The Y Chromosome: Its Functions and Impact on Modern Society

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The late Sir Gordon Arthur Ransome served Singapore as Professor of Medicine for nearly his whole professional life with a short stint in Burma during the Second World War where he was twice mentioned in despatches. His contributions to medicine in Singapore were innumerable but the most significant of all was the teaching of clinical medicine by apprenticeship. He took all who worked with him under his personal wing and imbued in them a rare sense of clinical acumen, intellectual honesty and a deeply humanistic approach to patients. He was a superb clinician with experience gained from master neurologists in London, among whom was Sir Gordon Holmes, and experience gained from the Burma campaign. He popularised intragastric feeding when the Ryle's tube was used mainly for gastric aspiration at that time.

I was one of his housephysicians in the early 1950's and he saw to it that I learned not only medicine but also some philosophy of life. He was wont to remind me that there were only 2 professions, medicine and the cloth and all the others are trades, whenever I presented patients to him as so-and-so, a tailor or teacher by profession! He remembered well those who worked with him and was always interested in whatever professional field they had gone into. When I became a paediatrician, of course, we had long conversations and with his fierce loyalty to adult medicine, it was inevitable that we had friendly disagreements. However, in later life as he mellowed, he allowed that the child is indeed not a miniature adult! He was first amused and then interested when I started delving into human genetics, and here again we had some deep discussions on the impact of molecular biology on the human body, on disease and human behaviour. Thus, I feel that if he were alive today, he would be deeply interested in the subject which I wish to discuss today.

The present state of modern society has been determined by two processes of evolution. The *first* is *genetic evolution* which is a process affecting all living organisms. Genes mutate accidentally and change the phenotype of the particular organism which is then pitted against the environment. If the new phenotype has a poorer chance. of survival in the then-environment, the gene will be eliminated, while, on the other hand, if the phenotype is superior, it will have a better survival value and will thus pass on this new genotype to future descendents. In this way, by such a process of genetic selection or evolution, living organisms can only get better with time. It is precisely, in this manner that man evolved, with all the so-called "good survival genes" in him. However, such genetic changes in order to entrench themselves, take a long time, i.e., genetic evolution, in an unchanging environment takes millions of years. Thus, man has only a 10,000 year history at most since he came genetically on this earth, and within this short time-span, significant genetic

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changes have not taken place. In short, present day man, you and I, possess the same genes as our first human ancestors. Yet, we are in many ways, behaving differently from our first ancestors in spite of identical genotypes. This behaviour has been due to man's brain which is totally different from all other living organisms. It is true that the human brain has reached its present state and capability because of genetic evolution. However, the manner in which we have put our brain to work has nothing to do with genetic evolution. Therefore, we come to the *second* type of evolution which I term, *social evolution.* Given the basic genotype, man has created changes in his environment and in his way of living in a manner never before achieved by any other living organism. Our genes have programmed us to live by hunting, providing us with genes which optimally allow ourselves to survive in an environment of forests, trees, rivers, mountains, rain, ice and snow. Our brains have contrived, first, to take to agriculture instead of running around to gather food, then to domesticate animals for our carnivorous tastes, to hit on the scientific processes underpinning the behaviour of both living and inanimate objects. We have changed our environment to such an extent that we still survive relatively well, not because our genes have changed to adapt to this changed environment but because our genes fortunately possess that amount of reserve to adapt. We know, however, that many a time, this is not so, e.g., increase in the diseases due to life-styles such as vehicular and other accidents, coronary heart disease, psychoneuroses, to mention only a few.

Although many facets of human life have played a part in determining modern society, I would like to discuss only one facet, viz. the male sex and the female sex, i.e., man and woman. Human sex has shaped the world both from the point of view of genetic as well as from the point of view of social evolution.

Let us first discuss why there should be two different sexes. Primitive living organs, e.g. the unicellular organisms are asexual. With time, genetic changes produce unisexual multicellular organisms which evolved with both male and female parts within the same individual organism. Still later, genetic mutations produced bisexual organisms in different individuals. These latter obviously had better survival value since all mammals are bisexual. Why is there better survival value and hence why are they naturally selected? In being bisexual, there is an increase in the number of genes by a factor of two, so that genetic changes are doubled and hence mutation and selection are also doubled. In other words, the survival advantage lies in speeding up the process of genetic advance. In this process of development whereby separate male and female individuals are created, living organisms fall into two categories, those where the male and female do not appear very much different and those where the male is quite different from the female. For example, many male and female birds and reptiles are almost similar in appearance, and even in mammals, the male hyena looks superficially no different from the female. Zoos often find this to their cost, having bought two male or two female eagles instead of one each hoping to produce offspring for the zoo, or for exchange. Why then do we see obvious sex differences in some animals? Has sexual dimorphism good survival value? Genetically, sexual dimorphism ensures a better survival for that species, in that males are larger, more powerfully built and have secondary sex characters which can be easily recognised. These will allow them to fight among themselves for the control of the females of the animal pack. In so doing, two genetic advantages are gained: —

1. The victor's genes will be the most powerful and will be passed on to future generations.
2. The availability of *all* the females in the pack means that a large array of genes will be exposed to mutation and hence the changes of "better survival genes" will emerge.

Hence, sexual dimorphism leads to polygamy and this is practised by nearly all mammals which show this dimorphism.

Man demonstrates this sexual dimorphism to an extreme not only in regard to size but also in strength, agressiveness and maintenance of this dimorphism by social evolution itself, e.g. in dress, hair-styles, keeping of beard and moustaches, smoking habits etc. Throughout human history, men have waged war against each other and later, war between groups termed nations; upon winning victories, human male combatants exterminated their male rivals and enslaved the vanquished women and children, and even in modern society, wars are still being waged though with dif-, ferent weapons and with different strategies. However, the innate biological urge to rid other dominant males still lurks in the heart of the human male. However, because of the special unique brain development of man, he adopted certain ideas which only human brains can conceive -- the idea of 'spirit'. 'soul', "compassion', 'fair play', etc. This social evolution of man is termed *civilisation,* which essentially is a form of social evolution practised by humans to offset certain consequences of genetic evolution, consequences which, if, allowed to be carried on in an environment totally changed by social evolution, would lead to chaos. Thus gradually man came to practise monogamy because he realised that only the stable single male-female bond pair can deal adequately with the slow growth of the human infant, the long apprenticeship of the child and juvenile, so that they can be nutured weli, attain their full genetic potential under the tutelage and care of a father and a mother rather than multiple parental substitutes. When one talks of civilisation, one must realise that it is part and parcel of social and not genetic evolution and that the "base and obnoxious" aggressive and polygamous attributes of the human male, though curbed by appeals to his 'better nature', by laws and reason, these 'obnoxious' traits still surface off and on in human history including the present era. The existence of wars and extra-marital diversions, though kept down to a minimum, is mute testimony to man's genetic heritage.

Civilisation has brought on one form of social evolution which is becoming apparent in many countries in the last 50 years, viz. the realisation by both man and woman that there should be a blunting of social dimorphism. I am not referring to the rise of homosexuality, transvestism or transexualism but to the equal contribution of males and females to the trends in social evolution. Modern society has been shaped mainly by man and is still being so shaped, and terms like "it is a man's world" and "woman's liberation movement" portray man's genetic heritage and woman's dissatisfaction with the status quo. However, before we can consider the "equalisation" of the sexes, we must first discuss what are the genetic mechanisms which make a man or a woman. Once we know all the mechanisms, we can then consider the possibility and the desirability of minimising the differences between man and woman without stopping further propagation of the human race, for indeed much of the inequality between man and woman lies in the genetic responsibility being dumped on to the woman to nurture the foetus in her uterus for 40 weeks. The man's responsibiity in genetic terms is only the provision of the sperm which takes only a short time.

The Y Chromdsome

So, therefore, when we come down to the crucial question as what fundamentally differentiates a man from a woman, the answer is the Y chromosome, one of the smallest chromosomes in the male cell. At one time, it was thought that the Y chromosome housed many genes, for if it did not, how could all the many characters differentiating man from woman come about? Now we know that the Y chromosome is a dummy with few genes and most of the masculine characteristics of man are produced and controlled by other genes. But there is one gene on the Y

chromosome which *initiates* the processes whereby the primary and secondary sex characters of the male are produced.

Dummy or not, we know that an individual with one Y chromosome will 'code' for a male no matter how many X sex chromosomes he may possess. Hence, the classical Klinefelters Syndrome[1] with 47 XXY is totally phenotypically male, and even the 49 XXXXY individual is also male in external appearance (Fig. 1). Obviously, the masculinising gene on the Y chromosome over-rides whatever influence the female X chromosome has on the ultimate outcome of a person's sex. What is this 'all-powerful' male gene? In 1955, Eichwald and Silmser[2] carried out skin transplantation experiments with a highly inbred strain of mice and found that male to male, female to female, female to male skin grafts were relatively tolerated but male to female grafts were rejected by the female mice. They therefore postulated the existence of a transplantation antigen, determined by a histocompatibility locus (termed H) on the Y chromosome, and the antigen was termed H-Y antigen and the gene which produces this antigen the H-Y gene. By raising antibodies to this H-Y antigen.[3] a readily available serological method for identification of H-Y antigen on human cells was devised. It was then shown that H-Y antigen could be demonstrated on male cells of all vertebrates and not only man.[4] Therefore, for the first time, the 'male' gene on the Y chromosome was identified via its product, the H-Y antigen, and that this gene is ubiquitious in all male vertebrate cells.

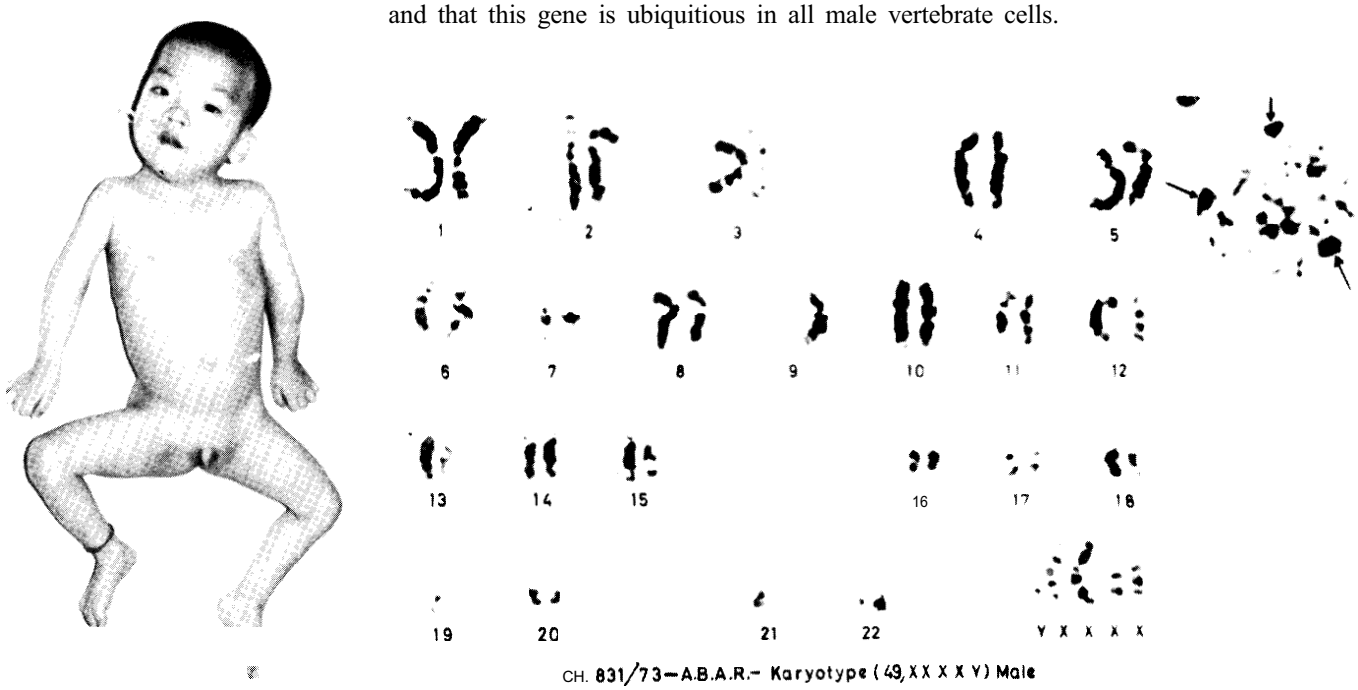


Fig. 1. (a) Baby with male phenotype, abnormal radio-ulnar synostosis and mental retardation; (b) Chromosome karyotype showing that in spite of 4 X chromosomes, the mere presence of a Y chromosome is sufficient for masculinisation.

If indeed the H-Y antigen is the expression of the H-Y gene on the Y chromosome, then it would be possible to demonstrate that individuals with multiple Y chromosomes (Fig. 2)[5] would have more H-Y antigens than normal 46 XY males. It was subsequently shown that leucocytes from males with multiple Y syndromes express more H-Y antigens than leucocytes of normal men.[6] Thus, there is a H-Y gene on the Y chromosome. It is easy to understand then that when there is a Y chromosome, testicular tissue is formed and this results in a male phenotype. However, there are two situations when a Y chromosome cannot be demonstrated in certain individuals and yet testicular tissue is present. The first example is the 46 XX males, who, in spite of absence of the Y chromosome, are male in appearance with testes though they tend to be infertile (Fig. 3). These peculiar individuals can be regarded as

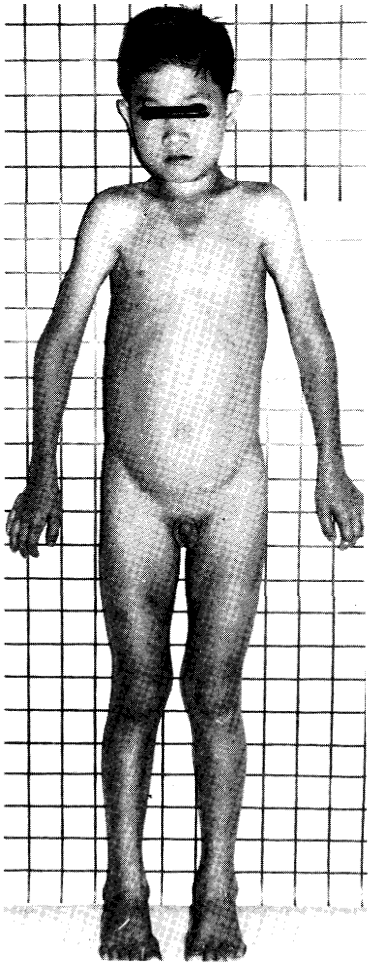


Fig. 2(a)

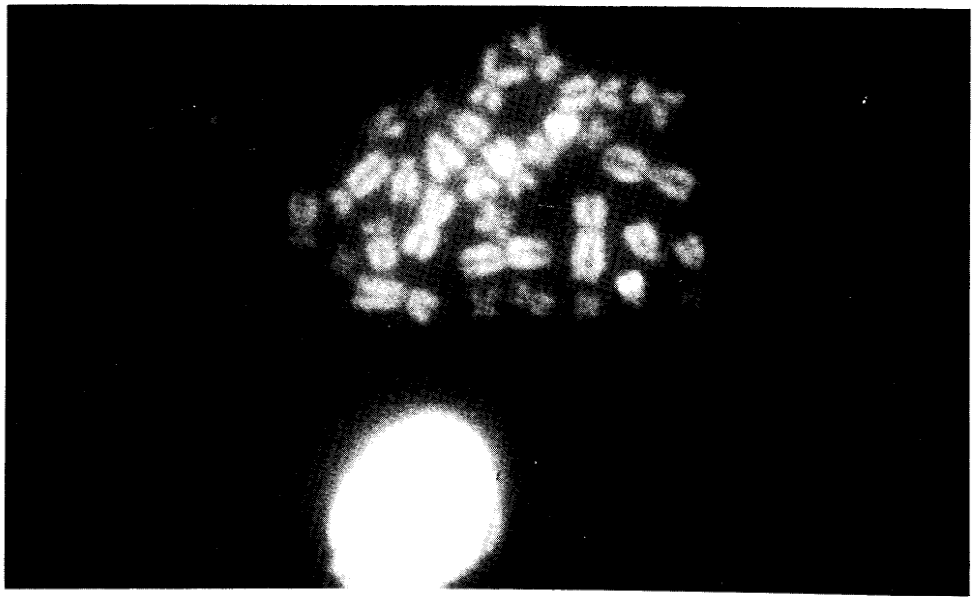


Fig. 2(b)

Fig. 2. (a) 18 years old patient with 47 XYY chromosome constitution with mental retardation and no signs of puberty; (b) Quinarine fluorescence seen in interphase cell (lymphocyte), below with 2 bright dots, and fluorescence in the long arms of the 2 Y chromosomes, above.

examples of cases with sex-reversal. Why did they reveal male characters in spite of absence of the Y chromosome? It has been stated above that the Y chromosome could be a dummy, and it is the H-Y gene which is important and not the Y chromosome. Could these individuals possess the H-Y gene in spite of absence of the Y chromosome? Indeed, these individuals were shown to possess the H-Y gene because H-Y antigen could be detected in their cells.[7] We have no idea where the H-Y gene is in these individuals; it could be translocated to an autosomal chromosome or to the X chromosome. The second situation is seen in true hemaphrodites[1] where the majority have a 46 XX karyotype while a minority also possess a Y chromosome as in 46 XX/46 XY, 46 XX/47 XXY and so on (Fig. 4). In those with 46 XX constitution, i.e. without a Y, it has also been demonstrated that H-Y antigen can be detected in their cells for without the action of the H-Y gene, testicular tissue cannot be formed in these true hermaphrodites.

In CONCLUSION, then, we normally expect a Y chromosome in a male but if it is absent, testicular tissue can still form so long as the H Y gene is present as determined by a positive H-Y antigen-antibody reaction in his cells.

Function of the H-Y Gene

As mentioned above, the H-Y gene is not responsible per se for all the male characteristics. It initiates the formation of a male. In all mammalian foetuses including those of humans, the gonad, which is formed by mesenchymal cells of the genital ridge, epithelial cells lining the ridge, germ cells migrating to this ridge from the yolk sac (Fig. 5), is an indifferent one during early foetal life. In other words, the early foetal gonad is neither a testis nor an ovary. This indifferent gonad can only

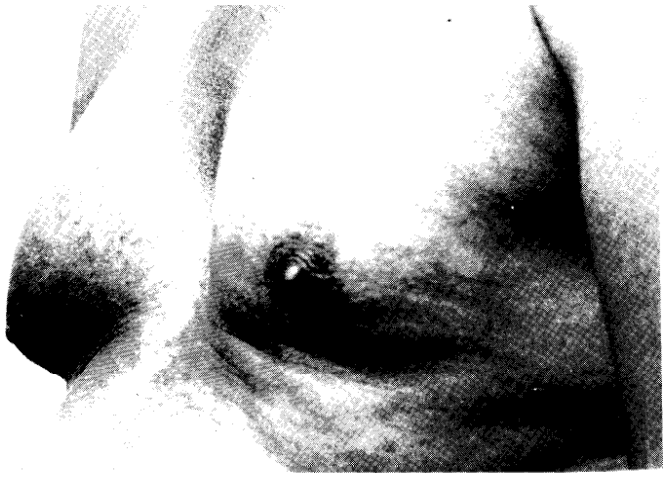
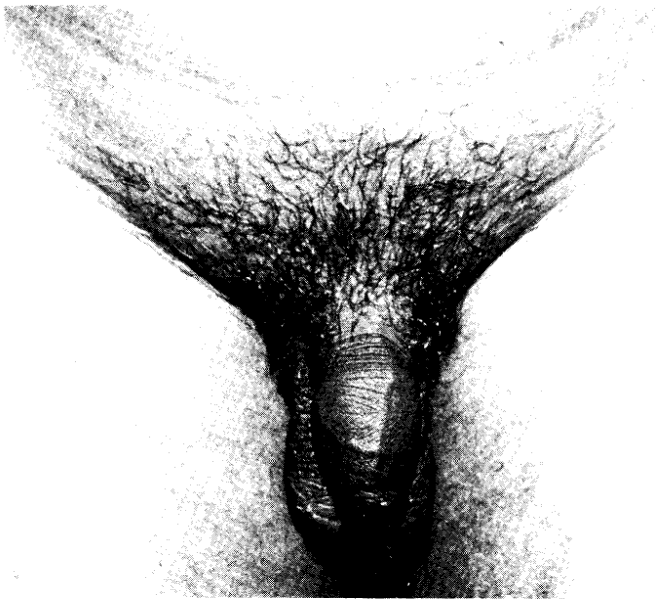


Fig. 3(a)



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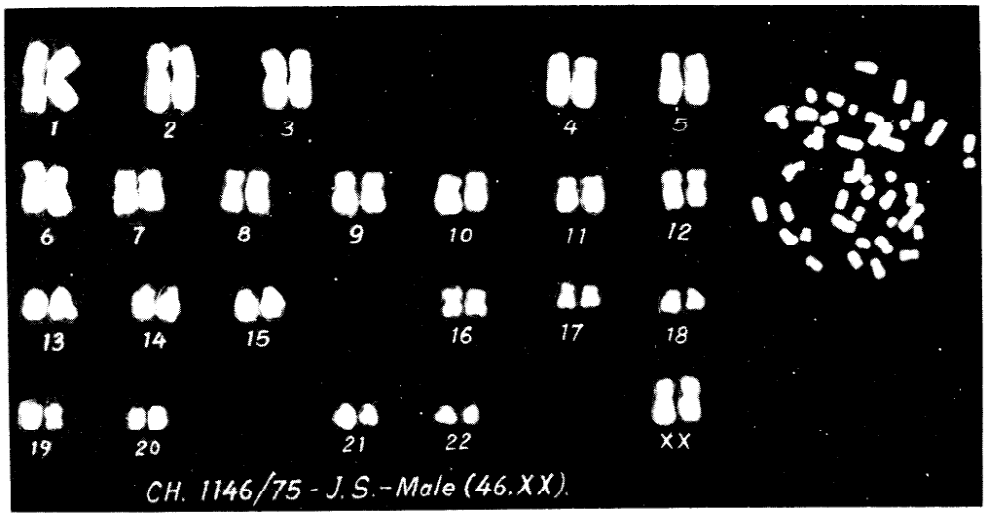


Fig. 3(c)

Fig. 3. (a) Adult male with 46 XX and gynaecomastia; (b) Note that external genitalia are male with poor male secondary sex characteristics; (c) No Y chromosome nor fluorescence in any of the other chromosomes.

develop into a testis or an ovary depending on its 'activation' by the H-Y antigen or an equivalent ovarian activating product, the actual nature of which is still not fully worked out.[8] Ohno postulates that the indifferent gonad has receptor sites on the surface. These receptor sites are occupied by polypetide chains produced by the HLA-A and HLA-B genes on chromosome No. 6 (Fig. 6). The core of the chain is buried in the cell membrane, its carboxyl terminus is directed inwards and its amnio-terminal end is exposed on the surface. To this amino-terminal is attached a β_2-microglobulin chain, forming a β_2-m-HLA dimer. To this dimer is attached the H-Y antigen produced by the H-Y gene or the hypothetical H-X antigen produced by the X chromosome. Hence, these two antigens compete for receptor binding and in this competition, the H-Y antigen has a preferential edge over the H-X antigen. The β_2-microglobulin is produced by a gene on chromosome 15. Once H-Y antigen complexes with the receptor, the indifferent gonad, which, at this stage shows a central medulla and a peripheral cortex, begins to favour medullary proliferation forming Sertoli cells, Leydig cells, tubules, spermatogonia, etc. However, if there is

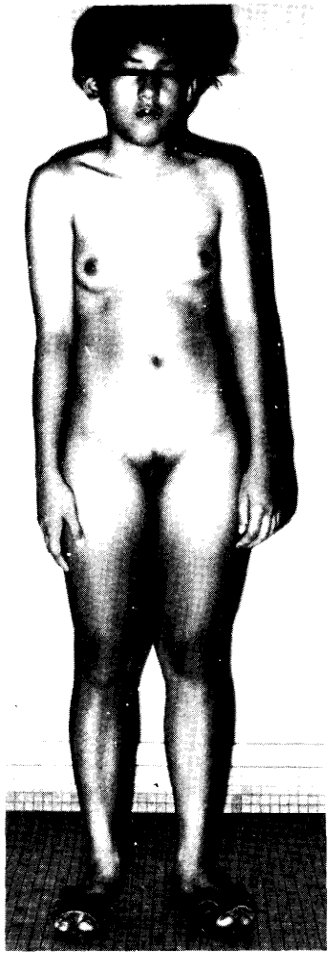


Fig. 4(a)

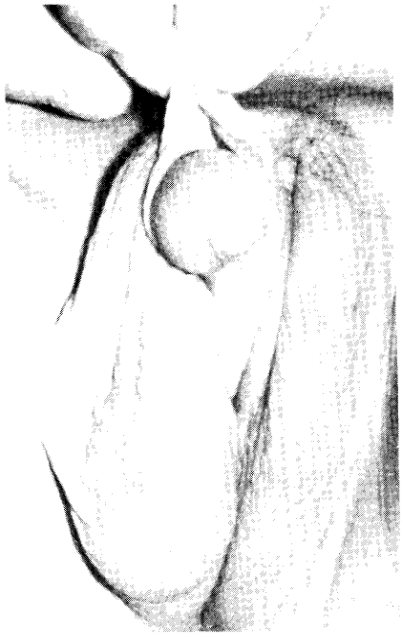


Fig. 4(b)

Fig. 4(c)

Fig. 4. (a) True hermaphrodite brought up as a boy, with breast tissue at puberty; (b) External genitalia demonstrate testis in right scrotal fold, empty left serotum, short penis, and introital opening; (c) Small uterus and tube on left side with ovary retnoved at operation.

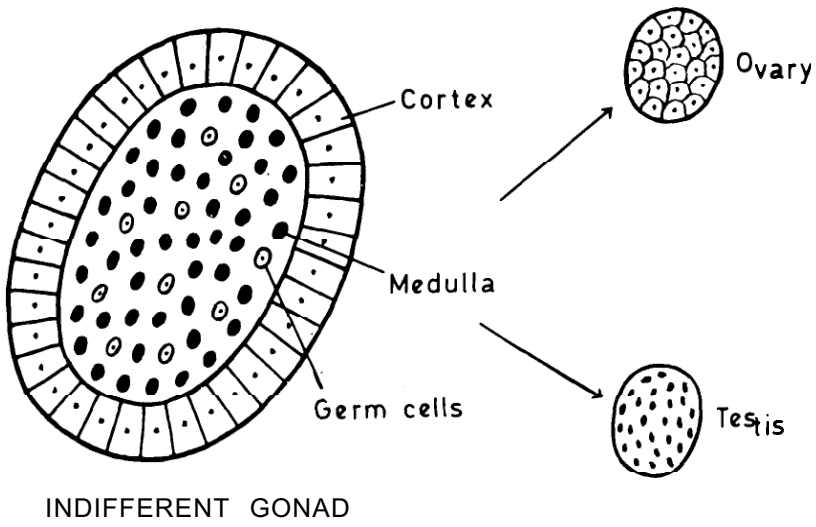


Fig. 5. Indifferent gonad with medulla and cortex. Ovarian development with proliferation of cortex, and testicular development with proliferation of medulla.

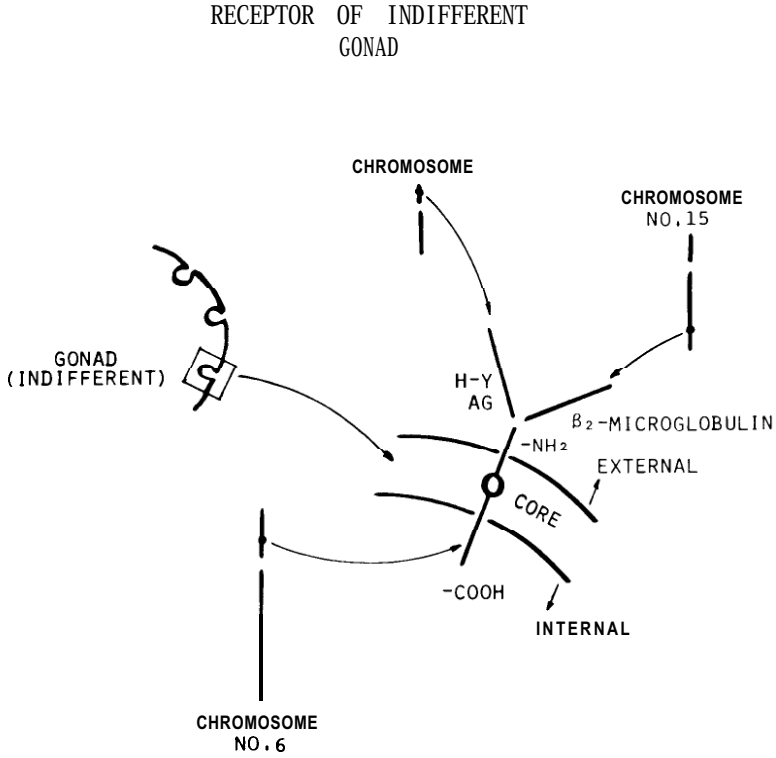


Fig. 6. Receptors on the surface of indifferent gonad on left, and schematic enlargement of one receptor site on right. The HLA locus on chromosome No. 6 produces a polypeptide, the core of which occupies the surface with its amino (NH,) end externally and the carboxy (COOH) end internally. A β_2-microglobulin produced by gene on chromosome No. 15 complexes with the $-NH_2$ end of the polypeptide, while the H-Y antigen produced by the H-Y gene forms a dimer with the polypeptide chain. This activates the indifferent gonad to differentiate into a testis.

no H-Y antigen, then H-X antigen complexes with the receptors, and cortical proliferation is favoured with the formation of the typical follicular structure of the ovary. On the other hand, if there is absence of H-Y antigen and deficiency of H-Y antigen, as in Turner's Syndrome (45 XO), then the gonads fail to develop as there is failure of receptor complexing, so that streaked gonads are formed.

A hypothesis is only as good as its ability to explain all facts of observation. In 1976[9] a peculiar form of sex reversal in the Scandinavian wood lemming, myopus schisticolor, was described. Offspring show a skewed sex ratio favouring females, i.e., F:M ratio = 4: 1. However, when these offspring were karyotyped, it was found that almost half the females had a male karyotype, i.e., 32 XY[10] and in spite of the intact Y chromosome, their gonads are ovaries and NOT testes. These females are fertile but they bear only female offspring, both XY and XX. In terms of the H-Y antigen studies,[11] it was found that XY males were H-Y positive. However, *all* females, both XX and XY, were H-Y negative. Therefore, it seems that XY females are an exception to the above hypothesis. But we also have examples of this type of sex reversal in humans, e.g., the 46 XY gonadal dysgenesis, a Syndrome where the subjects complain of primary amenorrhoea, enunchoid habitus and absence of breast development. The external genitalia (Fig. 7) are female though they may be underdeveloped and the clitoris may be slightly enlarged. Internally, uterus and tubes are present but there are no testes and in their place are streaked gonads. These streaked gonads differ from the streaked gonads of those of Turner's Syndrome in that in 25% of cases, they may become malignant. In these individuals, there is no H-Y antigen in spite of the presence of the Y chromosome. Because of the findings in the wood lemmings and in women with 46 XY gonadal dysgenesis, it was proposed that the H-Y gene on the Y chromosome does not function by itself without any constraints from the activity of any other genes. Those of us studying human genetics realise that genes seldom work in isolation but often interact with other genes.[12] It was thus proposed, logically, that[13–15]:—

1. The H-Y gene on the Y chromosome is a structural gene but there is a REGULATOR gene, probably on the X chromosome (Fig. 8) tending to suppress the

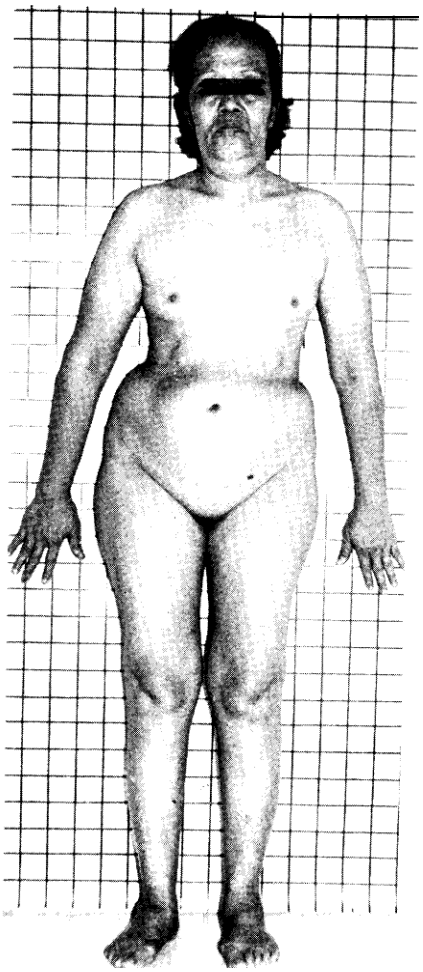
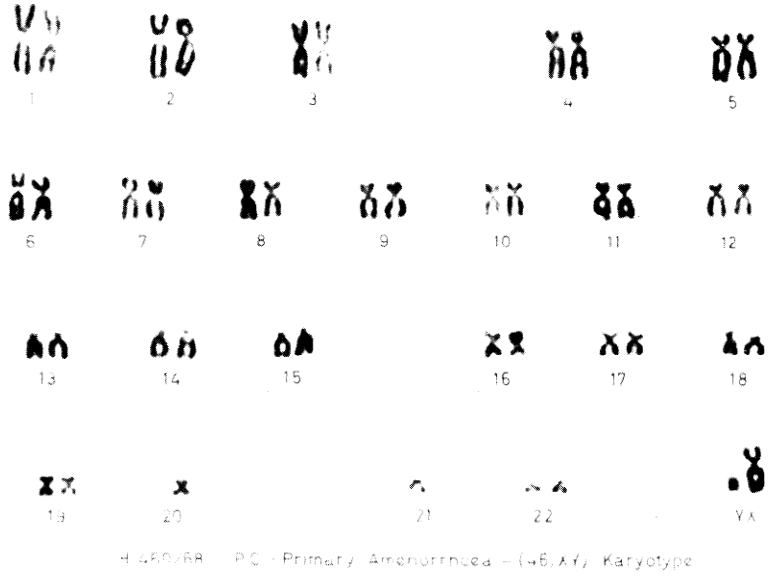


Fig. 7(a)



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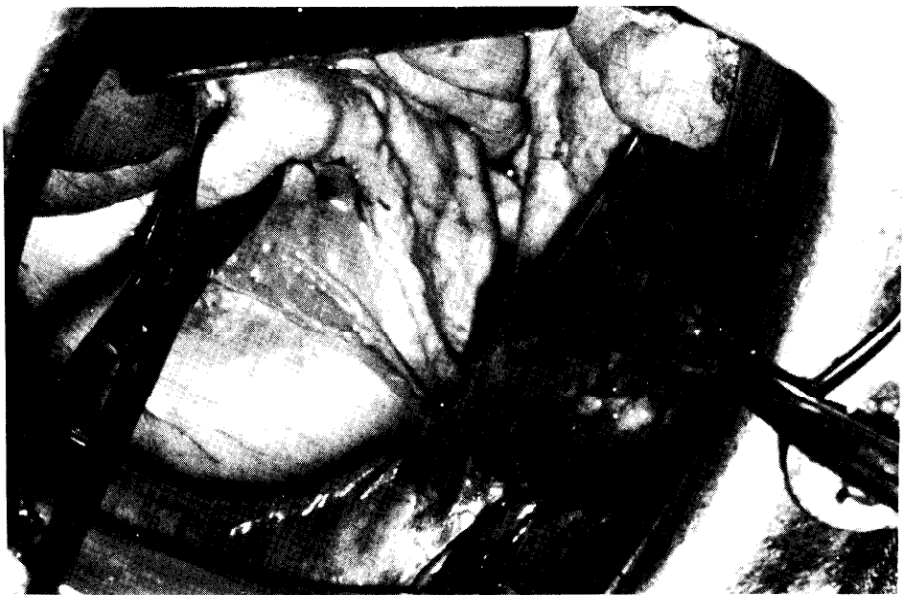

Fig. 7(c)

Fig. 7. (a) Patient is a phenotypic female with primary amenorrhoea,. (b) However chromosome constitution is male 46 XY; (c) Laparotomy revealed that intra-abdominal gonads are fibrotic ovuries. Hence this is an example of a sex-reversed male. Note the difference from syndrome of testicular feminisation where the phenotype is also female, chromosomes also 46 XY but gonads are testes.

formation of H-Y antigen by the H-Y structural gene on the Y chromosome. In the wood lemming and in 46 XY gonadal dysgenesis, there is an abnormal H-Y structural gene or an abnormally strong H-Y regulator gene.

2. The H-Y gene on the Y chromosome is a REGULATOR gene while the H-Y STRUCTURAL gene is on the X chromosome. The H-Y regulator gene on the Y chromosome acts on the H-Y structural gene on the X chromosome in a stimulatory manner but there is another regulator gene on an autosomal chromosome which also acts on the structural gene on the X chromosome but depressing its activity. It is the resultant of the activities of the two regulator genes which produces a certain level of H-Y antigen (Fig. 8).

That there is a regulator gene on the short arm of the X chromosome is seen in a family described by Bernstein *et al*,[16] where the propositus was a mentally retarded girl with female internal genitalia with microscopic ovarian remnants consisting of

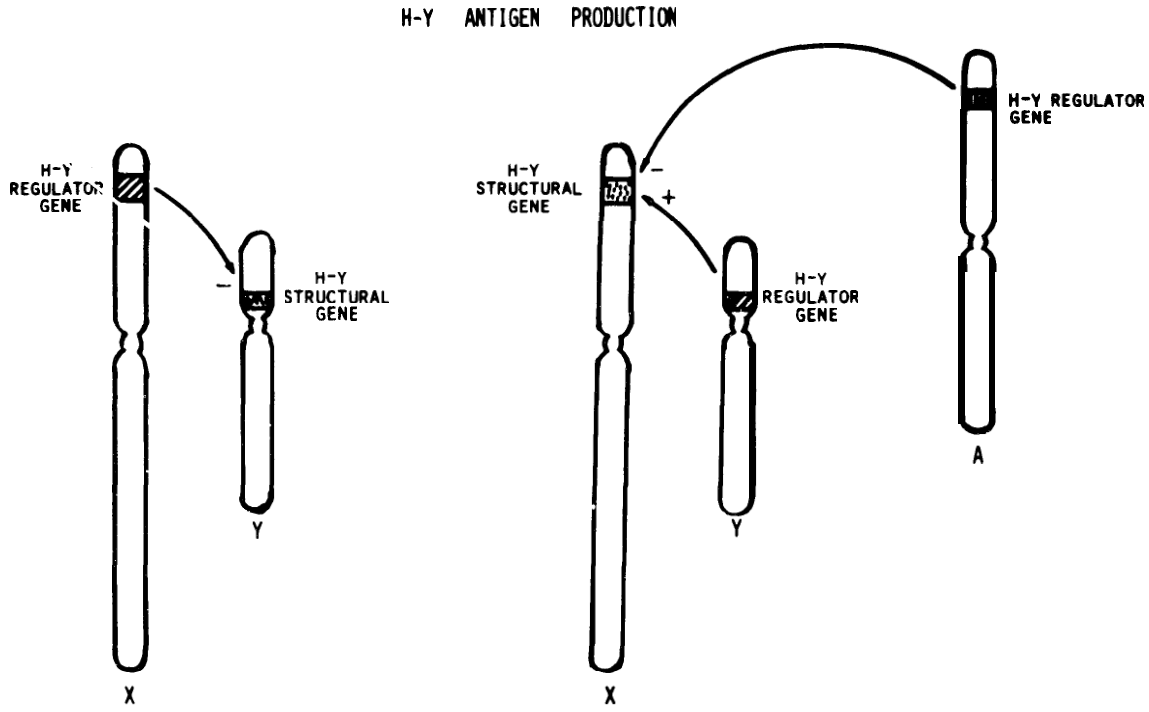

Fig. 8. Hypotheses concerning H-Y genes in humans. On the left, the H-Y gene on the short arm of Y chromosome producer H-Y antigenwhile a gene on the X chromosome regulates its activity. On the right, however, the H-Y gene on the Y chromosome and another H-Y gene on an autosomal chromosome both regulate the activity of a H-Ygene on the X chromosome which actually produces the H-Y antigen.

ovarian stroma and degenerating primordial follicles. Yet, she had a Y chromosome which was indistinguishable from that of the father, but her X chromosome was larger than a normal X, in that there was a duplication of the terminal end of the short arm of a normal X. There was no H-Y antigen and this could be due to suppression by a double dose of the H-Y regulator gene on the abnormal X chromosome on the normal H-Y gene on the Y chromosome. The mother carried this abnormal X as did the maternal grandmother, and the sister of the propositus. When the mother was pregnant again, amniocentesis revealed the foetus to be 46 XY with the abnormally long X chromosome again. Therapeutic abortion was performed at the request of the parents and again the internal and external genitalia were female in spite of the possession of a normal Y chromosome and presumably normal H-Y gene. There was no H-Y antigen, and histological examination of the fetal ovaries did not reveal any testicular tissue.

In CONCLUSION, then, the H-Y gene on the Y chromosome produces H-Y antigen which attaches to receptors on the indifferent foetal gonad to produce a testis. Its production of H-Y antigen is regulated by genes on the X chromosome and probably also other genes on autosomal chromosomes. The X chromosome produces ovarian-producing H-X antigens but compete against H-Y antigen at a disadvantage, and can only react with sufficient receptors on the indifferent gonad in the absence of the H-Y antigen.

Site of H-Y Gene on Y Chromosome

The Y chromosome is small and resembles the smallest G group of chromosomes. The short arm is very short and at the terminal ends of the long arms are areas which fluoresce brightly when stained with quinacrine. Hence, interphase male cells and the long arms of the Y chromosome show this fluorescence (Fig. 9). The short arms do not show fluorescence. In 46 XX males, no fluorescence is seen in any part of any of the chromosomes. [17] Yet, such individuals are H-Y antigen positive, so that the H-

Y gene cannot be at the terminal ends of the long arms of the Y chromosome. Furthermore, in individuals with deletion of almost the whole of the long arms of the Y chromosome, testicular tissue can still be formed (Fig. 10). Therefore, the H-Y gene is on the short arm, the centromere or on the proximal part of the long arm near the centromere.

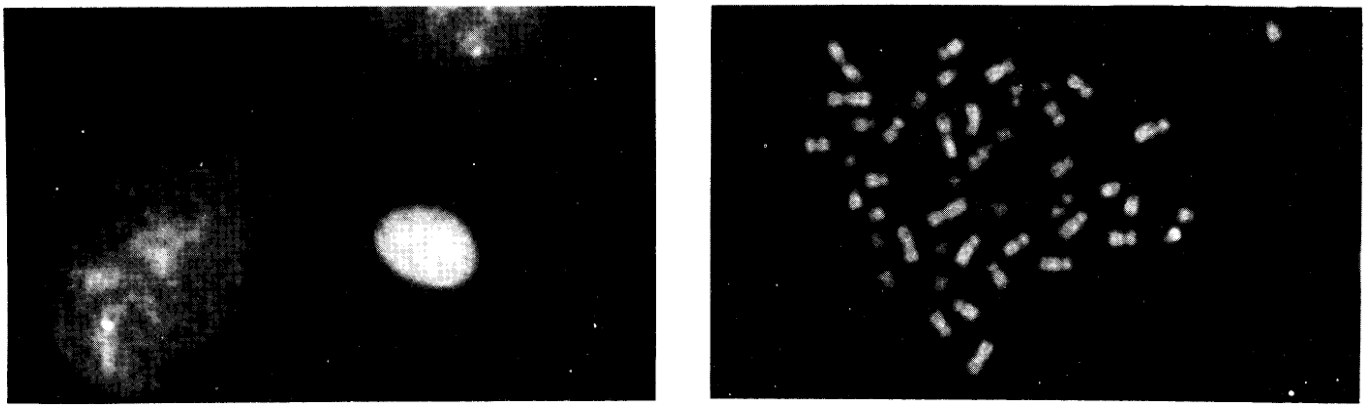

Fig.9. (a) Quinacrine Y fluorescence in a lymphocyte of a 46 XY mule (large cells on left and top); (b) Quinacrine Y fluorescence in the long arms of a Y chromosome (periphery on right)

There is no doubt that the short arm is the site of the H-Y gene or one of the sites for this gene because indivdiuals with isochromosome of the long arms of the Y chromosome (i.e., those without any short arms of the Y chromosome) are female without testicular tissue.[18–24]

The site of the H-Y gene on the short arm is probably not at the terminal end. This can be ascertained by studying dicentric Yq chromosomes in individuals with this abnormal variant. A dicentric Yq is formed when there is a break in the short arms of the Y chromosome with loss of the segment distal to the break leaving only the proximal portions of the short arm, i.e., near the centromere. Three such cases have been described and they were all phenotypically normal males with testes.[25–27]

Indeed the Y chromosome is probably the only chromosome with few significant genes. H-Y gene is one and there is some evidence that individuals with deletions of the distal portions of the long arm of the Y chromosome (so that fluorescence is lost) plus the neighbouring non-fluorescent part, still have testes but are infertile.[28–31] Therefore, there may be gene (or genes) on the long arm of chromosome Y proximal to the fluorescent terminal portions which is responsible for male fertility. Thus, a diagrammatic representation of the known genes on the human Y chromosome is depicted in Fig. 11.

Post-Gonadal Development

The H-Y gene determines the gonad and after this, it has no more part to play in the subsequent development of the sex organs. The internal genital ducts comprising the Mullerian and Wolffian ducts, and the external genitalia comprising the genital tubercle, genital folds and genital swellings develop in accordance with secretions from the gonads. It was Jost[32] in 1947 who showed that without secretions from the gonadal testis, both the genital ducts and the external genitalia feminise, i.e., the Mullerian ducts form the uterus, tubes and upper vagina, the Wolffian ducts regress, the genital tubercle becomes the clitoris, the genital folds the labia minora and the genital swellings the labia majora (Fig. 12). However, in the presence of secretion from the testis, the Mullerian ducts regress while the Wolffian ducts form the epididymis, vas deferens and seminal vesicles, and the genital tubercle becomes

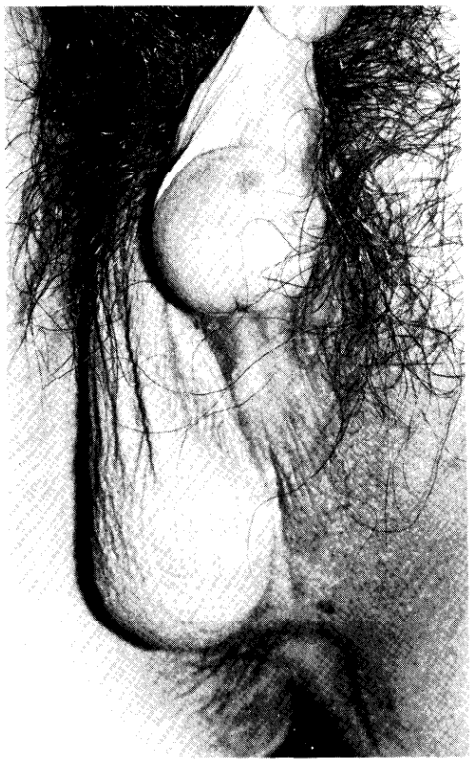

Fig. 10(a)

Fig. 10(c)

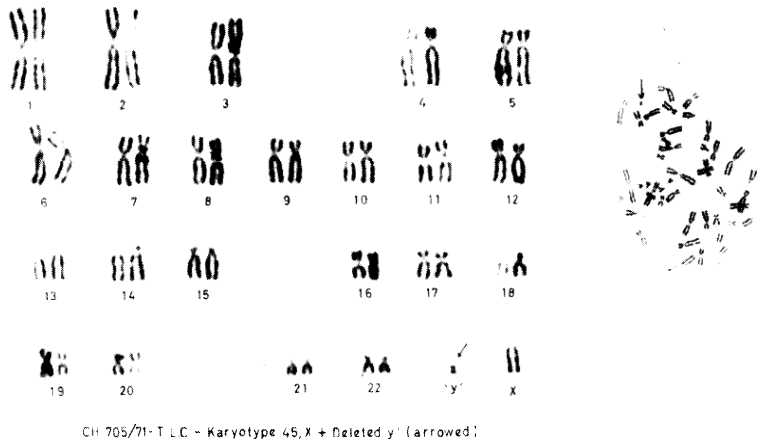

Fig. IO(b)

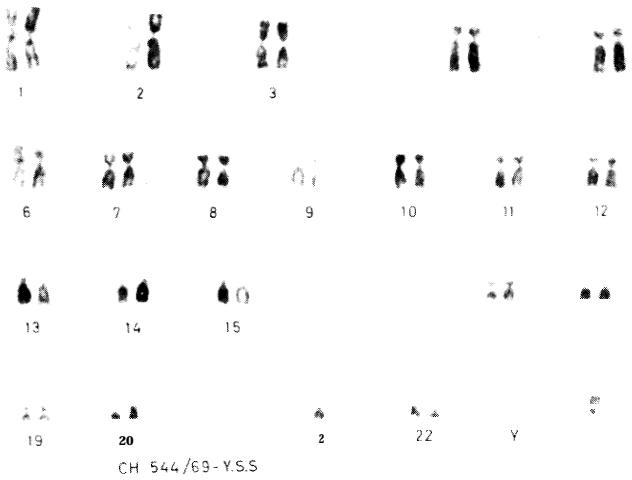

Fig. IO(d)

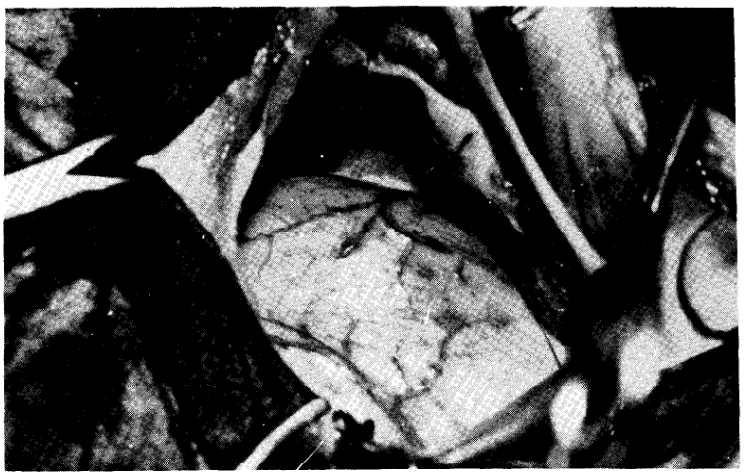

Fig. 10(e)

Fig. 10. (a) External genitalia of 17 year old male pseudohermaphrodite brought up as a male; (b) Chromosome constitution showing a small Y due to deletion of long arms, and yet testes are formed demonstrating that H-Y gene is on the short arm and/or centromere and/or proximal long arm. (c) External genitalia of a 22 year old brought up as a female with primary amenorrhoea, with (d) showing deletion of long arms of Y chromosome and (e) intra-abdominal testes.

Fig. 11. Schematic diagram of probable structure of human Y chromosome. The H-Y gene is postulated to occupy the proximal short arm, centromere and proximal long arm. At the distal long arm is the site responsible for quinacrine fluorescence and proximal to this is a gene/genes which are responsible for male fertility.

the glans penis, the genital folds the shaft of the penis and the genital swellings the scrotum. These are summarised in Table I.

It is thus seen that the basic development of the genital ducts and the external genitalia is towards the female. Only the presence of secretions from the normal testes, is it possible for these structures to masculinise. Note that of these testicular secretions, there are two different substances. A Mullerian inhibiting factor (MIF) is

TABLE I

Indifferent Structures	Under Influence of: Testicular Secretions	Under Influence of: No Testicular Secretions	Final Structures: Final Structures
Genital Ducts			
Mullerian Ducts	Mullerian Inhibiting Factor	—	Regress
	—	Nil	Uterus, Tubes, Vagina
Wolffian Ducts	Testosterone	—	Epididymus, Vas, Seminal Vesicles
	—	Nil	Regress
External Genitalia			
Genital Tubercle	Testosterone	—	Glans Penis
	—	Nil	Clitoris
Genital Folds	Testosterone	—	Shaft Penis
	—	Nil	Labia Minus
Genital Swellings	Testerone	—	Scrotum
	—	Nil	Labia Majus

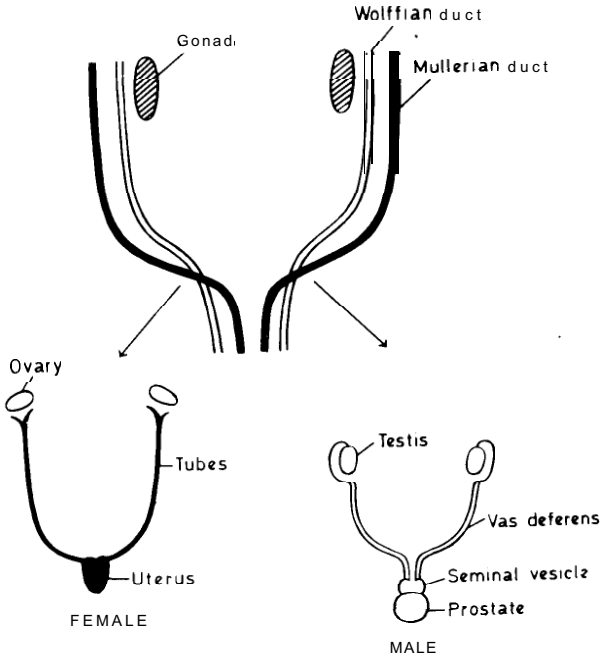

Fig. 12(a)

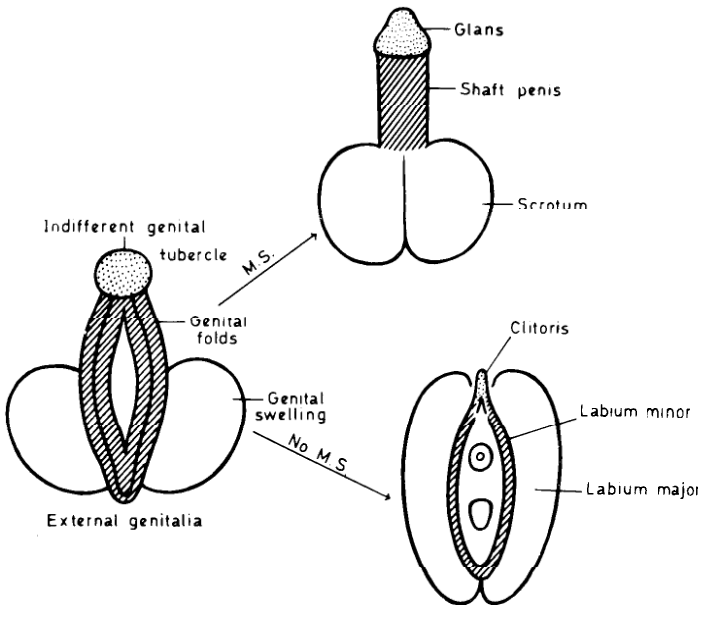

Fig. 12(b)

Fig. 12. (a) Internal genital ducts with male differentiation on right due to suppression of Mullerian ducts by Mullerian inhibiting factor from testis and development of Wolffian ducts by testosterone, and female differentiation on the left in the absence of testicular secretions; (b) Indifferent external genitalia on left and masculinisation on right (above) in the presence of masculinising substance (testosterone) and feminisation in the absence of androgens.

secreted initially in the male to suppress the Mullerian ducts and shortly after this, the testes secrete testosterone which masculinise the Wolffian Duct as well as the external genitalia. Thus, the H-Y gene in "abrogating" its control to the testes it had assisted in forming, allows of many intersexes to arise. For example, a female foetus with excess testosterone production from the adrenal glands, as seen in congenital adrenal hyperplasia will show degrees of virilization of the external genitalia, and on the other hand in a male foetus, if the testes fail to form MIF and testosterone at the correct time or in sufficient quantity, then there will be feminization of the genital ducts and external genitalia producing male pseudohermaphrodites. Female pseudohermaphrodites possess ovaries and female internal genitalia but with various degrees of virilization of the external genitalia and hence should be assigned a female sex upbringing as they can be fertile in later life. The commonest causes of female pseudohermaphrodism are:—

1. Congenital adrenal hyperplasia in a female
2. Use of progestrogens during pregnancy
3. Maternal androgen-producing tumours.

Male pseudohermaphrodites who possess testes may show degrees of feminisation of the genital ducts besides ambiguity of the external genitalia and their causes are much more varied than those causing female pseudohermaphroditism.

One of the reasons for this variation is that during foetal life certain sex tissues in the male are more sensitive to 5-dihydrotestosterone formed from testosterone by an enzyme 5α reductase. Hence, in the autosomal recessively inherited conditon of 5α reductase deficiency,[33] these external genital structures do not masculinise as they should and sexual ambiguity results. However, this differential sensitivity to DHT disappears at puberty and virilization takes place. If the child had been brought up as a girl, problems may arise during puberty. Another reason for the variation in the cause of male pseudohermaphroditism is that testosterone as with all steroids act on testosterone-sensitive tissues by combining with specific receptors in these cells. In the sex-linked condition where these androgen receptors are absent, the affected individual will possess testes as the Y chromosome and H-Y gene are normal. The testes produce MIF, so that there will be no uterus or tubes. Testosterone is produced but because there are no testosterone receptors, the Wolffian Ducts regress and the external genitalia will be female. This is the syndrome of testicular feminisation and since the external genitalia are female, they are brought up as females and are totally female in outlook and appearance, although they possess testes and have a 46 XY chromosome constitution.[34] However, if there is a PARTIAL receptor deficiency, then the external genitalia will be partially masculinised so that a male pseudohermaphrodite results. The third reason is that just as enzyme deficiency in the adrenal cortical metabolic pathway can occur in female foetuses resulting in female pseudohermaphroditism, so also an enzyme deficiency in testosterone synthesis can occur with the result that another type of male pseudohermaphrodism results.

Therefore, male pseudohermaphrodites, i.e., individuals with XY chromosomes and testes (normal or dysgenetic) but with various degrees of feminisation of the genital ducts and external genitalia, are very heterogenous in aetiology, as can be seen in Table II.

Another effect of the testosterone steroids must be considered besides their obvious role in masculinising the genital ducts and external genitalia. This is their effect on non-sex organs such as bone and muscle. They have an "anabolic" action on these structures so that human males are taller and heavier than their female counterparts. In all studies on the pubertal male and pubertal female, the physical strength of the male far exceeds that of the female. It has usually been stated that this increased growth is due to the direct action on the muscles and bones but there is

TABLE II

A: Disorders of Testicular Differentiation:

1. XO/XY mixed gonadal dysgenesis
2. Deletion of short arm of Y chromosome
3. Gene mutation of H-Y gene
4. Abnormalities of H-Y structural or regulator genes

B: Disorders of Testicular Function

1. Gonadotrophin unresponsiveness
2. Deficiency/Abnormality of mullerian inhibitory factor: syndrome of hernia uteri inguinale
3. Deficiency of enzymes for testosterone synthesis
   (a) Cholesterol 20α, 22 hydroxylase
   (b) 20, 22 desmolase
   (c) 17α hydroxylase
   (d) 17, 20 desmolase
   (e) 3 β hydr oxysteroid dehydrogenase
   (f) 17β hydroxysteroid dehydrogenase

C: Disorders of Function at Androgen Dependent Target Areas

1. Androgen receptor defects: partial testicular feminisation syndrome
2. Enzmye deficiency in testosterone metabolism: 5α reductase deficiency

evidence that they may act via the hypothalamopituitary axis by altering the secretion of growth factors controlled by this endocrine axis.

In CONCLUSION, then, the testes formed by the action of H-Y gene, takes over the role of masculinisation of the male endowing him with not only the male sexual apparatus but also the paraphernalia of the male sexual dimorphic state such as hairiness, voice changes, body odours, and most significantly, greater size and physical strength. However, in this process there are many steps which could be faulted either by inherited and acquired conditions which may produce intersex states, the study of which has enriched our knowledge of the manner in which the two human sexes have been developed.

Male and Female Behaviour

At the beginning I mentioned the behaviour differences of the human male from the human female, and in social evolution, it has come about that male behaviour has shaped so-called norms of present-day society. Subsequent to this, I discussed the role of the Y chromosome in this difference and the conclusion was reached that the male sex hormones, testosterone and DHT play a great part in this differentiation in terms of greater physical strength, aggressiveness, etc without the burden of birth and upbringing of children, responsibilities which perforce had devolved mainly on the human female.

However, male behaviour is not totally dependent on just physical attributes. Many animal experiments have been carried out to see if sex hormones given during the foetal and neonatal stages will have an effect in later life no matter what the sex of the baby. For example[35] administration of testosterone to pregnant guinea pigs revealed that daughters behaved more like males than females. Similarly, injection of testosterone into female rats at 5 days of age permanently impaired the regulation of the sexual cycle post-pubertally.[36] In fact, these neonatally masculinised females, if properly primed post-pubertally manifest masculine sexual behaviour: attacking adult males and attempting to mount estrous females.[37] There is evidence that these changes in sex behaviour due to early priming by sex hormones are brought about in the developing hypothalamus. This has been confirmed when the experiments were carried out by implanting micro-amounts of sex hormones directly into the hypothalmus.[38,39] However, paradoxically, it was found that if certain doses of oestrogen

are given instead of androgens, the same masculinising imprint on the CNS can take place, and it was a blow to male chauvinism when it was found that hypothalamic neurones are rich in microsomal aromatase which is responsible for conversion of testosterone to 17β-oestradiol.[40] Why then does not the neonatal mouse become neurologically masculinised by the action of their own oestrogens? This is prevented by a circulating β-foetoprotein which shows an extremely high binding affinity to this female steroid hormone, thus very effectively reducing the oestrogen levels in the CNS.[41,42] Thus, sex hormones during the foetal and neonatal stage can play a great part in the subsequent behaviour of males and females in adulthood. The relevance of such findings in experimental animals may not be so easily extrapolated to human beings. However, one cannot exclude the CNS in the part played by different organs and tissues in man, and which determine subsequent adult behaviour.

One valid and most important observation in this regard is sex assignation or sex of rearing selected for any child. Our follow-up studies on large numbers of pesudohermaphrodites reveal that these individuals behave appropriately in the sex assigned to them if this is done early during infancy in spite of opposite chromosomal and gonadal sex. This was originally pointed out as early as 1955.[43] One example will suffice. A 12 year old Indian boy was referred to me from the School Health Services because at routine examination he had a perineal hypospadias and empty scrotal sacs (Fig. 13) with a moderate-sized phallus. On investigation it was found that the parents had always regarded him as a boy since birth in spite of the appearance of the external genitalia. He went to a boys' school and was totally male orientated. However, he was chromosomally female with a 46 XX karyotype and had excess 17-ketosteroids in the urine categorising him as a female suffering from congenital adrenal hyperplasia due to 2 1 -hydroxylase deficiency. The parents refused treatment and absconded and I lost touch of him till recently he was referred to me by a gynaecologist to whom he had gone so that he could be made "more male", for by now he had some breast tissue also. By now he was 24 years old, stunted in stature, as expected, but totally male-orientated and he said he had a girl friend and that was the reason for his seeking medical assistance. I recognised him and he told me that he was working as a 'rigger', climbing high telegraph poles, attaching and repairing electric wires — a totally hazardous male occupation! The neurological imprinting by the psychological environment occasioned by the male sex of upbringing and probably also the testosterone excess acting on his foetal brain have made him totally male-orientated in spite of his female sex. On the other hand, all our other cases of female congenital adrenal hyperplasia with ambiguous external genitalia have been assigned a female sex of rearing and they also have assumed this role without any problem at all, though the parents say that they tend to be more "tomboyish" in their behaviour. This has also been noticed in other series[44] where they tend not to play with dolls as most girls would. Therefore, although psychological imprinting is important, prenatal and neonatal sex hormonal influences are also not negligible in determining subsequent adult behaviour.

Finally, the role of excess androgens during foetal life and subsequent intelligence as measured by standard IQ tests has been investigated in both male and female congenital adrenal hyperplasia patients.[45–48] It was discovered in all series that their average IQ was greater than controls. This was not due to the disease as such but due to prenatal exposure to excess hormones, e.g., Dalton[49] in 1968 reported a follow-up study of children (both male and female) who had been exposed to progesterone administered to their mothers for relief of toxemic symptoms. The dosages varied from 50–300 mg/day I/m injections. In NO case was evidence of genital masculinisation observed. Two control groups were taken and matched with the trial group, one of next born children listed in the labour ward register whose mothers had a normal pregnancy and delivery. The second control group included children

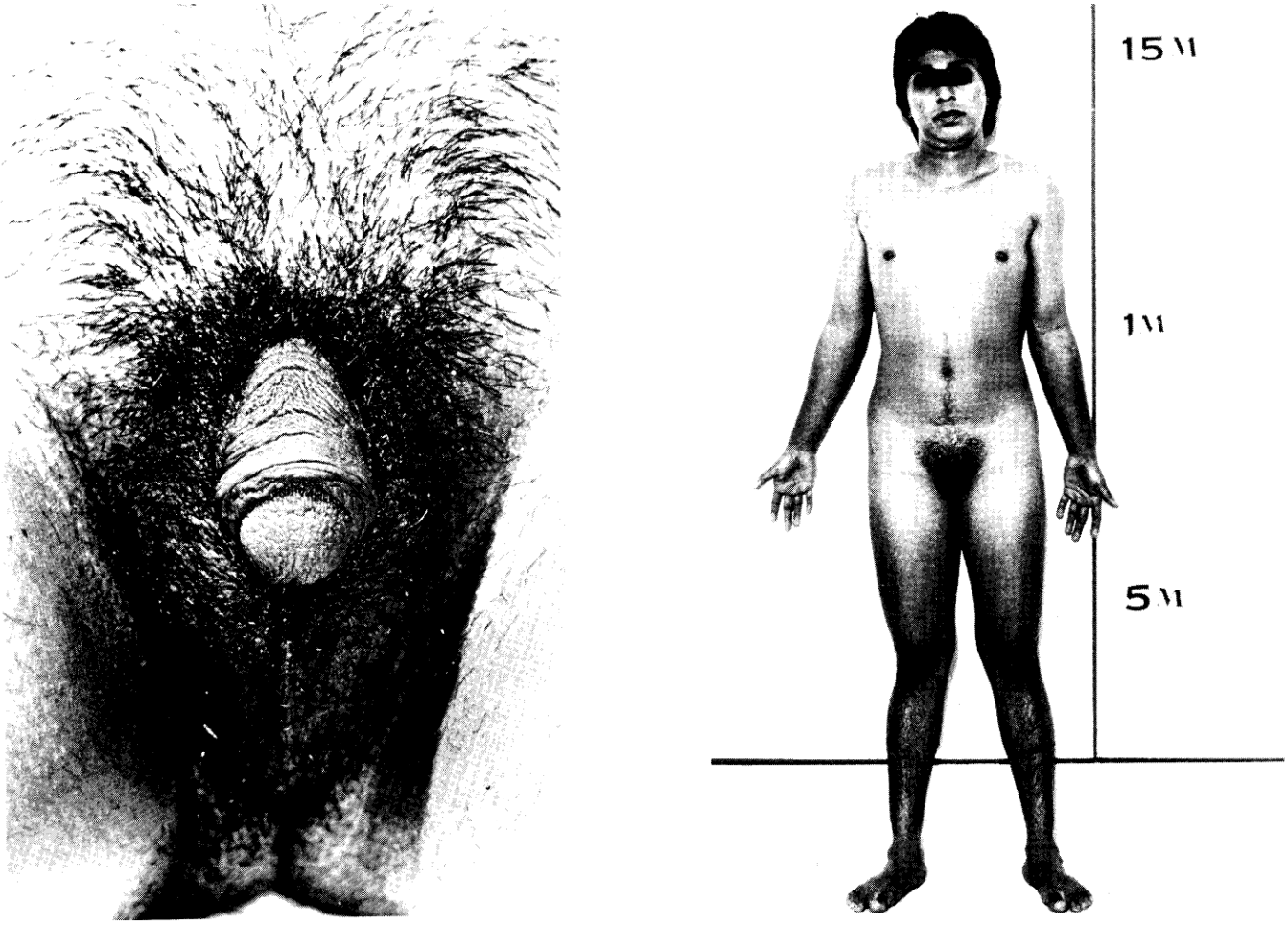

Fig. 13(a) Fig. 13(b)

Fig. 13. Patient with congenital adrenal hyperplasia brought up as a male in spite of 46 XX chromosome constitution. (a) Appearance of external genitalia; (b) Patient now at age of 24 years, stunted with breast tissue but totally male-orrentated.

delivered to women who had toxaemia during pregnancy without hormonal treatment. The children were 9–10 years of age at the time of follow-up. The progesterone children did better than the other two control groups in their scholastic grades in school. The earlier the injections were given, the better the school performance. He concluded that prenatal treatment with progesterone was likely to be related to enhanced school performance! However, we are still uncertain what the side-effects could be, but the point is made that sex hormones during prenatal life have an influence on subsequent adult behaviour. I must sound a word of caution. Throughout medical history, it has been proved again and again that drugs used in medicine always exact a price in terms of a possible deleterous side-effect, as a drug is always a foreign body in terms of genetic evolution. The use of diethylstiboestrol in pregnancy has resulted in vaginal adenosis or adenocarcinoma in female foetuses when they grow up. Besides these growths, congenital malformations of the genital tract have been described as well as menstrual irregularities, difficult conceptions and a high fetal wastage. In the case of male fetuses, malformations of the genito-urinary tract have also been described.[49–54]

Quo Vadis

I have briefly outlined the scientific evidence underlying the main differences between the human male and female sexes, evidence which have been obtained

relatively recently although there are still unsolved problems. It is genetic evolution which has been responsible for these sex differences. However, the human race having inherited its genetic potential has altered the environment beyond all recognition; some of these alterations have been good and some deleterous. In this social evolution, the human race has been unable to throw off the sex difference, e.g. the male capacity to wage wars, relegation of the all-important duty of upbringing of progeny to females, to mention only two. In this process of human social evolution, there is already considerable blunting of differential sexual zones of influence and work, so to speak, in the more modern states, as in Singapore. The social evolution of family planning to adapt to a situation created by other areas of social evolution, means that there will be less human "hands" for the purpose of carrying on a livelihood. Computerisation and "robotisation" have come and must needs become more sophisticated. There is no male computer or male robot! The fewer human digits left behind will then have to devise ways and means whereby every one will have to be more productive, and the artificial division of labour for the sexes must be blurred in the future. With our knowledge of genetic evolution, we know what we can change and what we cannot. For the moment, and for a long time in the future, or even never, can we ever hope for the male to carry a foetus for 40 weeks and undergo labour. Thus, the time will surely come when the man will have to claim sex equality by being more involved, and even taking over the most important task of child rearing as well as home making!

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