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Human Population Cytogenetics: Dilemmas and Problems

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In 1961 L. C. Dunn, in his presidential address to this Society, entitled "Cross-currents in the History of Human Genetics," reviewed the history of human genetics and its interaction with the eugenic movements. Much of what he said then is highly relevant to the situation in which we find ourselves today. Dunn was speaking at a time when human genetics and, in fact, all branches of genetics were at the beginning of a sudden upsurge of interest, the beginning of an era in which the rate of acquisition of new knowledge far outstripped the ability to assimilate it. In his opening remarks, Dunn [1] commented:

> There is, I believe, general agreement that interest and activity in human genetics has today reached a peak never before attained. The periodical literature of the last ten years and the reports of the increasingly frequent symposia and conferences devoted to genetic problems in man provide convincing evidence of this. It is also clear that interest in these problems is likely to increase greatly in the next years so that what we may be witnessing now is only the beginning of a kind of renaissance in which genetics in general stands a chance of being greatly enriched by research on man. [1]

The next 15 years were to see unprecedented developments in all fields of human genetics. In cytogenetics we saw the development of chromosome banding allowing identification of each human chromosome pair and, as a result, much information about karyotype-phenotype correlations, and the clinical significance of chromosome abnormalities. We now have a reliable body of data indicating that about one in 200 newborns has a major chromosome abnormality. At the other end of the scale, one autosomal linkage group was known in 1961; now there is one group assigned to each autosome and one to the X, and several remain unassigned [2]. The following is a discussion of a development in the field of human population cytogenetics which is currently causing much concern and controversy. This is the question of newborn chromosome screening, in particular the identification of the XYY karyotype.

In the past few years genetic screening programs of various sorts have developed in many areas, some under legislative fiat, some voluntary, and some initially for research purposes. These have raised numerous social and ethical problems relat-

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ing to informed consent, distribution of the information obtained, confidentiality, reliability and so on. There have been many conferences on ethical and social issues raised by genetic research and genetic screening. The National Academy of Sciences Committee on Genetic Screening has just presented a comprehensive report on genetic screening programs and the social and other related problems raised by such programs [3]. A committee within the American Association for the Advancement of Science reported on scientific freedom and responsibility. The ethics commission has recently suggested guidelines for research on human fetuses. In addition, numerous conferences, symposia, and workshops on genetics and related social and ethical problems have been held during the last year. In our own Society we have a Social Issues Committee relating to human genetics thus demonstrating our own interest in and concern for these problems. Rarely does a human genetics meeting take place today without some discussion of these problems. These events reveal the existence of real concern in all sectors of society that research and other programs involving human subjects should be properly designed, scientifically valid, and take due consideration of the rights and dignity of the subjects being investigated. The dilemma we find ourselves in was stated clearly by Dunn in 1961:

> Such considerations remind us of the dilemma which scientists face in their desire both to advance in sound knowledge and to make it serve its essential social function. In the case of human genetics, I do not believe that the problems posed by the cohabitation of these two purposes are to be settled by divorce, as Bateson suggested. The problems posed by the continuing accounts of diseases and defects are real and they must be faced both as biological and social problems. Both sets of interests must be free to develop, and better together than separately for this is the condition under which common criteria for criticism and rigorous judgments, so badly needed in all fields affected by potential social applications may be evolved. [1]

During the past two years considerable discussion has developed over newborn chromosome screening programs, in particular, identification of the males with 47,XYY chromosomes at birth and their subsequent follow-up. This has been said, by Beckwith and King [4], to be poor science, socially harmful to the families, ideologically dangerous, and ethically and morally reprehensible. In this paper, I shall try to put this whole controversy into perspective.

Genetic screening programs have been defined recently as being of four types [3]: (1) screening for medical intervention; (2) screening to provide reproductive information; (3) screening for enumeration, monitoring, and surveillance; and (4) screening for research. Newborn screening falls essentially into the latter three categories. Most of the children requiring immediate medical intervention are those with unbalanced chromosome complements, who *should be but are not always* detected in the course of normal neonatal practice as having congenital malformations or other abnormalities. These include the trisomies, the 45,X females, and those with an unbalanced chromosome rearrangement. Screening, either

by use of the X- and Y-chromatin test or chromosome analysis, will allow the early detection of children with sex chromosome anomalies (47,XXY, 47,XXX, and 47,XYY). The question which must be answered is whether such tests in the neonatal period serve a valid health related purpose (i.e., Is there a valid health reason for detecting these subjects at birth rather than later in life or not at all?).

It may well be that data will shortly be available indicating an increased risk of nondisjunction in such families and suggesting that future pregnancies should be monitored by amniocentesis. In the case of the XXY male, research may indicate clear advantages in some or all instances of ameliorative treatment before puberty with endocrine or other therapy [5]. In some instances it may be important to know early of a son's future sterility, thus allowing further attempts to produce male offspring, something which may be of great importance in some families and societies. Most individuals with balanced chromosome rearrangements are phenotypically normal; most such rearrangements are familial. Families in which rearrangements are segregating may be at an increased risk of spontaneous abortion, or more serious, of having children with multiple congenital malformations due to an unbalanced chromosome complement. Such fetuses can now be detected by amniocentesis. Is it then important to detect such families early, so that they may be offered appropriate genetic counseling and any future pregnancies monitored by amniocentesis? I mention these points to show that there may be other valid reasons for newborn chromosome screening, apart from the detection of XYY males, a point which in all the discussions sometimes seems to be missed.

It has been 10 years since Jacobs et al. [6] gave the first significant reports of XYY males and drew attention to the possible association of this karyotype with certain types of deviant behavior. Since then this particular karyotype has received more unfortunate publicity, more speculation and has led to more controversy than any other single discovery in human cytogenetics. The Y chromosome has been termed the "criminal chromosome" and the presence of an XYY karyotype has been used on two or three occasions in murder trials as part of the defence plea of "diminished responsibility." This unfortunate and unscientific use of inadequate data has led to a call by a group called "Science for the People," informally headed by Beckwith and King [4, 7–11], for the stopping of all studies aimed at identifying XYY males. The major focus of this attack was the Harvard Newborn Study carried out by Stanley Walzer and Park Gerald. It should be stressed that the Harvard study was approved by Harvard's standing committee on medical research, by the Human Studies Committee of the faculty, by an overwhelming vote of the whole medical faculty as well as by a National Institutes of Health Peer Review Panel [9]. Nevertheless, due to continued external pressures and harassment of the investigators, this study has been stopped. To me, the termination of the study is of less importance than the means used to bring this about; the ignoring of normally accepted methods of review and the continued harassment of individuals and their families [10] are methods which in an earlier era might have been called "genetic McCarthyism." These finally resulted in the curtailment of most attempts to ascertain XYY males at birth.

Beckwith and King are entitled to their views as to the worth of the Harvard study:

> Not only does this study appear to us to be worthless, but there is a serious risk that it will be positively harmful to the subjects involved. The impact of the XYY studies illustrates how genetic screening, much of which has proved beneficial to people, has also provided the opening wedge for programs with much more serious eugenic implications. Isn't it time that we stopped wasting society's resources on poorly conceived and ideologically influenced studies on the genetic basis of antisocial behaviour and, instead, concentrated on changing the social and economic structure which generated most of these problems? [4]

They are not, however, entitled to force their views on others by methods which, at best, can be termed doubtful, and at worst, thoroughly unethical. This, I believe, raises issues of concern to all human geneticists and others involved in biomedical research using human subjects, a highly sensitive issue in today's society.

The major criticisms made by Beckwith and his group, Science for the People, of the Harvard, and by implication, all other newborn chromosome screening programs have been summarized recently by Hook [12]:

> 1. The sole purpose of these studies is to determine the nature and extent of alleged excess psychopathology associated with an extra Y chromosome.
>
> 2. This alleged excess psychopathology, however, is a myth based primarily on methodologically flawed studies (or if it exists involves only a trivial fraction of XYYs). The alleged excess moreover may simply result from the possibility that the XYY genotype is a marker of adverse social factors in the parent's background which resulted for some reason in this chromosomal condition.
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> 3. If parents are told that their infant has a chromosomal abnormality as they are in the Boston Study—or specifically of the presence of the XYY genotype—and are familiar with or learn of the allegedly specious evidence linking the genotype with possible behavioural consequences, the handling of the child may result in the behaviour feared.
>
> 4. There is no behavioural therapy or intervention that can be provided; those with chromosome abnormalities (or specifically the XYY genotype) detected in the study that can benefit the child, certainly none that can outweigh the consequences of telling the parent the diagnosis.
>
> 5. These studies are ideologically influenced and undermine programs which attempt to eliminate environmental inequality and improve social conditions of those who are deprived.
>
> 6. Informed consent is mandated at the Boston Institution but is essentially impossible to obtain for the study.

If these criticisms are to be examined seriously, and there is no doubt that they do raise serious concerns, then we must first look at the background to the XYY controversy and examine what is known about the effects, if any, of this karyotype.

EARLY STUDIES OF XYY MALES IN SECURITY SETTINGS

In 1965 data became available from a survey conducted in two British state hospitals for patients considered to be mentally unstable because of consistently violent or aggressive behavior. This was a sex chromatin study and among the 942 male patients examined, 21 were sex chromatin positive. Of these, one-third were found to have a 48,XXYY karyotype, a finding which differed significantly from the findings of sex chromatin surveys in other institutions and among newborn males, in which the majority of chromatin positive males were XXY [13].

As a result of these findings, Jacobs et al. [6], Price et al. [14], Price and Whatmore [15, 16], and Jacobs et al. [17] examined the chromosomes of almost all the male patients in the Scottish Maximum Security Hospital at Carstairs near Edinburgh in an attempt to ascertain whether the extra Y chromosome had any significance. They studied 315 male patients and found nine with a 47,XYY chromosome constitution, one 47,XXY, one mosaic chromosome complement, and one 48,XXYY chromosome constitution; four other patients had an abnormality of the autosomes (table 1). Of the males with two Y chromosomes, 50% were over 182 cm tall. Casey et al. [13] reported an unusually high frequency of XYY individuals in two institutions among males taller than 182 cm (12 out of 50 in a mentally subnormal group, four out of 50 in a mentally ill group, and two out of

TABLE 1

PREVALENCE OF SEX CHROMOSOME ABNORMALITIES AMONG MALES IN MAXIMUM SECURITY HOSPITALS IN THE UNITED KINGDOM

		Sex Chromosome Mosaics			Aneuploid Mosaics		
Reference	Males	47,XXY	48,XXYY	47,XYY	With YY Cell Line	Without YY Cell Line	Autosomal Abnormalities
Jacobs et al. [17]* ..	315	1 (3.2)	1 (3.2)	9 (28.6)	...	1 (3.2)	4 (12.7)
Casey et al. [18]* ...	943‡	12 (12.7)	5 (5.3)	...	2 (2.1)	2 (2.1)	...
Price et al. [19]†	611	...	1 (1.6)	13 (21.3)	1 (1.6)	...	...
Total	1,869	13 (7.0)	7 (3.7)	22 (23.8)§	3	3	4

NOTE.—Maximum security hospitals: Broadmoor, Rampton, Moss Side, Carstairs. Figures in ( ) = prevalence/1,000.

* Residents.

† New admissions.

‡ In their first paper Casey et al. [13] refer to 942 subjects studied (see text p. 111). In the paper quoted in the table, the figure is 943.

§ The rate for 47,XYY males refers only to studies of Jacobs et al. [17] and Price et al. [19]. Only chromatin positive males would have been detected by Casey et al. [18].

24 in a criminal group). Court Brown [20] reviewed our knowledge about XYY males and concluded:

> That in concentrating on males with gross antisocial conduct as currently is being done, we may be guilty of biased selection.

and further,

> There are so many unknown factors that the sort of estimates that have been made in this review have to be regarded with considerable circumspection. In the end there can be no substitute for an extensive and prolonged study of newborn children. Very adequate grounds for justifying such studies come from considering what is known at present about the overall frequency of children at birth with an abnormality detectable in mitotic cells. [20]

Thus, Court Brown recognized that extensive newborn chromosome studies were essential in order to ascertain a random sample of XYY males who might then be followed.

XYY MALES IN THE GENERAL POPULATION

Seven newborn chromosome studies in different parts of the world have now been completed comprising 39,082 newborn male infants (table 2). The incidence of male babies with an XYY chromosome constitution among newborns was just over 1/1,000 live births.

TABLE 2

MALES WITH SEX CHROMOSOME ABNORMALITIES DETECTED IN CHROMOSOME SCREENING STUDIES OF NEWBORN INFANTS

Chromosome Abnormality	No. Babies		Rate/1,000
47,XYY	36	43	1.10
47,XYY mosaics	7		
47,XXY	36	42	1.07
47,XXY mosaics	6		

NOTE.—Total males = 39,082. References: Edinburgh [21]; London (Ontario) [22]; Winnipeg [23]; Boston [24]; New Haven [25]; Moscow [26]; Aarhus [27].

In addition, three recent studies on the prevalence of the XYY karyotype among unselected older males are worth noting (table 3). Noel et al. [28] studied 15,386 males selected in two ways: (1) a group of 2,002 young men conscripted into the French army were selected on the basis of a height of 178 cm or greater; (2) a randomly selected group of 13,384 males were called in for a health check by the French National Health Scheme and unselected for height. They found seven XYY males in the first group and 13 in the second, a prevalence of 3.5/1,000 among males 178 cm or taller and 1/1,000 among males unselected for height. In a sample of 1,021 Danish males undergoing examination for military service, selected

TABLE 3

PREVALENCE OF 47,XYY MALES IN FOUR NON-NEWBORN MALE POPULATIONS

Reference	Total Males	47,XYY	Prevalence (Rate/1,000)	Country of Origin	Criteria for Selection
Noel et al. [28]	2,009	7	3.5	France	Conscript > 178 cm tall.
	13,397	13	1.0		Randomly selected males for health check.
Zeuthen et al. [29]	1,028	5	4.9	Denmark	Conscript > 181 cm tall.
	3,840	5	1.3		Not selected for height.
Borgaonkar and Shah [30]	1,715	...	...	U.S.A.	Maryland school boys. Unselected for height.
H. Lubs (personal communication, 1975)	2,437	3	1.2	U.S.A.	Random 7 yr sample.
Total	3,018	12	4.0		Height > 178 cms.
	21,371	21	1.0		Unselected for height.

for chromosome studies because of a stature of 181 cm or greater and a testicular volume of 12 ml or more, five had a 47,XYY chromosome constitution, a prevalence of 4.9/1,000 [29]. In addition, a further 94 males were examined cytologically and 2,725 males with a testicular volume greater than 12 ml but a height of less than 181 cm, were included in the group but not studied, thus giving a minimum overall prevalence in this group of 3,840 young males of 1.30/1,000. In the collaborative study of 7-year-old boys in six urban centers in the United States selected initially as a random sample of newborns in urban obstetric clinics (H. Lubs, personal communication, 1975), three XYY boys were detected in 2,440 males, a prevalence of 1.23/1,000. Borgaonkar [30, 31], on the other hand, found no XYY males in a group of 1,715 Maryland schoolboys.

It is now clear, therefore, that the incidence of XYY males in newborn populations approximates to 1/1,000 male births and, that so far as can be determined on the basis of the limited data available, the prevalence among older randomly selected males is similar. It would seem, however, that the prevalence among tall males is about four times that found in the unselected population.

This suggests that, as expected, there is no significant lethality of the XYY karyotype postnatally and, as early studies predicted, many of these males are significantly taller than the general population of males. To assess the significance of these findings it is necessary to consider certain background material in order to answer two questions: (1) What is the current situation about the frequency in certain special sequestered populations of males? (2) What, if any, are the special characteristics of XYY males ascertained in general population groups?

XYY MALES IN SPECIAL POPULATIONS

Data on the prevalence of males with an XYY chromosome complement in security settings has been reviewed extensively by Hook [32, 34, 35]. The types of

population being discussed fall into three classes: penal, mental, and mental-penal. The term "security setting" is used to refer to the penal and mental-penal groups.

A recent summary of this data by Jacobs [36] shows that there is a 4- to 20-fold increase in the frequency of males with a 47,XYY karyotype in security settings compared to the general newborn and unselected older male populations. The same applies to a lesser degree to the XXY males who show a 2- to 10-fold increase in security settings while the 48,XXYY males show a 40- to 100-fold increase in the mental and mental-penal groups over the general newborn incidence (table 4).

TABLE 4

COMPARISON OF PREVALENCE RATES FOR SEX CHROMOSOME ABNORMALITIES IN NEWBORN, NON-NEWBORN, AND SPECIAL POPULATIONS

Chromosome Abnormality	Population	No. Studied	No. Abnormal	Prevalence (rate/ 10,000)	Rate Increase over Newborns	References
47,XYY..	Newborn	39,082	43	10	...	[21–27]
	Non-newborn	21,371	21	10	...	[28–30] (H. Lubs, personal communication, 1975)
	Mental	2,243	6	27	> 2	[32]
	Penal	4,012	17	42	> 4	[32]
	Mental-Penal	3,852	80	208	> 20	[32]
47,XXY..	Newborn	84,769	99	12	...	[21–27, 32, 33]
	Mental	2,243	10	44	> 4	[32]
	Penal	4,012	11	27	> 2	[32]
	Mental-Penal	3,852	46	119	10	[32]
48,XXYY	Newborn	84,768	2	0.2	...	[21–27, 32, 33]
	Mental	2,243	2	9	> 40	[32]
	Penal	4,012	0	...	...	[32]
	Mental-Penal	3,852	9	23	> 100	[32]

Among older males in the general population selected for height, 40/10,000 have an XYY chromosome complement. There is thus a possibility that the increased prevalence in security settings is simply in part due to an increase in frequency of tall males in these groups. Hook and Kim [37] and Hook [32] have shown, however, that there is no excess of tall XY males in these groups which might have been expected if tallness per se were a factor leading to incarceration; whereas there is a significant excess of tall XYY males in security settings. A further suggestion made to account for the findings in security settings was that the length of stay of the XYY males was longer than XY males. Recently, Price et al. [19] have studied 611 new admissions to the four maximum security hospitals in Britain and found 15 males with two Y chromosomes (13 XYY's, 1 XYY/XXYY, and 1 XXYY), a prevalence of 250/10,000 or identical to that found in the resident population. This does not support the contention that the higher frequency

among these groups is simply a function of length of stay. A further statement was made about the XYY male by Miller [38]:

> The behavioural problems that have been associated with the XYY karyotype are conclusively correlated with socioeconomic status. Rather than search for genetic bases for social problems we might better attack the conditions and the social and economic structure responsible for behavioural problems.

No reference is given for this remarkable and authoritative statement, nor is any data given in support, and so far as I have been able to ascertain, there is no evidence for this assertion. Ratcliffe and Evans [39] have analyzed the social class distribution of the Edinburgh XYY males and have concluded:

> Thus, neither in the newborn nor in the small proportion of the XYY's found in the maximum security hospitals is there any evidence for a preponderance of lower socio-economic classes. There is, nevertheless, a 20-fold increase (0.1% to 2.0%) in the frequency of XYY's from the newborn population to patients in maximum security hospitals.

In this connection also, Hook [34] analyzed the racial differentials in the prevalence rates of XXY and XYY males in security settings in the United States. He found that for both karyotypes white males in such settings were about three times more likely to be affected than blacks.

We must conclude from this data that: (1) there is an increased prevalence of males with XYY and XXYY and to a lesser extent XXY karyotypes to be found in security settings compared to the incidence in the newborn or general male population; (2) the height distribution of the XYY and XXYY male is significantly skewed to tallness when compared to XY males; (3) increased height does not account for the increased prevalence of XYY males in security settings; (4) XYY males in security settings do not stay longer in such settings than XY males; and (5) there is no excess of males from the lower socioeconomic classes among males with an XYY karyotype.

CHARACTERISTICS OF XYY MALES IN THE GENERAL POPULATION

The second question to be answered was, Are there special characteristics of the XYY males ascertained in the general population groups which might account in part or in whole for the findings in these security settings?

Noel et al. [28] carried out a double blind psychological evaluation on seven XYY males and 28 controls. In addition, a further seven XYY males detected in an earlier study and selected for height were included. The nature of the psychological study included assessment of the subjects' "maturity level," "degree of emotionality," "emotiveness," and their use of "defence mechanisms." In addition, the intellectual level of the sample was also measured. The authors report differences between the XYY and the XY males and conclude:

> It seems that all the examined XYY subjects occasionally became aggressive with fits of temper, and behaved impulsively when faced with

> frustration. The control group tended to show greater tolerance in this respect. In particular, XYY individuals, with below average IQ's and immature and unstable personalities appeared to have a lower threshold for the control of aggression in frustrating or provocative situations. A most significant impression gained of the XYY subjects was their apparent inability to integrate aggression normally into their perception of reality. It would seem that, for these subjects, the aggressive drive has to be strictly controlled and can only be freely expressed in fantasy.

They further indicated that,

> Although the psychological examiners had no knowledge of the chromosomal diagnosis (nor did the subjects) they were able, through a subjective appraisal of the test results to classify all subjects correctly as XYY or normal.

A study from Denmark on nine XYY males examined for military service using a similar battery of psychological tests and using siblings as controls, but unfortunately not carried out in a double blind fashion, concluded:

> That such males differ from their siblings in several ways, they are more immature, more impulsive, and have greater contact difficulties. Psychological testing shows immaturity, passivity, unreflectiveness, emotional lability, need for social contact, insecure male identification, and weak defence mechanisms.

Thus, from these two studies, slight as they may be, it does seem reasonable to conclude that at least some XYY males in the general population do show psychological differences to their XY counterparts that may be recognizable by detailed psychological testing.

XYY MALES IN NEWBORN POPULATIONS

A relatively small number of XYY males have been ascertained in newborn screening studies. To date 13 have been followed up for varying lengths of time. Valentine et al. [40] studied four XYY infants and stated:

> None of them show any distinctive physical characteristics, though three of the four lack a C triradius in the palmar dermatoglyphics. All four are of normal stature. Three appear of normal intellect and personality. One is of borderline intelligence and by two years was exhibiting aggressive, defiant, and destructive behaviour.

In Winnipeg [41] we have followed four XYY male infants and one mosaic from 22 months to 4½ years in age without any obvious significant findings. Four out of the five were tall for their age; all showed appropriate intellectual development. In three cases there was slight evidence of shyness; in two, speech delay. One child showed some signs of aggression and impulse restraint. A. Robinson (personal communication, 1975) has followed five XYY males up to 4 years in age and found

that during the first two years development was average. Emotional development was normal except that two out of four had a high activity rating and a high level of impulsivity during their second year. XYY infants have been followed in detail in other centers, but as far as I know, the results have not yet been published. Thus, the very limited data available at present do not allow us to make any useful comment on the characteristics or lack of them in XYY infants ascertained at random in the general population. There is, however, evidence from a number of sources, including the French and Danish population studies quoted above, of early behavioral difficulties and learning disabilities at school.

To summarize the current state of our knowledge about the XYY male, we know that about 1/1,000 males in the general population have an XYY karyotype whereas in security settings the frequency is about 20/1,000. The original observation made by Jacobs et al. [6] of an excess of XYY males in these population groups is thus amply confirmed. In addition, data are now available which indicate psychological differences between young noninstitutionalized adult XYY males when compared to XY controls. These differences indicated that XYY males were less able to control the normal male aggressive drive in frustrating or provocative situations and were more impulsive and immature than XY controls. There is also some evidence of an increased frequency of behavior problems and learning disabilities among children with this karyotype. At present, little can be said about the early childhood of XYY males; follow-up has not proceeded far enough on sufficient numbers of children to draw conclusions. Finally, it is now clear that perhaps only a small minority of XYY males spend part of their lives in security settings. There is little doubt, however, no matter which way the data is examined, that these males, or some of them, are at a greater risk than XY controls, due perhaps to adverse environmental influences interacting with the XYY genotype.

With these *facts* in mind let us look at Beckwith and King's [4] specific criticisms. First, they say that the alleged psychopathology of the XYY male is a myth. I have tried to show that this psychopathology, far from being a myth, is real and that XYY males can be identified by detailed psychological testing in the general population. Second, they say that if the parents of an XYY child are told of his karyotype, their subsequent handling of the child will be different, leading perhaps to the very behavioral problems which are feared. I believe, and I think that others involved with parents will agree, that this depends on how they are told, when they are told, what they are told, and what help is offered to them. In our own studies [41] the parents have normally been told of a chromosome abnormality (but unless they ask, not specifically of an extra Y chromosome) when the child is between 2- and 4-years-old, after a full pediatric and developmental assessment. In this way they could, at the same time, be assured of their child's normal development for his age. Furthermore, by that time they have had a period of several years without the knowledge of the XYY karyotype in which to see their son growing and developing normally. The parental reactions to this approach have usually been good. They are offered continued help at this time and

sign an informed consent to a continued follow-up in this study. This has, in all instances, been accepted.

This approach may need modification, however, if it is shown that there is an increased risk of aneuploidy of all sorts after one aneuploid child has been born, thus making the birth of a child with a sex chromosome anomaly an indication for amniocentesis in subsequent pregnancies. If this happens, then telling the parents when their child is 2- to 4-years-old is obviously too late, in which case it becomes even more important that we have some hard data about the behavioral effects of these karyotypes so that parents can be properly counseled and advised.

The third criticism is that there is no behavior therapy or intervention that can be provided for those with chromosome abnormalities, particularly the XYY. This may or may not be true. It is possible, indeed even probable, that by means of a regular follow-up, potential problems will be identified before they reach serious proportions and before the average parent would normally have become sufficiently worried to seek help. If so, considerable help might be provided in the form of suggestions for environmental modification, advice on handling, et cetera. This would not be possible without a prior knowledge of the karyotype, until the problem became significant enough for the parents to seek help in the usual way.

As for the other chromosome abnormalities, detection early in life will allow reproductive and genetic counseling to be provided to the families including the monitoring of future pregnancies by amniocentesis as appropriate. In addition, for the XXY male, endocrine therapy earlier than puberty when the condition would normally have been detected, may prove to be advantageous.

Finally, Beckwith and King [4] state that newborn chromosome screening studies are ideologically influenced and detract from social programs. This is not scientific criticism but reflects a particular ideological and social viewpoint. It is not even a valid criticism as there is no evidence whatsoever of any abnormal distribution of socioeconomic status among individuals with chromosome abnormalities. While no one would disagree that additional funds are needed for social programs, there is no reason to suppose that if these genetic studies were to be discontinued, money saved would automatically be spent in the type of program proposed.

The most difficult problem of all in relation to these and other studies using human subjects is that of "informed consent." This has been discussed on numerous occasions. A good description of what is meant by informed consent is difficult to come by. The following is a recent one by DeBakey and DeBakey [42]:

> "Informed consent" means that the researcher has explained honestly, objectively, and as fully as practicable the procedure proposed, its experimental nature, and its potential risks and benefits to the patient. "Informed consent" means avoiding coercion, duress, or other devious means of inducing the patient to submit to the procedure. In clinical experimentation, the Golden Rule remains a useful guide for the investigator. If the scientist subordinates his fervor for experimentation and his desire for recognition to the welfare of the patient, he is unlikely to commit ethical breaches.

Great care must clearly be taken to assure that proper informed consent is obtained for all these studies, that the subjects are aware of the study and its implications and have an opportunity not to participate or to withdraw whenever they so wish, and that they are aware of what information will be given to them and their physician. Parents also should be aware of all the ramifications of the study including any follow-up procedures. They should be given an opportunity to assess the study before deciding whether they wish to participate.

It has, on many occasions, been pointed out that true informed consent is difficult if not sometimes impossible to obtain, and this is accepted by most reasonable people involved in the biomedical sciences. In the Harvard study informed consent procedures satisfied the faculty, the faculty ethics committee, the committee on medical research, and the Department of Health, Education and Welfare guidelines but did not satisfy Beckwith and his local supporters. It seems likely that in truth, no procedures however rigorous would have been acceptable to this group, unless they brought the study to a close because they were impossible to fulfill. This is not to say that I am in any way belittling the importance of informed consent. I believe that in the current social and ethical climate it is most important that we do our best in any investigation involving human subjects to obtain a truly informed consent so that the rights and dignity of our subjects and our patients are protected.

The final question we are left with is my first: Is there enough evidence of a genetic effect of the presence of two Y chromosomes which, on interaction with certain unspecified environmental situations on some occasions, leads to deviant behavior? If so, should we continue to try and identify such genetic and environmental components in the hope of being able to offer help to those individuals with this genotype and their parents? I have tried to show that there is some evidence that the XYY genotype does show a psychopathology, but at present this needs further identification and characterization. For these reasons, studies such as that at Harvard and elsewhere should continue provided there is adequate protection for the patients concerned and the informed consent procedures are adequate.

There are other reasons why it is important that we know more about the effects, not only of the XYY, but also the XXX and XXY. There is no doubt, for instance, that these karyotypes are going to be detected with increasing frequency during prenatal diagnostic procedures. What are we to do with this information? We must, I submit, inform the parents, or would Beckwith and his group advocate the withholding of this information? I believe they should tell us how they would handle this dilemma. If the parents are to be told, as I feel they must be, how should they be counseled? For this purpose, we need data which can only be obtained by random ascertainment of large numbers of individuals at various ages with these karyotypes and by following them to see how they develop, what their problems are, and what can be done about these problems. Once we have this knowledge, intervention may indeed be possible to benefit the children with these genotypes and their families. The nihilist approach advocated by Beckwith and King [4] is not helpful and will undoubtedly hinder the solution of these complex behavioral problems.

In conclusion, then, it seems that there is no scientific basis for the major criticisms made by Beckwith and his group, Science for the People, and that these criticisms are not supported by available scientific data. This raises the question of Beckwith's scientific ability and objectivity outside his own field and his ability to mount valid criticisms of work in human and behavioral genetics, fields in which, so far as I am aware, he has no experience. The whole case put forward by this group is based on a misplaced ideological approach to scientific investigation. If this prevails, the truth about the genotype-environmental interactions which must lie at the root of the problems faced by men with XYY, XXY, and XXYY karyotypes will remain hidden for decades to come, a disservice to them and to society, which I believe must not happen.

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The Bar Harbor Course in Medical Genetics

The Short Course in Medical Genetics, given since 1960 by the staffs of the Jackson Laboratory and Johns Hopkins University, will be held at Bar Harbor, Maine, August 2–13, 1976. Drs. Victor A. McKusick and Thomas H. Roderick are codirectors of the course. Application for admission to the course should be made before May 1, 1976 to Dr. Victor A. McKusick, Johns Hopkins Hospital, Baltimore, Maryland 21205.