is essential that such heterogametic organisms equalize the expression of sex-linked genes in males and females.

The existence of dosage compensation in *Drosophila* has been studied in various ways.

(a) At the level of terminal phenotype:

   Homozygous white apricot (w_a) females have the same level of pigment as hemizygous w_a males (Muller, 1932).

(b) At the level of a gene product:

   Glucose-6-phosphate dehydrogenase (G6PD) and 6 phosphogluconate dehydrogenase (6PGD) are two X linked enzymes whose activity is the same in males and females (Komma, 1966; Seecof and Kaplan, 1967). Korge (1975) showed dosage compensation for synthesis of larval salivary gland secretion protein 4 in wild type males.

(c) At the level of gene activity:

   The hypertranscription of the male X chromosome can be observed at the level of messenger RNAs (Birchler et al., 1982; Ganguly et al., 1985; Breen and Lucchesi, 1986) or by detection of the amount of tritiated uridine incorporated into nascent transcripts in larval polytene chromosomes (Mukherjee and Beermann, 1965; Mukherjee, 1966; Holmquist, 1972).

(d) At the level of X chromosome morphology:

   In polytene chromosome squashes the single male X chromosome appears diffuse and lightly stained suggesting that it has a chromatin structure different from that in an autosome or female X chromosome (Dobzansky, 1957).
Control of dosage compensation

In the regulatory hierarchy, since the control of dosage compensation diverges after Sxl, all the genetic elements acting upstream to Sxl presumably affect dosage compensation through Sxl.

An active Sxl+ product is necessary in females to keep the transcription at the lower female level and must be absent in males to allow transcriptional hyperactivation. Females heteroallelic for a null Sxl allele, Sxl^fl, and a homozygous viable, partial loss of function Sxl allele, Sxl^fv, have X chromosomes which are morphologically diffuse and also hyperactive implying that absence of the Sxl product leads to the presence of hyperactive X chromosomes (Lucchesi and Skripsky, 1981).

Genes that appear to function after Sxl are the male specific lethals-msl-1, msl-2, msl-3 and mle. The genes msl-1, msl-2 and mle appear to function in the same pathway since a triple mutant for null alleles of all three genes survives as long as each single mutant. The lethality is probably due to a general reduction in X chromosome transcription and a consequent failure of dosage compensation (Belote and Lucchesi, 1980a; 1980b; Belote, 1983).

It appears that X chromosome transcription is regulated by a cascade of signals in females.

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Sxl^ON  \rightarrow  \text{Productive splicing of } \text{tra}^+  \rightarrow  \text{Dxs}^F  \rightarrow  \text{X chromosomal transcription}

\text{nonproductive splicing of } \text{tra}^+  \rightarrow  \text{Dxs}^M  \rightarrow  \text{X chromosome hyperactivity}
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Absence of these signals in males results in the expression of those genes whose products are required for X hyperactivation.

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Sxl^OFF  \rightarrow  \text{positive expression of msls}  \rightarrow  \text{X chromosome hyperactivity}
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In order to achieve this special rate of transcription by simply interacting with the general cellular transcription machinery, the X chromosome must have acquired, through evolution, special regulatory sequences that must respond to transacting regulators in a sex-specific manner.

Cis-acting control of dosage compensation occurs on a local level at many sites along the X chromosome. Pardue et al. (1987) have shown that a synthetic polynucleotide \((dC-dA)_{n\cdot}(dG-dT)_{n}\) hybridizes to twice as many sites on the X chromosome than on the two major autosomes in salivary gland nuclei. These data seem to indicate that there are cis acting regions on the X chromosome that confer the capacity for dosage compensation. These may act as binding sites for male-specific trans-acting regulators which would alter the conformation of chromatin.

Trans-acting regulatory factors that are most directly involved with enhanced male X linked transcription, like the mle\(^+\) product, bind specifically to the entire length of the X chromosome in the males (Kuroda et al., 1991). Preferential binding of Histone 4, acetylated at lysine 16, to the X chromosome in males has been shown by Turner et al. (1992). Allfrey (1964) had suggested that acetylated histones were preferentially associated with transcriptionally active chromatin. It was shown by Jeppesen and Turner (1993) that in the inactive X chromosome of female mammals histone H4 is underacetylated. Keeping in line with trend it was shown by Lee et al. (1993) that histone acetylation facilitates access of transcription regulatory molecules like TFIIIA by destabilizing the nucleosome. Like H4Ac16, a preferential binding to the male X chromosome has also been shown for the msl-1 product (Palmer et al., 1993). The specific association of the three proteins - Mle, Msl-1 and H4Ac16 with the male X chromosome implies the possibility that these proteins act in concert to regulate hyperactivity of the male X chromosome (Kuroda et al., 1991; Palmer et al., 1993; Turner et al., 1992). The mechanism of such protein association is not yet clear. Mle, Msl-1 do not contain DNA binding motifs like helix-loop-helix, helix-turn-helix or b-ZIP domains. So these proteins probably act by 'protein-protein interactions.
H4Ac16 has a DNA binding domain, implying that this may recognise specific sequences on the X chromosome and help in association of the other proteins to the DNA. However, whatever be the mechanism, at least one of the key players have to be differentially processed in one of the two sexes which allows the sex specific binding of this multimeric complex to the X chromosome of the male only.

Bone et al. (1994) have shown that H4Ac16 does not associate with the X chromosome in males mutant for mle or any of the three msl loci. By double labelling and immunolocalisation they have also shown that Mle and Msl-1 proteins occupy identical sites on the X chromosome in males and these are mostly coincident with the sites of H4Ac16 accumulation. They have also demonstrated that Sxl+ prevents X chromosome localisation of H4Ac16 in females where Sxl is ON. Neither the Mle protein nor H4Ac16 can be the direct targets of Sxl regulation as they are present in the female nuclei (Kuroda et al., 1991; Turner et al., 1992). Palmer et al. (1994) have reported that the Msl-1 protein is present in males but is greatly reduced in the female nuclei. They have also shown that Msl-1 accumulates and associates with the X chromosome in Sxl mutant females implying that probably this msl product is subject to Sxl regulation. Furthermore, they have also demonstrated that Msl-1 is present in mle and msl-3 mutants but is reduced or absent in msl-2 mutants suggesting an epistasis in msl expression as the msl-2 product is probably required for the translation and/or stabilization of Msl-1. It has been speculated (Palmer et al., 1994) that probably msl-2 bridges the regulatory gap between Sxl and the other msls.

The discovery of new genetic elements involved in the regulation of sex differentiation and dosage compensation makes it virtually certain that all the pieces of the puzzle are not yet available.

There are several gaps and anomalies that have not been explained yet:

1. There are regions on the X chromosome whose action have not yet been explained, e.g., 11DE-12E is lethal if duplicated in males; 16E-17A is haplo insufficient in females; do these regions interact with Sxl to produce their sex specific lethality or is there any other mechanism?
2. Genes have been identified which interact with Sxl but their position in the regulatory hierarchy have not been elucidated.

a) Liz (located at 4F on the X chromosome) has the same dosage related effects on viability as (11DE-12E). It has been shown to interact with Sxl (Steinmann-Zwicky, 1988). This gene is required for the correct splicing of Sxl mRNA produced from the late Sxl promoter (Albrecht and Salz, 1993).

b) Daughter killer (Dk) is a dominant maternal effect autosomal mutation whose female-specific lethal effect is suppressed by Sxl\textsuperscript{M1} (Steinmann-Zwicky et al., unpublished, cited in Lucchesi and Manning, 1987).

c) Female lethal fl (2)d. This female specific autosomal mutation suppresses the lethal effect of Sxl\textsuperscript{M1} in males (San Juan and Sanchez unpublished - cited in Lucchesi and Manning, 1987). Granadino et al. (1992) identified fl(2)d as one of the genes required for regulation of Sxl expression.

d) Hermaphrodite (Her) - Described by Baker and Belote (1983). This autosomal gene is thought to affect sex determination as males are slightly feminized and females are transformed into intersexes. As the viability of the flies are also reduced, this gene is also thought to affect dosage compensation. However, Pultz et al. (1994) have shown that her has non-sex specific maternal and zygotic functions which are required for viability of flies.

e) Virilizer (Vir) - It apparently provides functions for both sex determination and dosage compensation (Hilfiker, et al.; unpublished cited in Steinmann-Zwicky et al., 1990).

It is likely that additional dosage compensation genes remain to be discovered, because,

(a) XY flies that carry Sxl\textsuperscript{M1} die earlier than do msl, mle XY flies, although in both cases death appears to be due to inadequate X chromosome transcription.
(b) All male specific lethal mutants exert their lethal effect during late larval or early pupal stages. Thus msls are responsible for dosage compensation late in development. These genes are distinct from another set of, as yet, undiscovered regulatory genes responsible for embryonic dosage compensation. This is probably the reason why msl mutants do not affect dosage compensation of runt whose action occurs at the blastoderm stage (Gergen, 1987).

Enhanced expression of the male X was first observed as incorporation of higher amounts of tritiated uridine compared to a single X of the diplo X female, in the polytene nuclei of salivary glands. There is also a morphological counterpart of hyperactivity. In polytene nuclei the single X chromosome in the male is more diffuse in appearance and pale stained compared to an autosome or the diplo female X.

It is not known whether the more diffuse X chromosome structure seen in males is a cause or consequence of elevated transcription levels per X linked gene dose. Results obtained by Mukherjee and Ghosh, (1986) seem to support the former view. In(1)BM2 (rv, mosaic) is a strain of Drosophila melanogaster in which an X chromosome inversion [In(1)BM2] had reinverted to a cytologically "normal" sequence. In male larvae of this strain the X chromosome has a puffy inflated appearance. It is about 1.5-2 times as puffy as the X chromosome in a normal male. This trait is expressed in a mosaic fashion, as, in a number of nuclei the X chromosome is intermittently puffy and in some nuclei the X chromosome is normal. At 18°C a 2 : 1 : 1 ratio of flabby : intermediate : normal is observed. The puffy inflated appearance of the X chromosome is accompanied by a level of transcription about 40% higher than that of the normal wild type male. The locus responsible for this mutation is termed modulator and the mutant modulator is termed modm. It is X linked and located at 16A-B region and is temperature sensitive (Mukherjee and Ghosh, 1986; Ghosh and Mukherjee, 1986).

When the modulator mutant is accompanied by duplication of the wild type locus or substituted by recombination with Bar (B), the super hyperactivity is reverted to the normal hyperactivity of the male (Mukherjee and Ghosh, 1986; Kar 1987). The modulator effect is also suppressed by Bar Stone (B) located at 16A7-B2 region, a finding
on the basis of which \textit{mod}^{m} has been tentatively assigned to the region, 16A7-B2, of the X chromosome.

Mukherjee and Ghosh (1986), Mukherjee (1986) have suggested that the gene termed as modulator (\textit{mod}^{m}) is mutated to a hypomorph allele in \textit{Im(1)BM}^{2} (rv, mosaic). It is hypothesized that \textit{mod}^{+} produces a protein product that is inhibitory in function. This product interacts with the enhancer products produced by the male specific lethal genes. The stoichiometric interaction results in neutralization of both products and the unreacted molecules that remain, function as inhibitor or enhancer and determine the level of activity of the X chromosome. \textit{mod}^{m}, as a hypomorph, produces less inhibitor. This probably results in the super-hyperactivity of the X chromosome in males.

\textbf{Present status of modulator mutant}

The strain carrying the modulator mutation has undergone evolution and has changed. The percentage of such puffy chromosomes have decreased and now about 30\% of such chromosomes are seen at 18°C. The temperature sensitivity is still present, as with decrease in the rearing temperature to 13°C, the number of puffy chromosomes increase and with an increase in the rearing temperature to 23°C the puffy chromosomes disappear.

An intriguing aspect of dosage compensation is that thousands of genes are coordinately regulated, based not on their function but on their genetic linkage. \textit{mod}^{m} is important because of its sex specific effect on the X chromosome organization. \textit{mod}^{m} causes the selective decondensation of the X chromosome in the male and concomitant increase in transcription. This would seem to imply that \textit{mod}^{m} acts at a time early in development, when the organization of the X chromosome is set. It is fortunate that the mutation has a leaky nature as a 100\% expression of \textit{mod}^{m} would probably be lethal in males.

The present study has been carried out to characterize this mutation

1. To understand the functional significance of such puffy X chromosomes, \textit{mod}^{m} has been combined with a regulatory gene \textit{maleless} (temperature sensitive) (\textit{mle}^{ts}) and their interactions have been studied.
2. To examine whether any protein factor is responsible for the \textit{mod}^{m} phenotype, protein profiles from the \textit{mod}^{m} strain have been compared with that of the wild type (\textit{mod}^{+}).

3. Poly-ADP ribosylation reactions are involved in all major chromatin functions like DNA repair, DNA replication and transcriptional activity. Since \textit{mod}^{m} involves a disruption in chromatin structure and function, it was decided to study the effect of 3-amino-benzamide, an inhibitor of poly-ADP ribosylation, on \textit{mod}^{m}.
Figure A

MALE (1X:2A)  

- $S_{x1}^{OFF}$
- Absence of Sxl protein allows msl expression
  - tra
  - tra-2
  - dsx

FEMALE (2X:2A)  

- $S_{x1}^{ON}$
- Presence of Sxl protein blocks msl expression
  - tra
  - tra-2
  - dsx

$s_{x1}^p E$

- $0.5 = \frac{X}{A}$
- $\frac{X}{A} = 1.0$

$s_{x1}^p M$

Expression:
- msl-2
- msl-1
- msl-3
- mle
- H4Ac16
- dsx

Functions:
- Activates male specific functions
- Represses female specific functions
- Activates female specific functions
- Represses male specific functions
- Inductive signal for germline sex determination