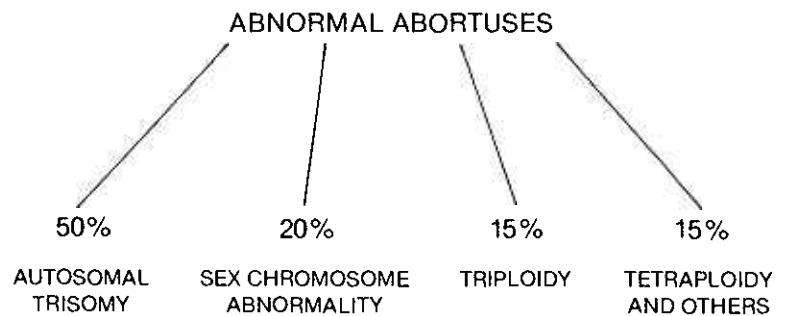


## SMA LECTURE

## THE SIGNIFICANCE OF HUMAN CHROMOSOME ABNORMALITIES IN SINGAPORE

Wong Hock Boon

Diseases associated with abnormal chromosomes comprise about only 5% of all genetic diseases. However, this is only the tip of the iceberg because many foetuses with abnormal chromosome constitution self-destruct and present as "spontaneous" abortions. For example, examination of very early abortuses have revealed 50-60% with chromosome abnormalities. The incidence would be much higher if the earliest conceptuses are included as many of these are so small that the abortion itself is missed. It is important to realise that most causes of abortions are due to foetal abnormality rather than maternal hormonal imbalance. The majority of the chromosome abnormalities is an autosomal trisomy, that is, an extra chromosome in the non-sex chromosomes, about half of them, 1/5 are sex chromosome abnormalities and of the remainder, 1/2 are due to triploidy and 1/2 due to tetraploidy, unbalanced translocation and others:—



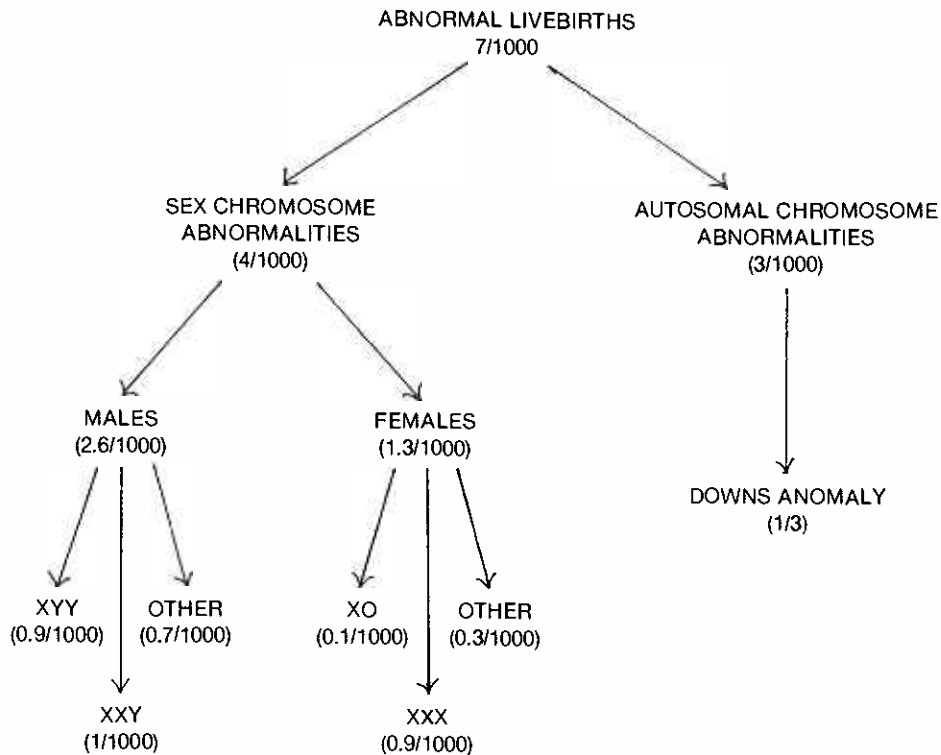
What is the significance, therefore, of 50% of abortuses? Because they are already abnormal, this is nature's way of getting rid of those whose chances of survival are less if they reach maturity and are live-born. Therefore, excessive efforts in preventing abortions in very early gestation MAY increase the congenital malformation rate. This is seen in chromosome cultures of macerated stillbirths (Alberman and Creasy, 1977) where 12% have abnormal chromosome constitutions; and among fresh stillbirths 5% and early neonatal deaths 6%. In other words, these abnormal foetuses who manage to reach term finally die, nature still taking care of them.

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Unfortunately, some of these foetuses with chromosome abnormalities survive, and I would like to discuss the significance of these, to themselves, to their families and to society. The incidence of this group is about 7 per thousand livebirths (Wong and Chua, 1970) with slightly more sex chromosome abnormalities than autosomal

chromosomal abnormalities. There is almost twice as many male sex chromosome abnormalities than female ones, and among the autosomal chromosomal abnormalities, one-third are Down's Anomaly (DA) — Mongols. The approximate distribution of the various abnormalities in live-births is as follows:—



I would therefore like to discuss some of the above liveborn chromosome abnormalities, their characteristics, and their significance, in terms of society.

**DOWNS' ANOMALY**

Down's anomaly or DA was previously termed Mongolism, and the latter term is still used by laymen. Besides certain physical stigmata, the most important characteristic is the mental retardation, and some serious organ defect besides that of the brain, for example, congenital heart disease. This defect often cuts down their life span.

The degree of mental retardation has been assessed extensively in regard to DA staying in institutions and in several series (Penrose and Smith, 1966) comprising more than 2,000 cases, the mean IQ had been around 25 with a standard deviation of 6-9. Those cared for in their own homes with maximal stimulation may attain IQ's between 35 and 55. Hence, the majority, if not all, have IQ's lower than 60. Therefore, DA patients are unable to earn a living on their own.

Genetically, DA individuals, possess an extra

chromosome No. 21, and hence the alternative term used for it is trisomy 21. Unfortunately, this was before identification of chromosomes became more accurate, and actually it is the smaller chromosome 22 which is trisomic. However, by conventional agreement, we still refer to the condition as trisomy 21 instead of trisomy 22. The extra chromosome 21 arises because of non dysjunction or other chromosomal division aberrations during meiosis of the parental gametes or during mitosis of the zygote. The parental chromosomes themselves are normal but the abnormality arises during the process of cell division. What causes this deviation of normal cell division is unknown; it could very well be due to drugs, infections, or other obscure causes. The important thing is that the cause is usually rare and operates more on a chance basis, although it could recur. This recurrence is rare. As the parents age, this aberration is more likely to occur, and hence standard trisomy 21 often arises when the mother is old, though paternal age plays a small part. The maternal partiality is due to the fact that female ova are already dividing when the female baby is born and hence are more likely to be exposed to triggers over such a long span of time.

However, some DA are definitely inherited, and this occurs when one of the parents has a chromosome 21 translocated on to another chromosome, and although they are normal because the number of genes are still normal, when they form gametes, there is the likelihood of transmitting this translocated chromosome to produce trisomy 21 with the translocated chromosome. The parent is therefore a carrier but does not suffer from the disease. The risk of trisomy 21 offspring in these cases varies from 1 in 5 to 1 in 20. The translocation can occur between chromosome 21 (Group G) and chromosome 15 (Group D) and hence termed D/G translocation.

G/G translocations can also occur. It is these translocated DA's where the risk of another DA in future offspring is high.

Since DA's are unable to function independently, they will be a handicap to themselves, their families and to society. It is therefore important to assess their significance in a population. From 1970 to 1977, the numbers of live-born DA in Kandang Kerbau Hospital, related to the total livebirths in KKH, the total livebirths in Singapore during those years, will give an idea of the MINIMAL incidence of new cases of DA in Singapore:—

YEAR	KKH		SINGAPORE	
	NO. LIVEBIRTHS	NO. DA	NO. LIVEBIRTHS	NO. DA (ESTIMATED)
1970	29,307	27	45,934	42
1971	29,950	37	47,088	58
1972	30,245	42	49,678	69
1973	28,917	32	48,269	53
1974	25,901	24	43,268	40
1975	23,006	25	39,948	43
1976	24,865	28	42,786	48
1977	22,183	34	38,364	58

Therefore, over a period of 8 years, a minimum of 411 DA patients were born. The impact of this number on the families and society is obvious.

However, we have no local figures of the survival of DA, but with antibiotics, DA who used to die from bronchopneumonia are saved. But, some still possess crippling organ defects such as congenital heart diseases which will kill off a certain number. Because of the excess genes, it has been observed that generally the life span is less than normal. Collman and Stoller (1963) in Melbourne estimated that 50% survive for 5 years, 25% survive for a mean 32-35 years. Hence, if these figures are applied over the 8 years in Singapore, there would still be over 100 DA surviving to their thirties.

Besides imposing a strain on Society, about half of that or more will be females who can produce offspring, and the chances of a DA as a result will be about 50%. The problem of voluntary sterilisation of female DA therefore arises.

Therefore, the problem of prevention of DA births is of paramount importance. To get an idea of the types of chromosome defects encountered in Singapore, 203 random cases of DA had their

chromosomes studied in the Department, with the following results:

REGULAR TRISOMY 21	173
D/G TRANSLOCATION (INHERITED)	9
D/G TRANSLOCATION (SPONTANEOUS)	8
G/G TRANSLOCATION (SPONTANEOUS)	9
MOSAIC NORMAL/TRISOMY 21	4

The spontaneous translocation (D/G = 8; G/G = 9) are equivalent to regular trisomies and hence not usually inherited. As can be seen, the vast majority are not inherited. If there is evidence that the DA can be inherited, of course, amniocentesis of subsequent pregnancies must be done and the foetal cells cultured to exclude translocation DA. But if a previous child is a non-inherited DA, should an amniocentesis be done to exclude DA in future pregnancies? Certainly, if a parent shows mosaicism of normal/trisomy 21, amniocentesis should be done.

The straightforward DA, i.e. regular trisomy 21, arises more often in older mothers, as explained above. What is the risk of a mother producing a

regular trisomy 21 baby at differet maternal ages?  
Generally, the risk is as follows:—

Less than 20 years:	1 in 2300
20 — 25 years:	1 in 1600
25 — 30 years:	1 in 1200
30 — 35 years:	1 in 880
35 — 40 years:	1 in 290
40 — 45 years:	1 in 100
More than 45 years:	1 in 46

As can be seen, the risks are all less than 1 in 30, a level of risk which is run by any woman of producing a baby with a significant congenital malformation. Under the circumstances, it is justifiable to culture the chromosomes after amniocentesis in those over the age of 40 years, because amniocentesis itself may occasionally have side-effects especially as it has to be done at about 16 weeks to allow of time for culture and possible repeat culture, so that abortion would be feasible. However, the doctor can only advise and inform, the decision to have an abortion on a DA foetus rests with the mother herself. Another way whereby the incidence of DA can be brought down is for mothers to have all their babies at 20 — 30 years of age when the risk is less than 1 in 1500, an extremely small risk indeed.

**KLINEFELTER'S SYNDROME:**

Klinefelter's Syndrome (KS) characteristically is a sex chromosome anomaly where there are 47 chromosomes, 2 X's and 1 Y, that is, 47XXY. They are male in phenotype but at puberty have poor male secondary sex characters with small testes and occasionally gynaecomastia. They are infertile, and their IQ is usually reduced.

We have studied 81 cases of KS of which the majority are 47XXY:—

47XXY	75
49XXXXY	2
49 (XXY + trisomy 21)	2
48XXY	1
XXXY	1

The more X's there are, the more retarded are the patients. There are two KS who are also DA, and this is evidence that in some individuals non-disjunction is a characteristic.

The significance of KS to society is not so much the infertility but the borderline mental retardation. Very few however, were referred to us because of mental retardation but the majority were referred because of infertility. Only after taking the history, it was found that the majority did not pass beyond the primary school level, nearly all failed the PSLE

examination, and many failed the lower primary levels but were automatically promoted.

Compared to DA, KS patients can earn a living but at a much lower level compared to those with normal IQ. However, because of their chromosome abnormality, and the consequent mild mental retardation, a larger number than usual of KS patients have been found in mental-penal institutions in the West. This problem is associated with the problem that is seen in multiple Y syndromes, where it has been postulated that possession of multiple Y predisposes a male to commit crimes of violence and also renders them resistant to rehabilitation.

**MULTIPLE Y SYNDROMES:**

Multiple Y Syndromes are those males with more than one Y chromosome. Although such individuals have been known to exist for some time, interest increased with the report by Jacobs et al (1965) who carried out a chromosome survey in Scotland on those who were mentally subnormal and under treatment in special security institutions because of dangerous, violent, or criminal propensities. Of 196 such men, 12 had an abnormal chromosome complement (6.1%) including 7 XYY men (3.6%) and one XXYY man. This prevalence was much higher than the incidence of such sex chromosome abnormalities in Scotland where Ratcliffe et al (1970) found 5 XYY and 3 XXY in 3496 newborn males. This peculiar finding triggered off great interest, and it was suggested that multiple Y and multiple X (KS) may be related to violent criminal tendencies. Hence, there were pronouncements such as those of Price and Whatmore (1967) that "it was reasonable to suggest that antisocial behaviour (of the XYY men) is due to the extra Y chromosome"; and those of Nielson (1968) that "It seems unlikely that punishment of any kind would change the risk of new crimes in patients who are genetically predisposed to criminality."

Following these findings and statements (Borgaonkar and Shah, 1974), the murder trial of Daniel Hugon in Paris was the first where the defence counsel claimed that his client had an extra Y chromosome and thus was not criminally responsible for his act. The court appointed an expert panel to review the mental condition and chromosomal constitution of the defendant, and, after Hugon had been convicted of the crime, a reduced penal sentence was imposed — presumably because of the chromosomal defect. Similarly, in Sydney, the murder trial of Hannell also involved a 47 XYY chromosome constitution. He was acquitted on grounds of insanity. It was obvious that the problem of the XYY male had

caught the attention both of the public and the law, so much so that many considered Richard Speck, the murderer of eight Chicago nurses, must have had a XYY constitution, even though it was subsequently proved that he was a normal 46 XY man. The main problem for doctors to solve was whether the XYY constitution itself was necessarily a cause for criminal behaviour. It was also stated that XYY men were all taller than usual and it is the extra Y which caused this as well as excessive male aggressiveness!

We have carried out studies to try and throw some light on the problem of multiple Y individuals. We have had 7 patients referred to us, who subsequently were found to possess multiple Y sex chromosomes, viz. 5 of them 47 XYY, and 2 of them 48 XXYY. The reasons for referral were not because of criminal tendencies but because of mental deficiency or male sterility. Many were short and timid rather than aggressive. Obviously, there are many multiple Y men who do not commit crimes. However, we decided to investigate male prisoners in Changi Prison (Wong, Chua and Singh, 1978), which is the main prison in Singapore, and where maximum security prisoners are housed together with other categories. The types and frequency of male prisoners at the time of the survey were as follows:—

Long sentence prisoners	62.6%
Criminal law detainees	27.3%
Short sentence prisoners	5.2%
Police detainees	1.8%
Condemned prisoners	1.2%
Others	2.4%

Therefore, 90% of the prisoners comprise those in the maximum security category where the majority of crimes were of violent or aggressive nature. Altogether 1,506 of these male prisoners were screened with Barr body and fluorescent Y techniques.

There were only two out of the 1506 male prisoners who had abnormal sex chromosomes, one with 47 XYY (multiple Y) and the other 47 XXY (Klinefelters Syndrome). Detailed histories were taken in these two cases, and it was found that both came from large families with poor social and economic backgrounds where there were concomitant family members who had fallen foul of the law. Both did not complete their primary school education because of repeated failures. The crimes they had committed were not violent crimes on other persons, one was gaoled for housebreaking and the other for attempted extortion.

Comparing these two who were discovered by selection of a prison environment, our other KS

and XYY patients were not uncovered because of crimes. Hence these two are a minority. In our newborn screening investigations, there was only one 47 XXY KS baby found in 3,000 male infants and no 47 XYY seen in 500 male newborns. It can therefore be concluded that there was no significant increased incidence of 47 XXY or 47 XYY among the maximum security male prisoners in Changi Prison compared to the normal incidence of males with these sex chromosomes abnormalities in Singapore. Therefore, our experience here in Singapore, demonstrates that such cases are more likely to be diagnosed because of mental retardation or infertility rather than criminality.

In spite of this difference in our findings compared to the findings in Great Britain, we cannot deny that the figures from Great Britain do point out to a higher prevalence of XYY and XXY males among psychopathic criminals, even though there is a selection bias. My view is that criminality is mostly indulged in by those with a relatively low intelligence and poor moral upbringing during the early formative years of a person's life. Of course, there are exceptions, but, by and large, those with lower intelligence and also those with a poor socio-economic environment with a poor moral educative upbringing during childhood, are more likely to commit acts against the law and against society. Because of their disadvantaged socio-economic status, they are more likely to offset this by theft, etc. and they are also more likely to commit acts of violence in trying to improve their life-style, probably as a justification for seeking "vengeance" against society, which they blame for their poor circumstances. However, if their intelligence is also low, they will be unable to weigh the pros and cons for taking part in such criminal acts, and of course, because of such limited IQ, they would be more easily caught. It is true that XYY and XXY are generally mentally disadvantaged, but I would venture the view that the majority of those in Changi Prison are also mentally disadvantaged, though due to reasons other than possession of abnormal sex chromosomes. My conclusion, therefore, is that persons with XYY and XXY sex chromosome constitution have a lower IQ than normal as a whole, and if the home circumstances are such as to disallow them to reach their maximum genetic potential during childhood, then they are more likely to take to crime. Individuals WITHOUT XYY and XXY with low IQ and poor upbringing will also stand a greater chance of taking the same path to crime.

#### PREVENTIVE MEASURES IN XYY AND XXY?

Most cases of XYY and XXY occur as a result of accidental non-disjunction during cell division either of the gametes during meiosis or of the

zygote during mitosis. Translocation cases are very rare. Hence, familial cases are uncommon, and I have not seen a single familial case. Therefore, there is no indication whatsoever for prenatal detection of the status of a foetus by amniocentesis, after the birth of an affected child.

However, it may be suggested that routine examination of all newborns by buccal smear and Y fluorescence will detect affected newborns since it is impossible to diagnose these cases before puberty on a clinical basis. Such affected newborns can then be channelled in terms of upbringing so that:—

1. Their maximal genetic potential for development of intelligence will thus be attained.
2. Childhood upbringing will stress moral issues of right and wrong. So that the child learns early in life, those issues which XYY and XXY MAY find difficulty in dealing with.
3. More attention may be paid to their careers, which would be more consistent with their abilities and psychological make-up.

Such a suggestion of identifying affected newborns is not far-fetched. After all, newborn screening is carried out for many diseases and potential diseases, a case in point being the highly successful G6PD rapid screening method applied to Singapore newborns by Wong (1968) in the prevention of brain damage as a result of severe jaundice. However, with regard to XXY and XYY, there are many parents who object to the categorisation of their babies if they should be XXY or XYY, because they think it stigmatises them. This is not true but some parents would prefer not to know about it, and bring up these children as if they would be perfectly normal. Yet without special knowledge and methods of upbringing, these children may not achieve their full potential. In fact, recently, when some human geneticists wanted to screen newborns in a hospital in Boston for XXY and XYY, and then follow them up to study intellectual performance and behavioural characteristics, there were strong protests from laymen, and the project was abandoned. This is an example of one of those potentially effective preventive health measures whose time has not "arrived" for full acceptance. Good examples include smoking and drinking, but therapeutic abortions seem to have "arrived" in many countries. Therefore, screening for XXY and XYY should still be considered, and may be carried out when people are ready for it.

### TURNERS SYNDROME

Turner's Syndrome is a sex chromosomal abnormality where there is absence at least of the short

arms of the X-sex chromosome. In the commonest variety, one whole X-sex chromosome is absent, so that the individual has 45 chromosomes instead of 46, that is, she is  $45 \times 0$ . The individual is a "she" because the outward appearance is that of a female, though at puberty, the female secondary sex characters are poorly developed, e.g. female breasts are small, pubic and armpit hair are sparse, and she does not menstruate, i.e. there is primary amenorrhoea. Because of the absence of one X-sex chromosome, she has no ovaries, these being replaced by fibrous structures. In addition to these deficient sex characters, there are also certain other structural abnormalities which allow one to diagnose Turner's Syndrome even before puberty. This is so because there are many genes carried by the X-sex chromosome, and when these are absent, the patient becomes short and stunted, has a webbed neck, a wide carrying angle at the elbow, a rather flat shield chest, rather typical facies, and abnormal length of fingers and toes. Renal tract anomalies are not uncommon.

How does one diagnose Turner's Syndrome at birth? Stature cannot be used as a criterion as stunting becomes evident only with time. However, webbing of the neck is seen, with a low hair-line. Often there is an abnormality of the lymphatics, so that there is oedema of the dorsum of the feet, often extending to the legs and arms. Clinical suspicions of this nature are easily confirmed by study of the buccal epithelium when Barr bodies are missing though the phenotypic appearance is that of a female, and chromosome culture will finally categorise them completely.

We have seen altogether 114 Turner's Syndrome or their variants, and they are as follows:-

TURNER AND VARIANTS	NO. PATIENTS
CLASSICAL $45 \times 0$ TURNERS	45
MOSAICS OF XO/XX	33
ISOCHROMOSOME OF LONG ARM OF X	9
MIXED GONADAL DYSGENESIS XO/XY	8
MOSAICS OF XO/XXX	5
VARIOUS OTHER VARIANTS	14
TOTAL	114

Many of these beyond puberty are married, and were referred because of infertility. In fact, many are happily married and fulfill the role of a wife very well. Their outlook and life are entirely female. Their intelligence is normal or only slightly below average, and some have passed the PSLE examination.

## TRUE HERMAPHRODITES

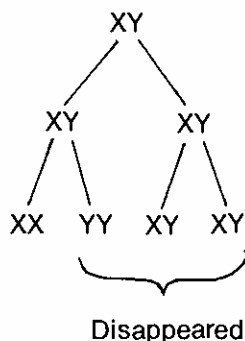
These individuals have both ovarian and testicular tissue, and as such the external genitalia are ambiguous, i.e. not entirely male or entirely female. This is in contrast to KS and multiple Y's who are male in appearance, and Turner's Syndrome who are female in appearance, so that at birth, there has been no question as to what sex to bring these latter babies up. However, in true hermaphrodites, because of features of both male and female external genital characteristics, often there is failure in sex assignment from birth. In the hermaphrodites, there are also representatives of both male and female internal genitalia, i.e. Fallopian tubes on the side of ovarian tissue, and vas deferens on the side of testicular tissue.

We have encountered 9 proved cases of true hermaphrodites (TH) after laparotomy, and it is interesting to observe that 5 cases had no Y chromosome detected at all:—

46 XX	5 cases
46 XX/47 XXY	2 cases
45 XO/46 XX/46 XY	2 cases

For both testicular and ovarian tissue to be formed in the same individual, there must be XX and Y at some stage of foetal development because the former produces ovarian tissue and the latter testicular tissue. How can one therefore explain the high incidence of 46 XX in TH? In fact, in all series of TH besides our own, the majority have been 46 XX. Several possibilities may be considered:—

1. The Y chromosome may be absent from the Somatic cells but present in the gonads, i.e. the testis. However, other workers have cultured cells from the testes in TH patients with leucocyte 46 XX, and found that the gonadal chromosome constitution was still 46 XX.
2. The Y chromosome may have been present very early in foetal life, determined the testis, and then disappeared, e.g.



This is very hard to prove or disprove.

3. The testis-determining gene in the Y chromosome may have been translocated on to another chromosome and being extremely small would not be recognised in the usual chromosome culture. However, the Y chromosome fluoresces brightly when treated with quinacrine (Y — fluorescence). No Y-fluorescence has been detected in our patients with 46 XX. Now we know that the testis-producing gene is on the short arm of the Y chromosome while the fluorescent part is on the long arms of the Y chromosome. Hence, absence of Y fluorescence does not exclude the presence of the testis-producing gene.

Recently, it has been shown that males produce a histocompatibility antigen from a gene in the Y chromosome, called H-Y antigen. H-Y antiserum (with H-Y antibodies) can be produced in mice by inoculating female mice with spleen cells from male mice. This antiserum can be used for detecting the presence of H-Y antigen in human males. Saenger et al (1976) investigated a 2 year-old child with 46 XX TH, and both gonads had also 46 XX chromosome constitution. In spite of this, the H-Y antigen was positive. Therefore, it seems that in all TH, the gene for the production of testis must be present in TH with 46 XX.

The management of TH is by surgery to remove the gonad "opposite" to the sex of rearing, and making the external genitalia conform to those of the sex role that had been assigned from birth.

## SEX ASSIGNATION

In all patients with ambiguous external genitalia, i.e. external genitalia not conforming fully with the male or female sex (intersexes), it is imperative that full investigations be carried out as an infant, and the decision made as to the sex of rearing before the age of 2 years. The sex assignment will depend on the results of the investigation so as to channel the child towards the sex in which he or she will be as normal as possible when he or she grows up. This is important because the psychologic and social sex of a person is almost totally determined by the environment in early life. A normal male baby brought up as a girl will think and act as a girl when puberty is reached though he has all the physical apparatus of a male, and vice versa.

I must stress that intersexes properly investigated and channelled towards the correct sex of rearing, have never demonstrated problems of transexualism after puberty. The transexuals, who make newspaper headlines, are NOT intersexes but normal physical male and female individuals who yearn for the role of the opposite sex because

of a disturbance of the mind, i.e. they are psychological and psychiatric problems and not physical problems.

## CONCLUSIONS

The majority of foetuses with human chromosomal abnormalities are not born alive, but, unfortunately, there are still a sizeable number who, in spite of these chromosomal aberrations, are born alive, and go through life with some form of handicap or other, some very severe, like Down's Anomaly, and others less severe, like TH. In those instances where culture of foetal cells is feasible, like in inherited Down's Anomaly, therapeutic abortion can be offered. In the others, diagnosis at birth by screening, may lead to optimal channelling of upbringing attitudes so as to realise the fullest genetic potential. Such newborn screening for chromosome abnormalities impinges on social ethics, and the majority are still against it. In the event, those who are diagnosed late because of referral as a result of the handicaps must be given all assistance, so that they may find a suitable niche in the world for themselves.

## REFERENCES

1. Alberman, E D and Creasy, M R: Frequency of chromosome abnormalities in miscarriages and perinatal deaths. *J. Med Genet* 14: 313, 1977
2. Borgaoukar, D S and Shah, S A: The XYY chromosome male or Syndrome. *Prog Med Genet Vol X*. Ed Steinberg and Bearn, Grune and Stratton, New York, 1974.
3. Jacobs, P A, Brunton, M, Melville, M M, Brittain, R P and McClelland, W F: Aggressive behaviour, mental subnormality and the XYY male. *Nature*, 208: 1351, 1965.
4. Nielsen, J: The XYY Syndrome in a mental hospital. Genetically determined criminality. *Brit J Criminal* 8: 186, 1968.
5. Penrose, L S and Smith, G F: *Down's Anomaly*, J and A Churchill, London, 1966.
6. Price, W H and Whatmore, P B: Criminal behaviour and the XYY male. *Nature*, 213: 815, 1967.
7. Ratcliffe, S G, Stewart, A L, Melville, M M, Jacobs, P A and Keay, A: Chromosome Studies on 3500 newborn male infants. *Lancet*, 1: 121, 1970.
8. Saenger, P, Levine, L S, Wachtal, S S, Korth-Schotz, S, Doberne, Y, Koo, G C, Lavengood, R W, German, J L and New, M I : Presence of H-Y antigen and testes in 46 XX true hermaphroditism, evidence for Y-chromosomal function. *J Clin Endocrinol Metab* 43, 1234, 1976.
9. Wong, H B: Singapore Kernicterus: A review and the present position. *Mother and Child*, 7: 8, 1968.
10. Wong, H B and Chua, T S: Incidence of sex chromatin abnormalities in newborns in Singapore. Unpublished data, 1970.
11. Wong, H B, Chua, T S and Singh, N: Sex chromosome abnormalities and crime. *Mod Med Asia* 14: 11, 1978.