Human cytogenetics / John L. Hamerton.

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Hamerton, John L.

Publication/Creation

New York ; London : Academic Press, 1971.

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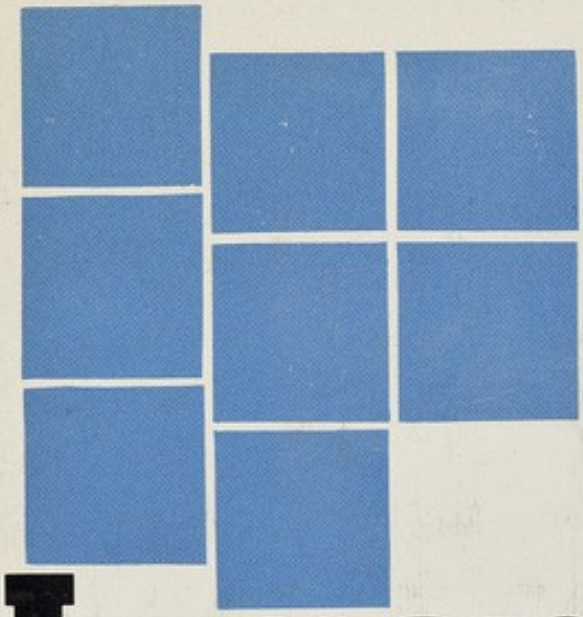
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Human Cytogenetics

JOHN L. HAMERTON

CLINICAL CYTOGENETICS

Volume II

GENETIC ORGANIZATION

Edited by Ernst W. Caspari and Arnold W. Ravin

VOLUME I

1969, 525 pp., 103 figures and illustrations, $29.00/Subscription price $24.65*

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*SUBSCRIPTION PRICES FOR INDIVIDUAL VOLUMES VALID ONLY ON ORDERS FOR THE COMPLETE SET RECEIVED BEFORE PUBLICATION OF THE LAST VOLUME.

Academic Press
NEW YORK AND LONDON
111 FIFTH AVENUE, NEW YORK 10003
BERKELEY SQUARE HOUSE, LONDON, W1X 6BA

ISBN 0–12–321002–X

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These volumes provide – for the first time in English – complete coverage of human cytogenetics in a manner understandable to both geneticists and physicians. They feature a new and unified hypothesis on sex determination and the origin of intersexuality in man and mammals. The work also includes a detailed analysis of the historical and comparative aspects of human cytogenetics – an examination which provides unique information for use in interpreting observations of human somatic chromosomes.

Volume II discusses medical cytogenetics and covers sex chromosome abnormalities, abnormalities of sexual differentiation, sex determination in man and mammals, and autosomal abnormalities of man and their clinical aspects. It also gives an overview of chromosome abnormalities in relation to pregnancy wastage and neoplasia. The bibliography contains over 2000 references to research in the past decade.

Volume I deals with general human cytogenetics in its historical context. It assumes no previous knowledge of cytogenetics and includes chapters on techniques, mitosis and meiosis, the human somatic chromosomes, the structure and significance of sex chromatin, and the origin of numerical and structural chromosome abnormalities.

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CLINICAL CYTOGENETICS

Volume II

HUMAN CYTOGENETICS

CLINICAL CYTOGENETICS

JOHN L. HAMERTON

DEPARTMENT OF MEDICAL GENETICS
CHILDREN'S HOSPITAL OF WINNIPEG
WINNIPEG, MANITOBA, CANADA

Volume II

1971

ACADEMIC PRESS New York and London

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ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
Berkeley Square House, London W1X 6BA

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FOREWORD

Those who were involved in the beginning of the modern phase of human cytogenetics never fail to be surprised and delighted by the quantity and variety of discoveries made in a field which burgeoned hardly more than a dozen years ago. New techniques and the successful adaptation of older ones, augmented by the application of principles derived from developments in genetics (especially plant and animal cytogenetics) to human investigations, have resulted in rapid advances. On the technical side, these developments were foreshadowed by the methods of Chrustschoff and Berlin and by the work of Hsu and Pomerat, but the really important advances came with the use of metaphase-blocking and chromosome-spreading devices and with the greater accessibility of experimental material. It therefore became possible to apply these practical methods to the study of promising "clinical" areas which had heretofore been examined by "inspired guess," "prescience," or by "beckoning indicators"—genetic, cytological, clinical, or epidemiological. Later, simplication of the techniques permitted the extension of cytogentic work to human populations and here, especially, we are dealing with work in progress, as we are where the study of human chromosomes is helping linkage and mapping. It is here that we are particularly concerned with the difficult problem of chromosome identification.

This work, in two volumes, is an accumulation of data on subjects as diverse as abnormal sex and soma development, sex determination and mental subnormality, dermatoglyphics and stature, gene and chromosome action, and chromosome behavior—both normal and abnormal, which only yesterday were practically uncharged territories of human genetics and which only now have reached a stage where synthesis and generalization begin to be possible. Dr. Hamerton has undertaken the heavy and difficult travail of bringing together this information in one source. He

has adopted the symbolic designation of the human karyotype and shorthand notation devised by the Chicago Conference. He has been able to draw heavily on the results recorded over the years from clinical and survey cytological studies performed in the Pædiatric Research Unit at Guy's Hospital. When faced with clinical descriptions and with the problems and difficulties of clinical terminology and classification, Dr. Hamerton has, in my opinion, succeeded in presenting a balanced view. Possibly not every clinical worker will agree with every statement made in this work, but the author has given references to a sufficient number of original works and reviews to allow the reader to make up his own mind on controversial issues. At the same time he has set out to provide a good deal of the fundamental theoretical and practical considerations on which the more applied aspects of human cytogenetics, with its host of clinical implications, must be based if the subject is not to be a sterile listing of deviant events.

This book has been carefully planned and well written. I am confident that it will prove useful not only to the student of human genetics but also to those clinicians whose work brings them in close contact with, and who require an explanation of, cytogentic principles and facts, and who need a guide to the original works on human cytogenetics.

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PREFACE

The rapid development of human cytogenetics during the past thirteen years and the discovery of numerous human cytogenetic abnormalities have opened up new aspects of both human genetics and pathology. As with most rapidly developing subjects, especially those bearing on human medicine, an extensive literature and a new terminology have developed.

The discovery of the sex chromatin two decades ago and the correct human chromosome number a few years later was rapidly followed by the discovery of the first human chromosome abnormalities in the late 1950's. These discoveries were followed by a worldwide outburst of research on human chromosomes. The result has been the setting up of numerous units and groups and an unprecedented collaboration between the geneticist and the cytogeneticist, on the one hand, and the clinician and the pathologist, on the other. Inevitably, this has resulted in many problems of communication among investigators from diverse backgrounds brought together as the result of their common interest in human chromosomes.

Several attempts have been made to improve communication. Conferences have been held, papers read, and articles written, but still the gap exists, and it is my hope that this two-volume treatise will in some measure provide the basic understanding of this new science which is necessary before a meaningful communication among the various disciplines can be established.

The intention of these volumes is to present the field of human cytogenetics in such a way as to be of interest not only to the geneticist and cytogeneticist but also to clinicians, pathologists, and medical students. The subject is presented in its historical context and examples are drawn and comparisons made not only within the human species but also between the human and other members of the animal and plant kingdoms. In

this way it is hoped that some of the problems of chromosome behavior which are obscure when considered in relation to man alone will become that much clearer.

This work, which was started in 1962 as a short monograph reflecting the knowledge available at that time has developed into a full synthesis of human cytogenetics based on the much wider knowledge available today. The first volume deals with the general principles of cytogenetics in relation to man, and aims to present the theoretical background necessary for a deeper understanding of the subject. It is hoped that it will serve as an introduction to the subject which will be of use to an investigator entering the field for the first time. The second volume deals with the clinical cytogenetics of man. The first three chapters consider the sex chromosomes and their abnormalities and the abnormalities of sexual development and differentiation. The fourth chapter considers some of the facts derived from a study of abnormal sexual development and differentiation, and, drawing on this data, presents a hypothesis on the normal mechanism of sex determination in mammals which has been developed over the past few years. The next four chapters deal with the major autosomal abnormalities found in human populations. The last two chapters consider chromosome abnormalities in relation to human pregnancy wastage and chromosome changes in neoplasia. The appendices to Volume I give some basic technical schedules which may be of some help to the novice investigator. The techniques are mainly those which have been tried over the past nine years and found useful in the Paediatric Research Unit, Guy's Hospital Medical School, London. Other appendices give, in full, the reports of the Denver, London, and Chicago meetings which are essential if a true historical perspective is to be obtained.

No attempt has been made to obtain a completely exhaustive survey of the literature and, despite a bibliography approaching 2000 references, many have been omitted, some from choice and some because I was unable to read or obtain them. My approach has been critical, and I have endeavored to provide not only a review of data but also critical comment where I felt this desirable.

I would like to express my appreciation and thanks to my colleagues and friends for valuable discussions during the time this treatise was in preparation. In particular, I should like to thank Dr. Georgiana Jagiello who read the entire manuscript; her critique was invaluable during the final revision. My thanks are also due to my former Chief, Professor Paul E. Polani, for his understanding and forbearance while I was engaged in the preparation of this work as well as for reading the manuscript, for many valuable discussions, and for allowing me to use certain of his un-

published data and illustrations. Many of the karyotypes and clinical photographs have come from the Paediatric Research Unit records, and I am grateful for being allowed to use them. I am extremely grateful to Dr. David Cox who expertly helped with much of the proofreading. I would also like to thank my former colleagues Dr. Rajinder Dhadial, Dr. F. Giannelli, Mrs. Ann Machin, and Dr. Angela Taylor for providing me with some illustrations and data both from their unpublished and published material. Any merit this work may have is the result of nine years of research and discussions with my many colleagues in the Paediatric Research Unit; the responsibility for any mistakes is, however, mine alone. I would also like to thank all those friends and colleagues who so kindly cooperated by allowing me to use their illustrations and for providing me with original and sometimes unpublished material. Detailed acknowledgments are included in the caption for each figure.

I would like to express my sincere appreciation to my wife, Irene, not only for her patience and forbearance while this book was in preparation, but also for her expert preparation of the bibliography and for her help with the indexing. I also thank Miss V. M. McGuire who not only helped with the preparation of Appendix I but also read Chapter 2 (Volume I).

My thanks are also due to Mrs. A. Besterman who did most of the line drawings on very short notice and to Mr. L. Kelberman who helped with the photography and the general preparation of the illustrations. I should also like to thank the following for help with the general preparation of the manuscript: Mrs. Hilary Aggett, Mrs. Wendy Foster, and Mrs. Barbara Saunders. Miss S. Burnett prepared some of the early drafts; the final manuscript was typed by Mrs. J. Colley. To all of them my sincere thanks. Finally, I should like to thank the staff of Academic Press for their help and patience throughout the production of these volumes.

During the period this treatise was in preparation, my research was supported by the Spastics Society, the Agricultural Research Council, and, latterly, the Canadian Medical Research Council.

JOHN L. HAMERTON

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HUMAN CYTOGENETICS

CLINICAL CYTOGENETICS

Volume II

Chapter 1

ABNORMAL SEX CHROMOSOME COMPLEMENTS IN THE MALE

I. Klinefelter's Syndrome and Variants

Klinefelter and his colleagues (1942) described a characteristic syndrome in nine male patients who had gynecomastia and a specific form of hypogonadism comprising small testes with hyalinized seminiferous tubules and absent spermatogenesis but with intact Leydig cells. The urinary gonadotrophins were increased to a level comparable with that found in castrates, but there was no increase in estrogen production. A normal or increased 17-ketosteroid production with either normal or subnormal development of the secondary sexual characteristics was also noted. The breast tissue showed marked hyperplasia of ducts and proliferation of interstitial connective tissue.

This syndrome is now well established in clinical practice and contributes significantly to infertility in the male. Nelson and Heller (1945) and Heller and Nelson (1945) have shown that neither gynecomastia nor eunuchoidism need necessarily be observed and that the most outstanding feature is the presence of small testes with generally hyalinized tubules (Ferguson-Smith *et al.*, 1957). The small size of the testes is generally detected first at puberty when they fail to enlarge.

Polani (1962) has stated that gynecomastia is more obvious in the more sthenic subjects but that a slender body build is commonly associated with eunuchoid bodily proportions and narrow shoulders. There is frequently poor androgenic response, lack of secondary sexual charac-

teristics, and feminine distribution of pubic hair (Fig. 1-1). Intellectual subnormality is common (Pasqualini *et al.*, 1957), and a higher incidence of this condition is found in populations of mentally subnormal males. The condition is often difficult to diagnose clinically before puberty unless routine sex chromatin or chromosome tests are carried out.

Affected individuals can be divided into two classes: those who are chromatin-positive and those who are chromatin-negative. The chromatin-positive group have been termed *true Klinefelter's syndrome*, while the chromatin-negative patients have been termed *false Klinefelter's syndrome* (Nelson, 1956). The validity of this term is, however, doubtful (Polani, 1962; Overzier, 1963a) since at the time when the syndrome was first described Klinefelter and his colleagues had no knowledge of the chromosome constitution or sex chromatin of their patients. It would therefore seem more correct to use the eponym *Klinefelter's syndrome*

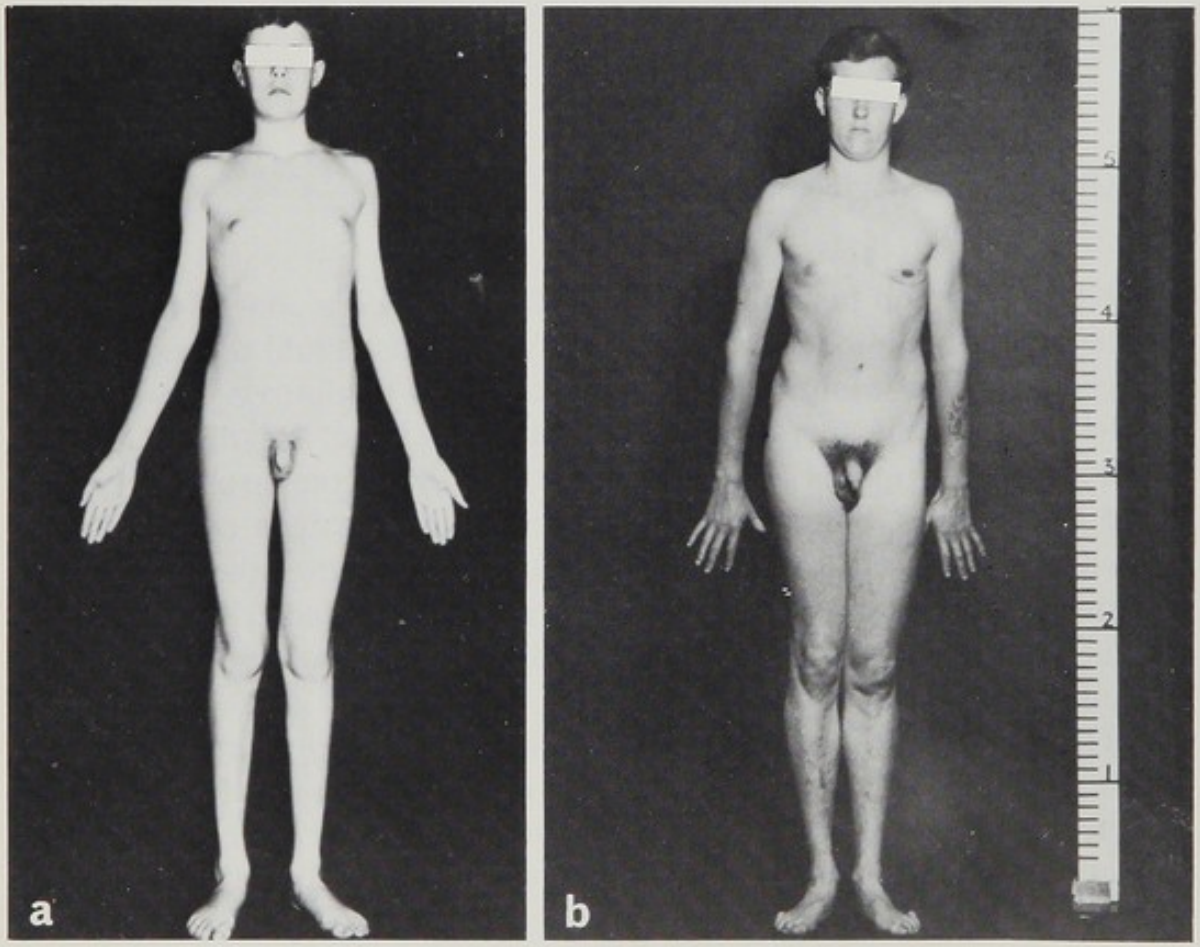


FIG. 1-1. Two patients with chromatin-positive Klinefelter's syndrome. (a) Age 15 years. Note absence of pubic hair, eunuchoid proportions, and slight breast development, but otherwise normal external genitalia. (b) Age 21 years. Feminine distribution of pubic hair, mastectomy scar under left nipple, slight gynecomastia on right. [Reproduced by permission of (a) Dr. R. J. Harrison and (b) Dr. A. W. Spence.]

and to divide it into a chromatin-positive and a chromatin-negative group (Polani, 1962); this practice will be followed here.

Numerous synonyms have been used, including testicular dysgenesis (Plunkett and Barr, 1956), chromatin-positive microorchidism or primary microorchidism (Ferguson-Smith, 1958, 1959), seminiferous tubule dysgenesis (Grumbach *et al.*, 1957), medullary gonadal dysgenesis (J. S. S. Stewart, 1959), and, finally, pseudohermaphroditism with gonadal dysgenesis (Nelson, 1956).

A. *Symptomatology and Clinical Observations*

1. Clinical Signs

a. External Genitalia After the onset of puberty the development of both the penis and scrotum is usually normal but may be delayed. In some cases, however, these organs may never reach normal size.

b. Testes The prepubertal testes are generally normal in size. Afterwards, however, they fail to enlarge and may remain small. In a series of 16 chromatin-positive cases (J. S. S. Stewart, *et al.*, 1959) a mean testis length of 1.8 cm was found compared to 5.1 cm in 16 normal fertile male controls, and 3.0 cm in 16 chromatin-negative males with Klinefelter's syndrome. In a series of fifty-three 47,XXY males the maximum length of the testes was 4.0 cm with a mean length of 1.7 cm. In a further 15 cases, the testes were referred to as small or very small, while in a few cases the testis was palpable only as a thickening in the scrotum. Rarely one or both testes failed to descend (Court Brown *et al.*, 1964a).

c. Pubic and Facial Hair The growth of pubic and facial hair is often late, and the pubic hair is usually feminine in distribution. Many males with this condition may find it unnecessary to shave or may shave less frequently than normal.

d. Gynecomastia Gynecomastia does not always develop in this condition. When it does occur, it usually develops soon after puberty, between the ages of 14 and 16 years; in some cases, however, its development may be much delayed. J. S. S. Stewart *et al.* (1959) found gynecomastia to be present in 10 out of 16 chromatin-positive cases and five out of 16 chromatin-negative cases, while only three out of the 16 controls had a very slight breast enlargement. Court Brown *et al.* (1964a) found from slight to marked gynecomastia in 25 out of 89 chromatin-positive cases, while the remainder had no breast enlargement. In the

34 chromatin-positive males with Klinefelter's syndrome studied at Guy's Hospital, J. Wilkins (1965) has found 27 subjects to have gynecomastia.

e. GROWTH AND PHYSICAL MEASUREMENTS The growth of boys with Klinefelter's syndrome is relatively normal until puberty, although by that time most are taller than the average for their age. In a series of 16 chromatin-positive males J. S. S. Stewart *et al.* (1959) found a mean height of 175 cm compared with 168.9 cm for the controls and a series of chromatin-negative patients. Comparison of the crown to pubis measurements shows that there is no significant variation between the different groups; in contrast the sole to pubis measurements did show variation; the chromatin-positive subjects generally having elongated legs and more "eunuchoid" proportions (Table 1-1). In three recently studied series the mean height is 177.4 cm while the arm span is 181.9 cm, and in two groups of subjects the crown-pubis measurement is significantly less than the publis-sole measurement (Table 1-1). Thus the increased height of these patients seems to result mainly from an abnormal length of leg rather than from the length of the trunk. Raboch (1957) studied 31 chromatin-positive cases and found the trunk to be short and the biacromial distance to be less than normal, while Overzier (1963a) agreed that long legs were more characteristic of the condition

TABLE 1–1

Body Measurements in Klinefelter's Syndrome

Reference	Chromosome constitution	Height [a] (cm)	Span [a] (cm)	Crown-pubis [a] (cm)	Pubis-sole [a] (cm)	CP/PS ratio
Court Brown *et al.*, 1964a	47,XXY	175.6 (70)	177.2 (65)	85.2 (63)	89.6 (63)	0.95
Court Brown *et al.*, 1964a	Mixoploids	170.5 (12)	173.9 (12)	84.3 (11)	85.9 (11)	0.98
Hambert, 1966	47,XXY	180.3 (30)	184.9 (30)	–	–	–
Hambert, 1966	Mixoploids	180.3 (3)	188.3 (3)	–	–	–
Zuppinger *et al.*, 1967	47,XXY	178.5 (23)	183.5 (22)	–	–	0.94
Total		177.4 (108)	181.9 (104)	85.1 (47)	88.5 (47)	

[a] Number of subjects indicated in parentheses.

than a short trunk. Tanner *et al.* (1959) have studied the skeletal age of 27 patients with Klinefelter's syndrome and found no significant difference from the average values of boys of a similar age. Overzier (1963a) suggested that these observations supported the hypothesis that an early acceleration of growth was probably the cause of the excessive length of the lower limbs rather than a later epiphyseal closure which in fact closes earlier than in girls (J. S. S. Stewart, 1959). Overzier (1963a) considered that large hands and feet were a noticeable feature but that the face was not acromegalic in appearance, and he considered these patients to be dysplastic rather than eunuchoid. Hambert (1966) studied 61 chromatin-positive males and found only three subjects with normal-sized testes while the remainder had small testes. Three patients were monorchid. Thirty-nine out of the 59 subjects who were measured had a span which exceeded their height. Thirty subjects had no gynecomastia, 18 had slight and 12 had well-developed breasts, while one had been operated on for mammary hyperplasia. Forty subjects had sparse or very scanty facial hair, 13 had a normal amount, while the remaining eight had no facial hair. Pubic hair was male in distribution in 46 subjects, female in 13, and juvenile in two.

f. Testicular Histology The histology of the testis is said to differ between the chromatin-positive and chromatin-negative groups (Ferguson-Smith *et al.*, 1957, 1960a; Segal and Nelson, 1957). The testes of chromatin-positive males contain large clumps of Leydig cells, and the seminiferous tubules are irregularly arranged either singly or in groups; these are frequently small, shrunken and hyalinized, devoid of elastic tissue, possibly completely sclerotic, and form the so-called "ghost tubules" (Fig. 1-2). The remaining tubules are small, immature, and lined exclusively with Sertoli cells. These testicular changes are mainly postpubertal, though some may be seen earlier (Ferguson-Smith *et al.*, 1960a). In an occasional pubertal subject there is evidence of spermatogenesis (Ferguson-Smith and Munro, 1958; Bunge and Bradbury, 1956a,b; Nelson, 1956; Segal and Nelson, 1957; Witschi *et al.*, 1957; Siebenmann, 1958). In chromatin-negative patients the tubules are more uniform in size and devoid of germ cells; Leydig cells may be diffusely increased or there may be no increase; and ghost tubules are less frequent, larger, and rich in elastic tissue (Polani, 1962).

B. *Incidence*

The frequency of chromatin-positive Klinefelter's syndrome in the general population has been studied by means of sex chromatin surveys



FIG. 1-2. Testicular histology in chromatin-positive Klinefelter's syndrome. Note tubular hyalinization and large clumps of Leydig cells. (Reproduced by courtesy of Professor P. E. Polani.)

of newborn males as well as in populations of mentally subnormal, defective, or psychotic subjects.

There are six comparable sex chromatin surveys of newborn males (Table 1-2), which, when combined, give an incidence of chromatin-positive males of 1.98/1000 live male births in the general newborn male population. Eighteen out of the 21 chromatin-positive males reported by Maclean *et al.* (1964) have had chromosome studies; 12 were 47,XXY, one 48,XXYY, and five 46,XY/47,XXY mixoploids. These data suggest that the frequency of XXY males is about 1.32/1000, while the remaining 0.66/1000 are either mixoploids or 48,XXYY subjects.

In mentally subnormal and defective populations the incidence of Klinefelter's syndrome is much higher (Table 1-3). In populations of mild mental defectives or educationally subnormal males about 9.0/1000 are chromatin-positive, while in the more severe cases the incidence is 7.45/1000. Of these, 6.34/1000 have only single sex chromatin masses, while 1.11/1000 have double, or, rarely, triple sex chromatin masses (Maclean *et al.*, 1962). In mental hospital populations about 6.0/1000 males are chromatin positive (Table 1-4). Maclean *et al.* (1968) have divided the 6000 patients which were included in that survey into various categories and find the highest frequency (20/1000) among the mental defectives and epileptics (Table 1-5).

TABLE 1–2

Incidence of Chromatin-Positive Males in Six Surveys of Newborn Males

Reference	Country	Number studied	Chromatin-positive		Frequency per 1000 male births
			Single masses	Double masses	
K.L. Moore, 1959	Canada	1,911	5	–	2.27
Bergemann, 1961	Switzerland	1,890	4	–	2.12
Wiesli, 1962	Switzerland	1,563	1	–	0.64
Maclean *et al.*, 1964	Scotland	10,725	18	–	1.68
Marden *et al.*, 1964	England	2,206	7	–	3.17
Taylor and Moores, 1967:					
Queen Charlotte's Hospital	England (London)	2,317	3	–	1.29
Guy's Hospital	England (London)	2,617	8	1	3.06
Total		23,229	46	1	1.98

The variation in frequency found by different authors (Tables 1-3 and 1-4) probably reflects both variable ascertainment and different methods of dealing with mental illness and retardation in different countries. Finally, about 10 to 20% of males attending infertility clinics are chromatin-positive and have Klinefelter's syndrome (Overzier, 1963a; Nowakowski *et al.*, 1958; Ferguson-Smith *et al.*, 1957; Lennox *et al.*, 1958; Jirásek and Raboch, 1957).

It has been pointed out several times that a proportion of males with Klinefelter's syndrome suffer from some mild mental or psychotic disorder (Mosier *et al.*, 1960; J. M. Anders *et al.*, 1968) and that they may have difficulty in adjusting themselves to society and are frequently convicted for petty criminality and sexual aberration (Mosier *et al.*, 1960; Court Brown, 1961; Court Brown *et al.*, 1964a). This is supported by the finding of an increased incidence of males with Klinefelter's syndrome in mental institutions and mental hospitals as well as in certain prison populations (Casey *et al.*, 1966a; Jacobs *et al.*, 1968).

In most clinical studies the frequency of the chromatin-positive subjects is considerably higher than that of the chromatin-negative. Nelson

TABLE 1–3

Incidence of Chromatin-Positive Males in Various Surveys of Mentally Subnormal Patients

Reference	Country	IQ range[a]	Total No. studied	Chromatin-positive	
				No.	per 1000
(a) Higher IQ range Special Classes or Schools					
Prader *et al.*, 1958	Switzerland	75-85	336	8	23.8
Ferguson-Smith, 1959	Scotland	45-85	663	8	12.1
De la Chapelle and Hortling, 1960	Finland	55-85	342	3	8.8
Gebala *et al.*, 1960	Poland	NK	123	2	16.3
Israelsohn and Taylor, 1961	England	37-101	1556	7	4.5
De la Chapelle, 1963	Finland	55-80	1851	6	3.2
Hambert, 1966	Sweden	NK	958	19	19.8
Total			5829	53	9.09
(b) Low IQ range Mental Deficiency Hospital or Institute					
Ferguson-Smith, 1958	Scotland	<20-75	283	3	10.60
Mosier *et al.*, 1960	U.S.	20-70	1252	10	7.99
Barr *et al.*, 1960	Canada	<20-70	1506	13	8.63
Ferguson-Smith, 1962	U.S.	20-86	916	9	9.82
Sanderson and Stewart, 1961	Scotland	NK	245	2	8.16
Gustavson and Akesson, 1961	Sweden	< 67	48	0	0.0
Breakey, 1961	N. Ireland	NK	157	1	6.37
Maclean *et al.*, 1962	Scotland	NK	2067	28	13.55
Hamerton *et al.*, 1962	England	NK	229	1	4.37
Gabr and Salam, 1963	East Germany	<50-75	83	1	12.04

TABLE 1–3 *(Continued)*

Reference	Country	IQ range[a]	Total No. studied	Chromatin-positive No.	Chromatin-positive per 1000
Davies, 1963	Great Britain	NK	550	4	7.27
Anderson *et al.*, 1964	South Africa	NK	763	5	6.55
Hambert, 1966	Sweden	NK	6265	30	4.79
Total			14,364	107	7.45

[a] Here NK stands for "not known."

(1956) found 49 chromatin-positive and only 13 chromatin-negative cases, while in the extensive series of Segal and Nelson (1957) the ratio was 54 positive to 13 negative. On the other hand, J. S. S. Stewart *et al.* (1958) found an inverted ratio of nine positive to 15 negative, and Lennox *et al.* (1958), using similar material, found an even lower proportion of 10 positive to 27 negative subjects. Schirren (1960), in a general survey of the literature, was able to find 164 positive and 69 negative cases. In a series of 133 subjects referred to the Paediatric Research Unit with sus-

TABLE 1–4

Incidence of Chromatin-Positive Males in Mental Hospital Populations

Reference	Country and type of population	Total No. studied	Chromatin-positive No.	Chromatin-positive per 1000
Carr *et al.*, 1961a	Canada General	254	1	3.94
Tedeschi and Freeman, 1962	U.S. Schizophrenia	248	3	12.10
Raphael and Shaw, 1963	U.S. Schizophrenia	105	1	9.52
Nielsen, 1964	Denmark General	450	5	11.11
J.M. Anders *et al.*, 1968	England Schizophrenia	530	5	9.43
Maclean *et al.*, 1968	Scotland General	6000	30	5.00
Total		7587	45	5.93

TABLE 1–5

Incidence of Chromatin-Positive Males in Different Groups of Male Patients Resident in Mental Hospitals in Scotland [a]

Group	Estimated No. in group	Chromatin-positive	
		No.	per 1000
Mental defect	479	10	20.87
Epilepsy	149	3	20.41
Schizophrenia	2895	11	3.80
Other	2477	6	2.42
Total	6000	30	5.00

[a] From Maclean *et al.* (1968).

pected Klinefelter's syndrome, 54 were chromatin positive and 79 chromatin negative. These patients were all infertile males with hypogonadism, as well as two or more of the cardinal features of Klinefelter's syndrome such as a feminine distribution of body hair, gynecomastia, and eunuchoid bodily proportions.

C. *Etiology of Klinefelter's Syndrome*

1. Parental Age and Birth Order

Lenz *et al.* (1959) were the first authors to consider the relationship of maternal age to the incidence of Klinefelter's syndrome; in a study of 65 chromatin-positive subjects, they showed that in nine the mother was over 40 at the birth of the proband and that the proportion of older mothers was greater than in the general population.

The parental age distribution for five separate series of chromatin-positive males is summarized in Table 1-6, and it can be seen that the mean maternal and paternal ages are raised for each group. The distribution of both maternal and paternal ages in five-year age groups (Tables 1-7 and 1-8) for two of these series showed that a far higher proportion of both mothers and fathers are over 35 than would be expected in the general population of both Sweden and Great Britain.

Birth rank is also abnormal in both these series of patients. In the Swedish population twenty-nine 47,XXY patients were last-born against an expected figure of 17.1 (Table 1-9), while in the Scottish population the comparable figures are 34 as against 21.5 expected (Table 1-10). Parental age and birth rank are of course interrelated, and at present there

TABLE 1–6

Maternal and Paternal Ages in Klinefelter's Syndrome

Reference	*n*	Mean maternal age (years)	Mean paternal age (years)	Difference	Chromosome Complement
Polani, 1967	75	30.6	–		Chromatin-positive males
J. Wilkins, 1965	36	29.5 (32)[a]	35.8 (31)[a]	6.3	Chromatin-positive males
Court Brown *et al.*, 1964a	92	32.1	35.5 (86)[a]	3.4	XXY males only
Hambert, 1966	32	31.2	36.8 (27)[a]	5.6	XXY males only
	42	33.1	36.1 (39)[a]	3.0	Chromatin-positive males
Court Brown *et al.*, 1964a	21	32.2	33.9	1.7	Mixoploids
Zuppinger *et al.*, 1967	24	30.2 (20)[a]	34.6 (9)	4.4	XXY males only
Over-All mean		31.3	35.5	4.2	
General population	1935	28.6	–	–	
England and Scotland	1958	28.7	30.7	2.00	

[a] Figures in parentheses are the number of cases.

TABLE 1–7

Distribution of Parental Ages at Birth of Patients with Klinefelter's Syndrome Compared to the Expected Frequency in the Different Age Groups [a]

Parental age group	Observed fathers	Observed mothers	Expected fathers [b]	Expected mothers [b]
<20	–	4	0.1	3.3
20–25	5	12	5.2	15.8
25–30	11	6	15.9	19.9
30–35	12	17	17.5	16.4
35–40	7	10	13.5	11.2
40–45	16	17	8.2	4.9
45–50	8	6	3.7	0.5
50>	7	–	1.9	–
Total	66	72	66.0	72.0

[a] From Hambert (1966).
[b] Official Swedish statistics.

TABLE 1–8

Distribution of Parental Ages at the Birth of 90 47,XXY Males in the United Kingdom[a]

Parental age group	Observed fathers	Observed mothers	Expected fathers[b]	Expected mothers[b]
<20	–	2	2.03	9.18
20–24	6	9	19.7	31.5
25–29	15	19	27.9	26.3
30–34	20	20	19.4	14.0
35–39	14	21	10.3	6.0
40–44	19	17	4.5	1.9
45–49	11	2	1.5	0.1
50>	1	–	0.6	–
Total	86	90	85.93	88.98

[a] Court Brown *et al.* (1964a).
[b] From Registrar General's data (1967).

are insufficient data to determine which of these three parameters is the most significant. However, this evidence, together with the fact that most 47,XXY males are X^MX^MY (see below), suggests a relationship to maternal age or birth order. If the latter is involved then it is possible that a poor uterine environment, owing to aging of the uterus, could influence nondisjunction during cleavage.

2. Familial Incidence

There is no good evidence of any increase in the frequency of Klinefelter's syndrome among the sibs or kin of chromatin-positive probands. Holub *et al.* (1958) described a pair of 17-year-old monozygotic twins with chromatin-positive Klinefelter's syndrome. Bunge and Bradbury (1956a,b) and Grumbach *et al.* (1957) described brothers with seminiferous tubule dysgenesis, one chromatin-positive and the other chromatin-negative. Lenz *et al.* (1959) described a chromosomally normal twin sister of a patient with chromatin-positive Klinefelter's syndrome who had had a normal daughter. Evidence from our own series shows that there is no increase in the frequency of Klinefelter's syndrome among sibs or relatives of affected males. It has, however, been suggested that there is an increase in sterility among uncles of chromatin-positive probands (J. S. S. Stewart *et al.*, 1958); however, Lenz *et al.*

(1959) were unable to confirm this. There is, however, considerable evidence of nonrandom association of Klinefelter's syndrome and other trisomic states.

Fourteen chromatin-positive males with Down's syndrome have been reported (see Chapter 5, Section I, I, 2 and Table 5-17 for references) as well as a number of reports of sibships containing a chromatin-positive male proband and a sib or sibs affected with Down's syndrome (Mosier *et al.*, 1960). Finally, several patients with 48,XXY,E+ have been reported (Pfeiffer, 1964b; Haylock *et al.*, 1963a; Taylor, 1967, 1968a), and Taylor estimated that 48,XXY,E+ males represent about 10–15% of males ascertained with Edwards' syndrome (see also Chapter 6).

Klinefelter's syndrome has also been found to be associated with pulmonary disorder and asthma (Daly and Rickards, 1964; Rohde,

TABLE 1–9

Birth Rank of 70 Patients with Klinefelter's Syndrome [a]

Size of sibship	No. of affected subjects in respective sibships by birth rank												Expected No. each rank
	1	2	3	4	5	6	7	8	9	10	11	12	
1	(4)												(4)
2	7	6											6.50
3	4	2	3										3.00
4	1	2	3	10									4.00
5	–	1	–	1	2								0.80
6	–	–	–	–	–	–							–
7	–	–	1	1	3	1	2						1.14
8	–	–	–	–	1	–	–	1					0.25
9	–	–	1	–	–	–	1	1	2				0.56
10	1	–	–	–	–	–	–	1	2	2			0.60
11	–	1	–	–	–	–	–	–	–	–	–		0.09
12	–	–	–	–	–	–	–	–	–	–	1	1	0.17
Total observed:	13	12	8	12	6	1	3	3	4	2	1	1	
Total expected:	17.1	17.1	10.6	7.6	3.6	2.8	2.8	1.7	1.4	0.9	0.3	0.2	

[a] From Hambert (1966).

TABLE 1–10

Birth Rank of 89 47,XXY Males[a]

Size of sibship	No. of sibships	Birth rank of affected subjects														Expected no. in each rank
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
1	6	(6)														(6)
2	18	9	9													9.00
3	12	2	5	5												4.00
4	13	2	1	4	6											3.25
5	3	–	–	1	1	1										0.60
6	7	–	1	–	2	1	3									1.17
7	9	–	2	–	1	2	2	2								1.29
8	5	1	–	–	–	1	–	1	2							0.63
9	7	–	–	–	–	1	1	–	2	3						0.78
10	5	–	–	–	–	–	–	2	–	1	2					0.50
11	2	1	–	–	–	–	–	–	–	–	–	1				0.18
12	–	–	–	–	–	–	–	–	–	–	–	–	–			–
13	1	–	–	–	–	–	–	1	–	–	–	–	–	–		0.07
14	1	–	–	–	–	–	–	–	–	–	–	–	–	1	–	0.07
Observed total:		15	18	10	10	6	6	6	4	4	2	1	–	1	–	
Expected total:		21.5	21.5	12.5	8.5	5.25	4.69	3.52	2.23	1.60	1.10	0.92	–	0.85	0.78	

[a] Data from Court Brown *et al.* (1964a).

1964), phenylketonuria (Benirschke *et al.*, 1962b), hyperparathyroidism (Spalding *et al.*, 1962), familial cerebellar ataxia (A. Hecht and Ruskin, 1960; Indemini and Ammann, 1963), leukemia (Baikie *et al.*, 1961a; Kemp *et al.*, 1961), congenital heart disease (Bogdan, 1962), and color blindness (Nowakowski and Lenz, 1961). It is interesting to note that Polani *et al.* (1958) were unable to find any cases of color blindness in a series of 55 patients with chromatin-positive Klinefelter's syndrome.

3. Fertility in Klinefelter's Syndrome

H. Kaplan *et al.* (1963) have reported a single apparently fertile 47,XXY male who claimed to have had seven children by three wives. His present wife confirmed that they had had four children, two males and two females. However, both females were dead, and the two males were not available for blood typing. It was therefore impossible to confirm these statements. A second fertile male was reported by Frøland and Ullrich (quoted by H. Kaplan *et al.*, 1963). Court Brown *et al.* (1964b) reported a fertile 46,XY/47,XXY mixoploid.

D. *Chromosome Studies*

The independent discovery by several groups of workers that some patients with Klinefelter's syndrome were chromatin-positive (Bradbury *et al.*, 1956; W. P. U. Jackson *et al.*, 1956; Nelson, 1956; Sohval *et al.*, 1956) led to the suggestion that these were sex-reversed females who would be found to have XX sex chromosomes (Sachs and Danon, 1957), and it was suggested that the condition should be classed as a type of female pseudohermaphroditism (Nelson, 1956; Prader, 1957; Marberger and Nelson, 1957). The demonstration, however, of testes and a 47,XXY chromosome complement (Ford *et al.*, 1959a; Jacobs and Strong, 1959) showed these subjects to be true males with an aneuploid sex chromosome complement and not sex-reversed females. Studies on chromatin-negative cases invariably demonstrated a normal 46,XY chromosome complement.

1. Chromatin-Positive Males with Single Sex Chromatin Masses

Polani (1962) reviewed the literature to the end of 1961 and showed that 22 out of 34 chromatin-positive males had an XXY sex

chromosome complement while the remainder were mixoploid. Table 1-11 summarizes the more recent cytogenetic data from four series of patients, and from this it can be seen that 82% of chromatin-positive males are 47,XXY, 11% are mixoploid, while 7% are either 48,XXYY, 48,XXXY, or 46,XX.

a. 47,XXY MALES. These males have 47 chromosomes, with 16 chromosomes in the C group as well as a Y chromosome (Fig. 1-3). Evidence that the additional C group chromosome is an X chromosome has been obtained from four sources.

1. The sex chromatin findings which are identical to observations on normal females with an XX sex chromosome complement, imply that there are two X chromosomes present.

2. The observation that there is a single late-replicating chromosome in the X+6-12 group as in normal females which is interpreted as an X chromosome (Muldal *et al.*, 1963; Giannelli, 1963; O. J. Miller *et al.*, 1963).

3. Abnormalities of sexual development.

4. A similar frequency of red-green color blindness among chromatin-positive males to that found in normal females (Polani *et al.*, 1958; Nowakowski *et al.*, 1958; J. S. S. Stewart, 1961; Lennox, 1961).

The identification of the additional small acrocentric chromosome as a Y chromosome is based on its characteristic morphological appearance, its labeling pattern, and the presence of testes.

The source of the two X chromosomes in the XXY state has already been discussed (Volume I, Chapter 7) and it has been shown that about 40% of these males are X^MX^PY while the remainder are X^MX^MY. Of these about 10% are $X^{M_1}X^{M_1}Y$ or $X^{M_2}X^{M_2}Y$ while 50% are $X^{M_1}X^{M_2}Y$ (Race and Sanger, 1969).

Parental ages in 10 patients in which the origin of the two X chromosomes is known are summarized in Table 1-12. It is interesting to note that the mean maternal age in the six X^MX^MY is slightly raised (29.7 years), while it is only average in the four X^MX^PY (27.8 years). This provides additional evidence for the hypothesis that maternal age is higher in syndromes where nondisjunction during oogenesis is implicated.

b. 48,XXYY MALES. A typical karyotype is shown in Fig. 1-4. About 40 subjects with this chromosome constitution are known, and some data are available for about 26 of these (Table 1-13). Apart from one patient who was located during a sex chromatin survey of the new-

TABLE 1–11

Chromosome Findings in 259 Subjects with Chromatin-Positive Klinefelter's Syndrome

Reference	Total[a]	47,XXY	48,XXXY	48,XXYY	46,XX	46,XX/47,XXY	46,XY/47,XXY	Other mixoploids and double trisomics
J. Wilkins, (1965)	36	30	1	1	2	–	1	1
Court Brown *et al.*, (1964a)	131	99	4	3	2	2	15	6
Hambert, (1966)	36	31	1	1	–	–	2	1
Makino, (1966)	32	29	1	1	–	1	–	–
Zuppinger *et al.*, (1967)	24	23	–	–	1	–	–	–
Total	259	212	7	6	5	3	18	8
		0.82[a]		0.07[a]			0.08[a]	0.03[a]

[a] Proportion of total.

FIG. 1-3. Karyotype of chromatin-positive male with 47,XXY chromosome complement. (×972).



FIG. 1-4. Karyotype of chromatin-positive male with 48,XXYY chromosome complement. (×729).

born (Court Brown *et al.*, 1964a) all the patients are mentally unstable, often of low grade intelligence, and may be aggressive; a high frequency of 48,XXYY males have been found in institutions for the criminally insane (Jacobs *et al.*, 1965, 1968; Casey *et al.*, 1966a, 1968). All the postpubertal subjects who have been studied have the typical features of Klinefelter's syndrome, including small testes which have a typical histological picture consisting of hyalinized tubules and Leydig cell hyperplasia. The majority of subjects have a "eunuchoid" habitus and about half have gynecomastia. Body hair is usually sparse and of feminine distribution. The mean maternal age at the birth of 22 of these patients is 29.7 while the paternal age for 19 patients is 32.8 years; there is thus no significant increase in either the maternal or paternal ages comparable to that seen in the 47,XXY patients. The birth rank is normal, only one of the 11 subjects on whom there is information being born at the end of the sib-

TABLE 1–12

Parental Age at Birth of 10 47,XXY Males for Whom the Source of the Two X Chromosomes is Known [a]

Patient	Age at birth of patient (years)	
	Father	Mother
X^MX^PY	22	16
	30	32
	44	36
	30	27
Mean	31.5	27.8
X^MX^MY	39	41
	36	31
	30	19
	32	30
	36	30
	30	27
Mean	33.8	29.7

[a] From Frøland *et al.* (1968).

ship. These men are taller than men with XY or XXY sex chromosomes, their mean height being 181.4 cm compared to 177.4 cm for 47,XXY males. This increase is entirely accounted for by an increase in the length of leg; the mean pubis-sole measurement is 94.9 cm compared to 88.5 cm for 47,XXY subjects.

There are three possibilities in accounting for the origin of the 48,XXYY chromosome complement.

1. Successive nondisjunction at the first and second meiotic divisions during spermatogenesis and syngamy of the resulting XYY spermatozoon with an X ovum.

2. Nondisjunction at the second meiotic division in both parents so that syngamy occurs between an XX ovum and a YY sperm.

3. Mitotic nondisjunction during cleavage in an XXY zygote, resulting in XX and XXYY cells, or of the X in an XYY zygote, giving XXYY and YY cell lines. In the first type both cell lines might be expected to be viable so that mixoploidy would result. In the second, however, the YY cells would probably be nonviable, leaving only the XXYY

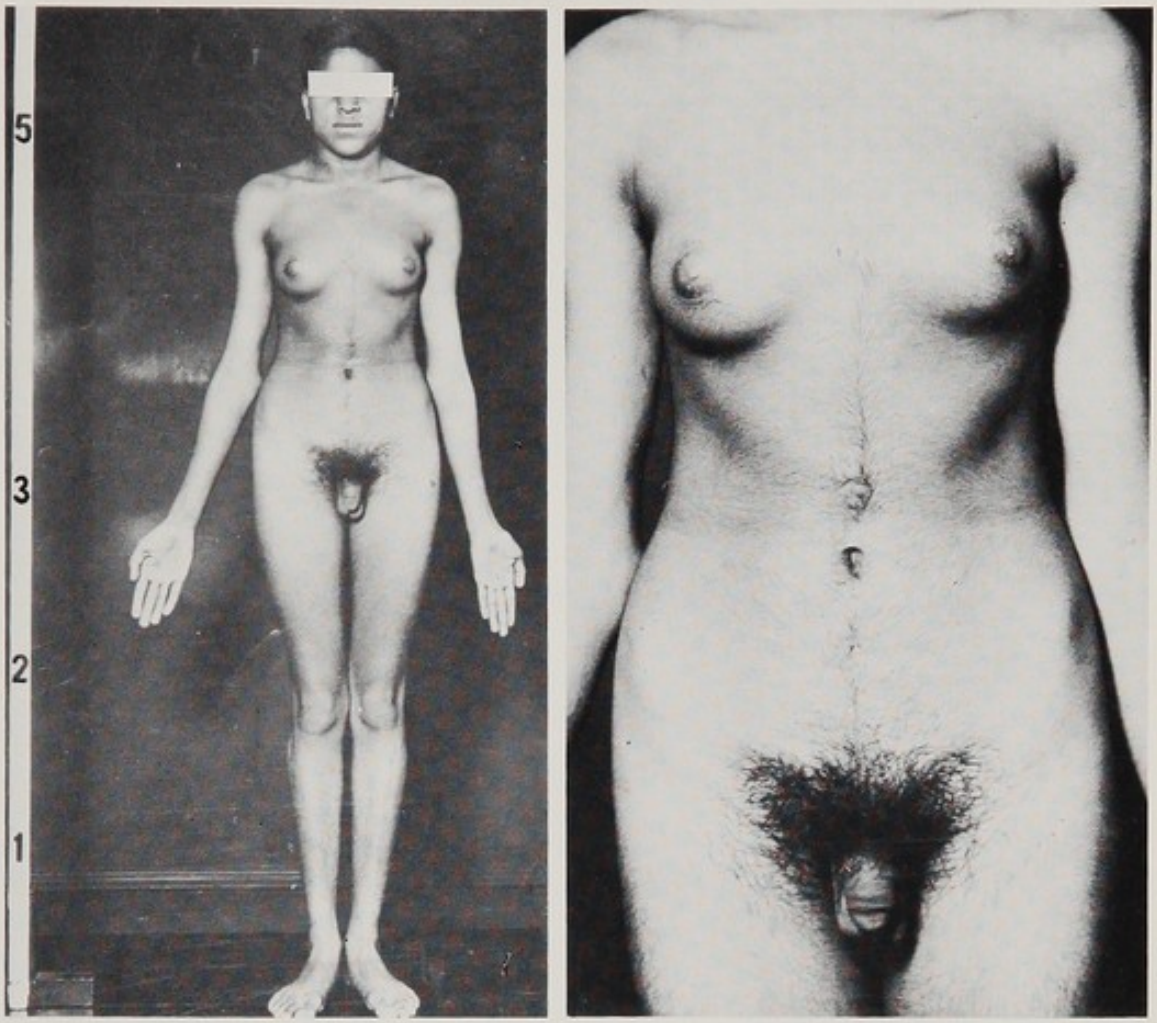


FIG. 1-5. Clinical photographs of a chromatin-positive male patient age 15 years with Klinefelter's syndrome and a 46XX chromosome complement. Note gynecomastia, excessive length of legs and arms, and gynoid proportions. Female distribution of hair. (Reproduced by permission of Dr. L. Adler.)

cell line. In view of the low frequency of mixoploids a postzygotic error seems less likely and either (1) or (2) above probably accounts for the majority of these patients.

Two families have been described in which successive nondisjunction at meiosis I and II in the male and the fertilization of an X ovum by an XYY sperm seems to have occurred since one X and both Y chromosomes can only have come from the father (see Volume I, Fig. 7-17). These are the first recorded examples of successive nondisjunction at meiosis I and II during spermatogenesis (De la Chapelle *et al.*, 1964b; Race and Sanger, 1969).

c. 46,XX MALES. Seventeen males with hypogonadism, testicular dysgenesis, and some features of Klinefelter's syndrome (Fig. 1-5) have been reported (Table 1-14). In each case several tissues have been

TABLE 1-13

Author's reference	Ascertainment	Maternal age (years)	Paternal age (years)	Height (cm)	Span (cm)	Crown-pubis (cm)
151/61	Newborn survey	26	31	–	–	–
15/61	Survey of mentally deficient patients	22	21	176.5	183.0	85.0
11/61	Survey of mentally deficient patients	–	–	193.0	190.0	97 97.0
23	Survey of patients with Klinefelter's syndrome	34	34	182.9	–	–
36	Survey of patients with Klinefelter's syndrome	30	30	190.0	183.0	–
3	Survey of patients with Klinefelter's syndrome	38	39	162.0	–	75.0
–	Survey of patients with Klinefelter's syndrome	33	54	–	–	–
1/RK	Survey of patients with Klinefelter's syndrome	–	–	119.4	116.8	–
2/EW	Survey of patients with Klinefelter's syndrome	–	–	182.9	175.3	–
1	Survey of mentally deficient patients	18	26	180.3	180.3	90.2
2	Survey of mentally deficient patients	24	22	182.2	182.9	81.9
3	Survey of mentally deficient patients	20	–	191.8	191.8	94.0
	Mentally ill patient	34	43	184.2	189.9	76.2
13	Criminal population survey	35	40	185.0	190.0	86.0
14	Criminal population survey	37	53	175.0	174.0	86.0
15	Criminal population survey	28	32	176.0	181.0	87.0
16	Criminal population survey	31	–	188.0	182.0	87.0
17	Criminal population survey	29	33	186.0	181.0	87.0

Some Clinical Data on 26 48,XXYY Males

Pubis-sole (cm)	No. in sibship	Rank of proband		Reference
–	1	1		Court Brown *et al.*, 1964a
91.5	7	2		
96	–	–		
–	2	2		Hambert, 1966
–	8	5		
87	3	–	Prepubertal 14 years	Makino, 1966
–	–	–		Laurence *et al.*, 1963
–	4	1	Prepubertal	G.C. Robinson *et al.*, 1964
–	5	3		G.C. Robinson *et al.*, 1964
90.2	4	2		Barr *et al.*, 1964
100.3	3	2		
97.8	2	1		
106.7	5	4		Carr *et al.*, 1961a
99	1	1		Casey *et al.*, 1966a, 1968
91	4	1		
91	6	1		
101	6	3		
99	3	2		

TABLE 1-13 (cont'd)

Author's reference	Ascertainment	Maternal age (years)	Paternal age (years)	Height (cm)	Span (cm)	Crown-pubis (cm)
18	Criminal population survey	27	27	160.0	160.0	76.0
19	Criminal population survey	29	30	166.0	166.0	80.0
JHH 926809	Not known	31	34	170.0	152.0	80.0
DW	Endocrine disorder	–	–	168.0	176.5	79.0
I/JV	Retardation	23	24	130.0	–	–
2/ER	Retardation	24	25	142.0	–	–
1	Chromatin-positive Klinefelter's syndrome	36	26	185.0	–	–
1	Chromatin-positive Klinefelter's syndrome	46	–	–	–	–
Mean		29.7 (22)	32.8 (19)	181.4 (17)	180.7 (15)	85.6 (13)

[a] Figures in parentheses are the number of cases.

[b] Only post-pubertal subjects included.

sampled for chromosome studies (Fig. 1-6), and no evidence of a cell line containing a Y chromosome has been forthcoming (Table 1-15). Furthermore, sex chromatin and autoradiographic studies (Fig. 1-7) have supported the interpretation that two X chromosomes are present (De la Chapelle and Wennström, 1966). The clinical features are summarized in Table 1-16 and illustrate that these are phenotypic males who fit into the general category of chromatin-positive Klinefelter's syndrome; they have relatively normal male external genitalia with a small penis and scrotum and usually small testes with hyalinized tubules containing only Sertoli cells.

There are three possible explanations for this condition:

1. Mixoploidy. These men started from a 46,XX/47,XXY zygote in which cell selection has eliminated or virtually eliminated the 47,XXY cell line after the Y chromosome had acted to stimulate gonadal medullary development and hence the formation of a testis (see Chapter 4). This would have resulted in the masculinization of the phenotype.

Some Clinical Data on 26 48,XXYY Males

Pubis-sole (cm)	No. in sibship	Rank of proband		Reference
84.0	5	1		Carey *et al.*, 1964a
86.0	3	2		
90.0	1	1	Prepubertal	Garcia *et al.*, 1967
89.0	4	2	Prepubertal	Muldal *et al.*, 1962
–	–	–	Prepubertal	Leisti *et al.*, 1964
–	–	–	Prepubertal	
–	3	1		De la Chapelle *et al.*, 1964a
–	–	–		Vague *et al.*, 1961
94.9 (13)		CP/PS = 0.90		

This explanation is supported in one instance, at least, by the finding of a very low frequency of 47,XXY cells in an otherwise predominantly 46,XX male (F. Hecht *et al.*, 1966). The frequency of these cells was very low—about 1% in both blood and skin—and this was cited as evidence for cell selection. Similar cell selection has been shown in other forms of mixoploidy (C. M. Clarke *et al.*, 1961, 1963; Taylor, 1968b), and there is no reason to suppose that complete elimination of the cell line might not occur.

2. Ferguson-Smith (1966) suggested that the region of the Y chromosome controlling male determination had become translocated onto the X chromosome. This is suggested not only as an explanation for these 46,XX males but also for certain 46,XX true hermaphrodites, depending on which X chromosome is inactivated.

3. These males are true sex-reversed females as a result of the action of a sex-limited autosomal recessive gene similar in action to the *P* locus in the goat, which in the homozygous state leads to a form of male

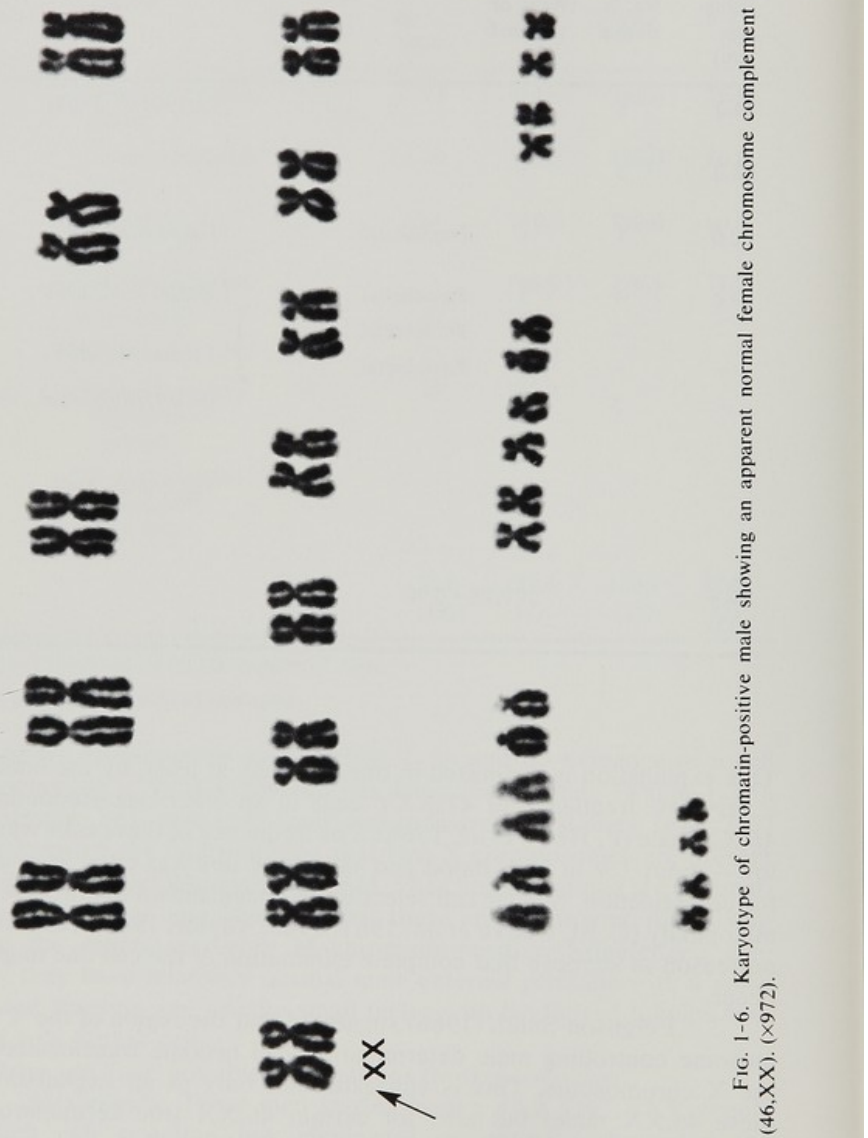


FIG. 1-6. Karyotype of chromatin-positive male showing an apparent normal female chromosome complement (46,XX). (×972).

TABLE 1–14

Some Clinical Data on 17 46,XX Males

Age of patient (years)	Maternal age (years)	Paternal age (years)	Height (cm)	Pubis-sole (cm)	Span (cm)	Birth weight (gm)	Reference
19	28	26	172.0	–	–	3200	De la Chapelle *et al.*, 1964a
–	19	–	–	–	–	–	De la Chapelle *et al.*, 1965
30	–	–	167.0	–	–	–	Therkelsen, 1964a
24	28	33	167.5	92.5	167.5	–	5/61 Court Brown *et al.*, 1964a
60	43	42	–	–	–	–	68/61 Court Brown *et al.*, 1964a
35	25	26	166.0	–	161.0	–	Strauch *et al.*, 1965 Zuppinger *et al.*, 1967
17	26	31	154.0	–	155.0	3000	Lindsten *et al.*, 1966
35	35	37	180.0	–	179.0	3400	Lindsten *et al.*, 1966
42	39	40	167.0	–	–	–	Von Mulert *et al.*, 1967
15	23	–	156.6	–	–	2700	De Grouchy *et al.*, 1967c
–	–	–	170.0	–	–	–	De Grouchy *et al.*, 1967c
21	24	25	170.8	96.1	179.6	–	PRU 692/SK 190544 J. Wilkins, 1965
23	29	31	158.0	78.0	164.0	3969	PRU 678/BG 100941 J. Wilkins, 1965
21	29	33	168.0	91.4	167.0	–	148454 Ferguson-Smith, 1968
16	32	29	167.6	88.9	169.5	–	174727 Ferguson-Smith, 1968
30	31	41	167.6	86.4	171.5	–	312751 Ferguson-Smith, 1968
76	–	–	–	–	–	–	Ferguson-Smith, 1968
MEAN	29.4(14)[a]	32.8(12)	166.6(14)	88.9(6)	168.2(9)	3254(5)	

[a]Figures in parentheses indicate the number of cases.

TABLE 1–15

Number of Cells Studied and Found to Have a Normal Female Chromosome Complement in 12 46,XX Males

Reference	Chromatin-positive cells in oral smears (%)	No. of cells studied				Total
		Blood	Skin	Testis	Other	
De la Chapelle *et al.*, 1964a	30	216	65	57	160	498
Therkelsen, 1964a	35, 23, 24	97	87	85	–	269
Court Brown *et al.*, 1964a						
5/61	34	30	30	–	–	60
68/61	57	30	30	–	–	60
Zuppinger *et al.*, 1967 Strauch *et al.*, 1965	31	38	72	54	–	164
Lindsten *et al.*, 1966						
(1)	34	191	195	164	–	550
(2)	32	100	92	–	–	192
Von Mulert *et al.*, 1967	25, 20	22	–	52	–	74
De Grouchy *et al.*, 1967c						
(1)	20	200	–	200	–	400
(2)	20, 30	100	–	20	–	120
PRU 692/SK190544	40, 45	50	9	–	–	59
PRU 678/BG100941	21	71	25	–	–	96

pseudohermaphroditism or true hermaphroditism in genetic females and perhaps at its extreme to complete sex reversal. A similar gene acting by controlling a "medullary stimulator" carried on the X chromosome (Hamerton, 1968b) could lead to complete, but sterile, sex reversal by causing the indifferent gonad to form a testis. The amount of medullary tissue present and both the amount and timing of its hormonal activity could determine whether the phenotype was that of a normal male or an intersex (Hamerton *et al.*, 1969; Short *et al.*, 1969) (for further discussion of these points see Chapters 3 and 4).

The finding of a male-type distribution of the Xg blood group in 20 46,XX males [14 Xg(a+) and six Xg(a–), Volume I, Chapter 7] tends to support the translocation hypothesis (Race and Sanger, 1969). However, this is not conclusive and a male type distribution would also be found if the mother had effectively only transmitted one X chromosome which then became duplicated. This could happen either at the second meiotic

division in oogenesis to give an $X^{M1}X^{M1}$ or $X^{M2}X^{M2}$ ovum or at an early cleavage division. If it occurs at meiosis II then the XX ovum might be fertilized by a sperm which did not contain a sex chromosome, in which case the sex reversal hypothesis (3 above) would need to be invoked. If duplication occurs at an early cleavage division in an XY zygote or at meiosis II with subsequent fertilization by a Y-bearing sperm, then loss of the Y from the XXY zygote must be invoked after it has served to cause the indifferent gonad to develop into a testis. This does not occur until 30-40 days' gestation, and loss of the Y or overgrowth of nullo-Y cells at this late stage seems less likely. It is, however, possible that the Y may exert its action much earlier than this and its subsequent loss may then be unimportant.

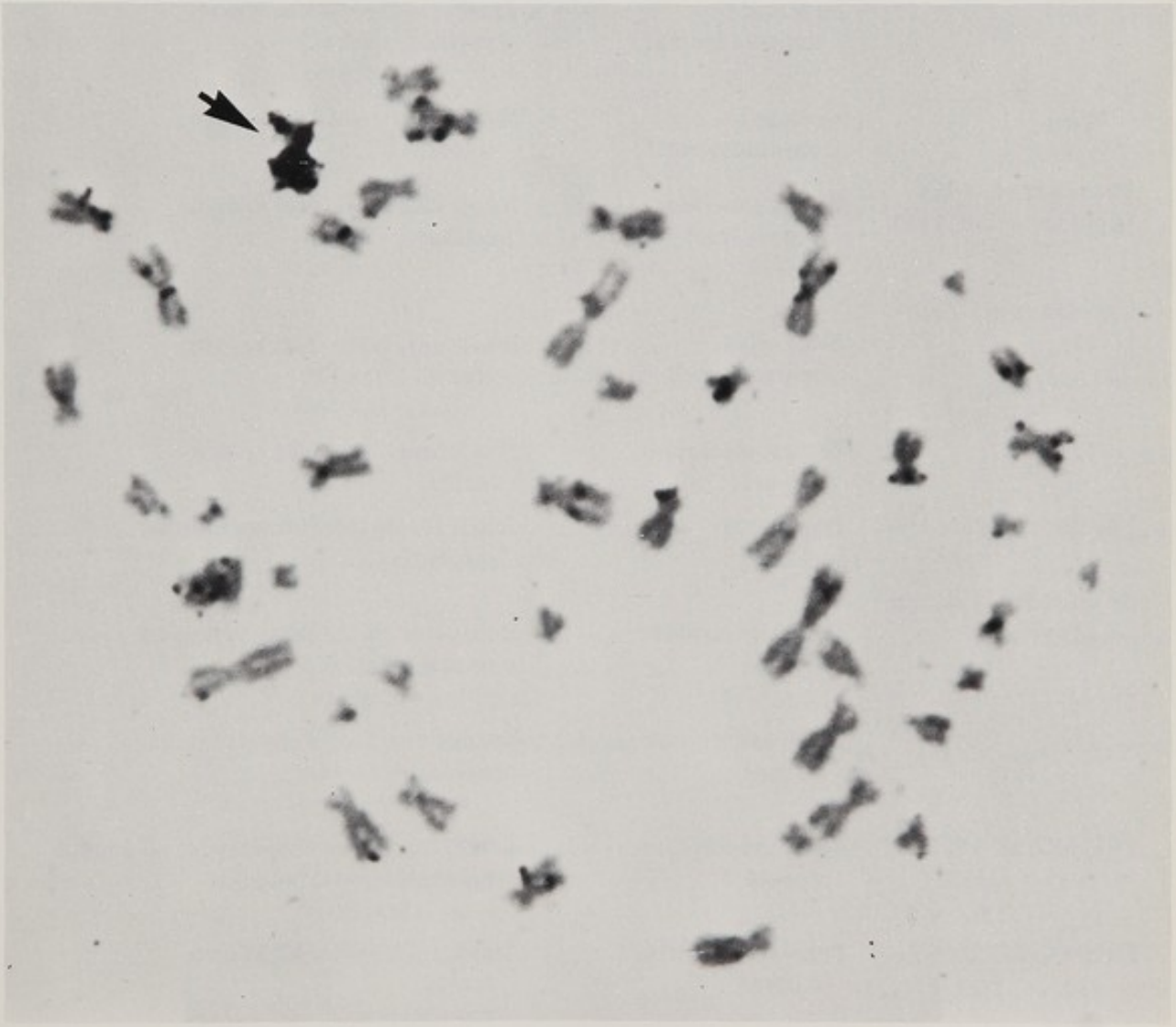


FIG. 1-7. (a) Metaphase from chromatin-positive male with 46,XX sex chromosomes after ^{3}H-thymidine labeling and autoradiography. Note single late replicating X chromosome. (Reproduced by courtesy of Dr. F. Giannelli.)

TABLE 1-16

Reference	External genitalia	Testes	Internal genitalia
De la Chapelle, 1964a	4 cm penis, scrotum normal	Very small, scrotal	Epididymis, vas deferentia. seminal vesicles, prostate normal
Therkelsen, 1964a	Small penis, scrotum normal	Small, scrotal	Epididymis, vas deferentia normal
Court Brown *et al.*, 1964a			
5/61	Penis and scrotum normal	Small, scrotal	Not known
68/61	Penis and scrotum normal	Small, scrotal	Not known
Strauch *et al.*, 1965 Zuppinger *et al.*, 1967	Hypoplastic penis and scrotum	Small soft, scrotal	Not known
Lindsten *et al.*, 1966			
(1)	Penis small; scrotum small	Small soft, scrotal	Not known
(2)	Penis and scrotum normal	Small hard, scrotal	Not known
Von Mulert *et al.*, 1967	Penis small	Small, scrotal	Prostate normal
De Grouchy *et al.*, 1967c			
(1)	Penis and scrotum normal	Small, scrotal	Prostate normal
(2)	Penis and scrotum normal	Small, scrotal	Prostate normal
PRU 692/SK 190544	Penis and scrotum normal	Small, scrotal	No prostate; no seminal vesicles
PRU 678/BG 100941	Penis and scrotum normal	Small, scrotal, azoospermic	Not known

Some Clinical Data on 17 46,XX Males

Gynecomastia[a]	Testicular histology	Sexual behavior	Hair[a]
–	Seminiferous tubules few and small, Sertoli cells few and immature, Leydig cells normal; no spermatogenesis; few spermatogonia present	Rare erections	Not known
–	Degenerate small tubules containing only Sertoli cells; no germ cells; Leydig cell hyperplasia	Normal but low libido	P+ ♂ A+ ♂ F+ ♂
+	Hyalinized tubules lined with Sertoli cells; Leydig cells present	Not known	P+ ♂ A ± F ±
+	Not known	Not known	P+ ♂ A+ ♂
+	Diffuse sclerotic tubules, several contain only Sertoli cells	Stated to be normal	P+ ♂ A+ ♂ F+ ♂
–	50% open lumens lined with Sertoli cells. 50% closed, sclerotic; Leydig cell hyperplasia	Not known	Not known
–	Not known	Not known	Not known
?–	Tubules reduced in size; irregular Leydig cell hyperplasia.	Sterile, ejaculates	Not known
–	Hyalinized tubules; Sertoli cell syncitium; several spermatogonia; Leydig cell hyperplasia	No libido	Prepubertal
–	Sclerosed and hyalinized tubules; Sertoli cell regression; Leydig cell hyperplasia	Not known	Not known
+	Numerous seminiferous tubules with Sertoli cells; other tubules hyalinized	Not known	P+ ♂ F+ ♂ A+ ♂
+	Not known	Married; sterile	P+ ♀ F ± ♂ A+♂

TABLE 1-16 (cont'd)

Reference	External genitalia	Testes	Internal genitalia
Ferguson-Smith, 1968			
KS(148454)	?	Small, scrotal	?
HMcG (174727)	Hypospadias	Left abdominal, right small, scrotal	?
JMcG (312751)	?	Small, scrotal	?
AH	?	Small, scrotal	?

[a] P, pubic hair; A, axillary hair; F, facial hair; +, normal amount; −, absent; ♂, masculine distribution; ♀, feminine distribution; Gynecomastia present (+); absent (−); well developed (++).

At present it is not possible to state which mechanism is operating and this must clearly await more data (but see also Chapter 4).

2. Mixoploid Subjects with a Single Sex Chromatin Mass

The incidence of mixoploidy among chromatin-positive males is relatively low. Among 259 chromatin-positive males with single sex chromatin masses (see Table 1-11) 21 were "two cell line" mixoploids, an incidence of 8.1%, and of these 18 were 46,XY/47,XXY, three were 46,XX/47,XXY, and five were "triple cell line" mixoploids. The early cases were reviewed by Polani (1962) who reported four mixoploid males. Two of these were XX/XXY and two were either XX or XY/XXY (Ford *et al.*, 1959b; Crooke and Hayward, 1960; Nowakowski *et al.*, 1960). Briggs *et al.* (1963) found a mixoploid individual with some features of Klinefelter's syndrome who had single sex chromatin masses and three cell lines (46,XY/47,XXY/48,XXYY) in a group of 44 mental defective and schizoid individuals in Sardinia. Nowakowski *et al.* (1960) and Bergman *et al.* (1960) reported two groups of mixoploid patients. In the first group the predominant cell line was 47,?XXY while the second cell line contained 48 chromosomes, XXY sex chromosomes, and a chromosome resembling No. 17 (47,XXY,?17+). The second had a major 47,XXY cell line with a minor 46,XX or XY cell line and a few 45,X cells (45,X/46,XX or XY/47,XXY). This extensive variation may of course result from abnormalities arising *in vitro* since the chromosome studies were all made after some considerable time in culture.

J. M. Anders *et al.* (1968) described five chromatin-positive males in a group of 530 males with schizophrenia, of whom four were pre-

Gynecomastia[a]	Testicular histology	Sexual behavior	Hair[a]
+	As for Klinefelter's syndrome	?	P+ ♂
+	As for Klinefelter's syndrome	?	P± ♂
–	Not known	?	P± ♂
++	As for Klinefelter's syndrome	?	P± ♂

sumptive 46,XY/47,XXY mixoploids. The clinical features of these patients, however, are relatively normal and at least one has normal-sized testes. Bergman *et al.* (1963) reported a single male with 47,XXY/48,XXYY mixoploidy. The patient was chromatin-positive and mentally defective with small atrophic testes, normal distribution of axillary and pubic hair, and no gynecomastia.

Comparison of the frequency of chromatin-positive mixoploid males in mentally deficient or mentally ill populations cannot easily be carried out. Maclean *et al.* (1962) found five mixoploids in 28 chromatin-positive mental defectives, an incidence of 17.0%, while J. M. Anders *et al.* (1968) found four out of five chromatin-positive schizophrenic males to be mixoploid (80%). In a survey of 20,725 newborn babies, Maclean *et al.* (1964) found that five out of 18 chromatin-positive males (27.8%) were mixoploids. These were, however, studied at too early an age to assess their mental state and it cannot be stated how many will subsequently be mentally ill or have impaired mental ability. Tentatively it seems that "pure line" 47,XXY males have a higher risk of becoming mental defectives or having impaired intelligence than do the mixoploids; on the other hand, these perhaps have the same likelihood as the XXY's of becoming psychotic.

3. Origin of the Mixoploids

The types of nondisjunction which result in different types of mixoploidy have already been discussed (Volume I, Chapter 7), and it is clear that the majority of mixoploids result from nondisjunction during an early cleavage division of a normal or abnormal zygote. It is perhaps of

some interest to determine whether the original zygote was normal or abnormal. The following types will be considered.

1. 46,XY/47,XXY—This is the most frequent group among chromatin-positive males (see Table 1-11) and comprises 18 out of 26 mixoploids (69.2%). A 46,XY/47,XXY zygote may be formed either by loss of one X at the first cleavage division of an XXY zygote [and distribution of the Xg blood groups (Volume I, Chapter 7) suggests that this may be the most likely mechanism] or by nondisjunction in an XY zygote at any cleavage division apart from the first. This would result in the formation of three cell lines: 46,XY, 47,XXY, and 45,Y. The 45,Y line would probably be nonviable, leaving a 46,XY/47,XXY zygote.

2. 46,XX/47,XXY—These are far less common and probably result from loss of the Y chromosome during cleavage of a 47,XXY zygote. Any other explanation requires several successive mitotic nondisjunctional events.

3. 47,XXY/48,XXYY—Two males with this chromosome complement have been reported. The simplest and most likely mode of origin is the loss of one Y chromosome from an abnormal 48,XXYY zygote at the first cleavage division.

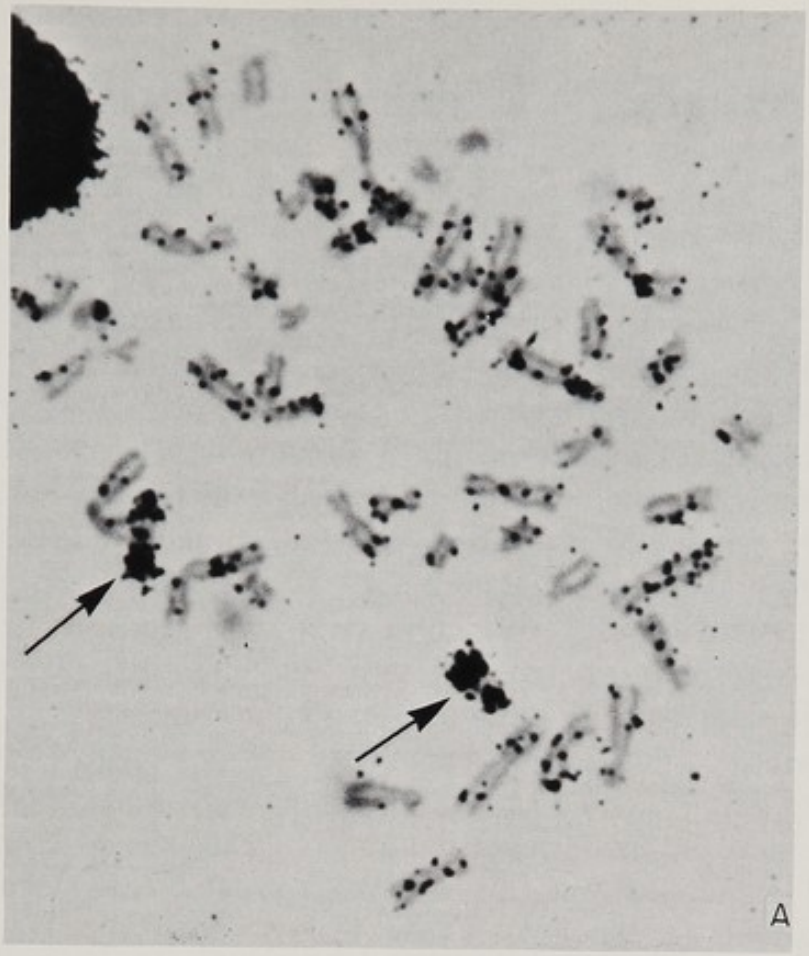
4. Triple cell line mixoploids (45,X/46,XY/47,XXY; 46,XX/46,XY/47,XXY; 46,XY/47,XXY/48,XXYY)—The origin of these more complex mixoploids must be a nondisjunctional event at a later cleavage division and must involve at least two consecutive nondisjunctional events in different cell lines. The original zygote can be either normal or abnormal.

The significance of the increased mean parental ages (see Table 1-6) at the birth of chromatin-positive males has already been discussed (Volume I, Chapter 7 and in Section I, C above), and while this increase is not so great as that seen in Down's syndrome it does suggest an error during oogenesis, particularly if the relative rarity of the $X^{M}X^{P}Y$ chromosome complement is also considered. If we now examine the available data for the different mixoploid classes (see Table 1-6) we find no significant difference between the mean parental ages for this category of patient when compared with the 47,XXY males, both having approximately the same degree of increase in mean parental ages. This perhaps suggests a similar origin, probably from an abnormal 47,XXY zygote.

II. Chromosome Studies in Males with Multiple Sex Chromatin Masses

A. *48,XXXY Males*

Several males with double sex chromatin and a 48,XXXY chromo-



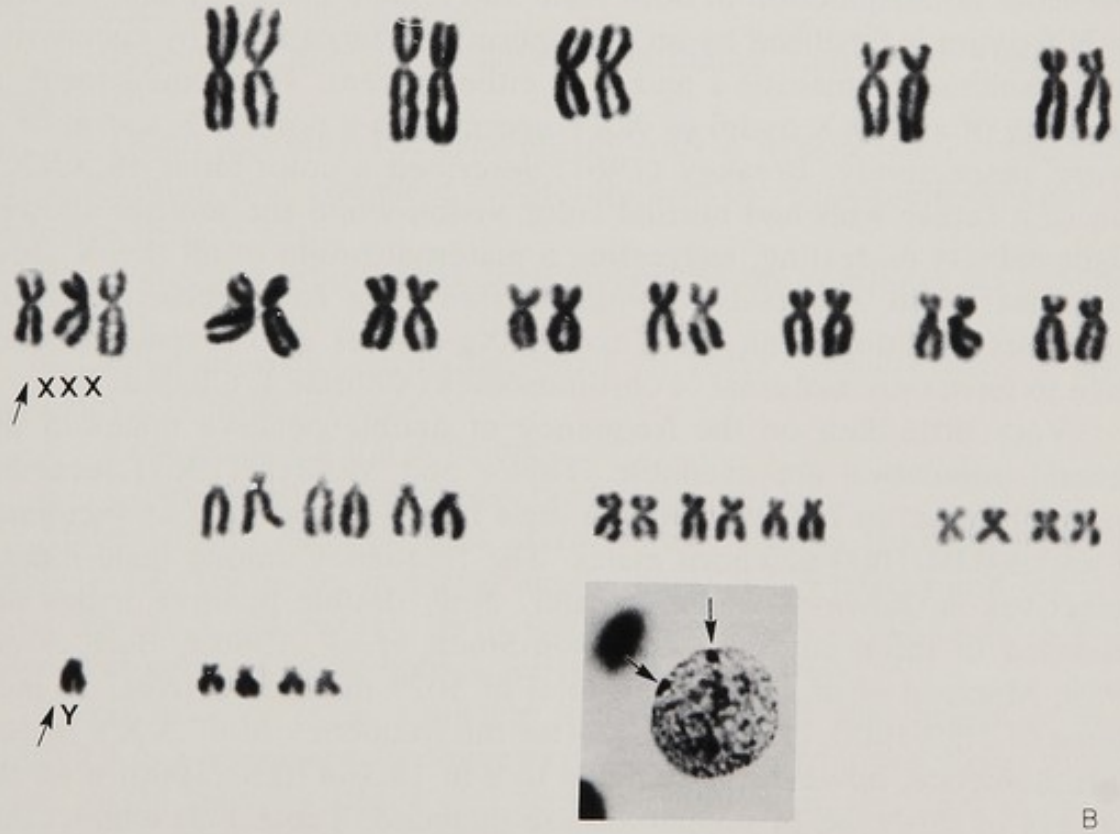


FIG. 1-8. A. Metaphase plate showing two late replicating X chromosomes (×800). B. Karyotype of double chromatin-positive male (sex chromatin inset) with 48,XXXY chromosome complement (×2700). (A. By courtesy of Dr. F. Giannelli.)

some complement (Fig. 1-8) have been reported (Ferguson-Smith *et al.*, 1960b; Maclean *et al.*, 1962; Barr *et al.*, 1959; Carr *et al.*, 1961b; Court Brown *et al.*, 1964a). These patients are all mentally defective with IQ's ranging from less than 20 up to 64, but who otherwise have the typical features of Klinefelter's syndrome. They are usually very tall and of "eunuchoid" proportions; and about half have gynecomastia. The size of the penis and scrotum is variable and may be either normal or considerably reduced in size. The testes are generally atrophic and small or very small and consist of hyalinized ghost tubules which completely lack a germinal epithelium and are lined by Sertoli cells (Table 1-17). There is often Leydig cell hyperplasia. Bray and Josephine (1963) have reported a 27-year-old phenotypic male with a 49,XXXYY chromosome complement. The patient has severe mental retardation with an IQ of 45-50. He is tall, moderately obese, and eunuchoid; his testicular histology is typical of chromatin-positive Klinefelter's syndrome.

The maternal and paternal age at the birth of ten 48,XXXY patients was found to be 30.2 and 33.5 years, respectively; thus, there is a slight increase of both the mean maternal and paternal age as compared with the general population but this is not so great as that shown by the 47,XXY patients (Table 1-6). These 48,XXXY zygotes may result either from nondisjunction in both male and female gametogenesis so that an XX ovum is fertilized by an XY sperm or alternatively by successive nondisjunction in meiosis I and II in either parent. This would result in syngamy of an XXX ovum or XXY sperm with a normal Y sperm or X ovum, respectively. Breakey (1961) described a color-blind 48,XXXY son of a father who had normal color vision while the mother showed slight defects on testing, suggesting a maternal origin of all the X chromosomes. If so, successive nondisjunction must have occurred during oogenesis resulting in an XXX ovum. Xg studies also reveal one such male to have only maternal X chromosomes (Volume I, Chapter 7).

Very little data on the frequency of double positive males in the general population are available. Taylor and Moores (1967) recorded one such infant in 23,229 newborn male babies, suggesting an incidence of about 0.04/1000 newborn males. The frequency among male mental defectives is, however, much greater. Nine double positive males are recorded in three surveys (Ferguson-Smith *et al.*, 1960b; Barr *et al.*, 1959; Maclean *et al.*, 1962) in a total of 5029 male defectives, an incidence of 1.79/1000, or about a quarter the frequency of 47,XXY males. This incidence, however, is reduced to 9 in 14,364 (0.62/1000) if all the surveys of this type of population are included (Table 1-3) which compares with 0.04/1000 among newborn males.

B. *Mixoploid Males with Multiple Sex Chromatin Masses*

The 46,XY/48,XXXY male reported by Barr *et al.* (1959, 1962a) had normal-sized testes with an almost normal histological appearance and all stages of spermatogenesis present. Court Brown *et al.* (1964a) described an XXXY/XXXXY mixoploid male with small testes, underdeveloped scrotum, and normal penis born at a maternal age of 30 and a paternal age of 28. He was mentally defective, psychotic, and of eunuchoid habitus.

C. *49,XXXXY Males*

The 49,XXXXY males form a quite distinct phenotypic group which can be readily separated from the variants of Klinefelter's syndrome. All these patients have three sex chromatin masses in a proportion of their interphase nuclei and have been shown to have 49 chromosomes with 18 chromosomes in the X + 6-12 group (Fig. 1-9), three of which incorporate DNA late in the synthetic period (Rowley *et al.*, 1963; Mukherjee *et al.*, 1964; T. C. Hsu and Lockhart, 1964; Coutts and Lewis, 1964) and are interpreted as 49,XXXXY (Fig. 1-9). The clinical features of 29 patients are summarized in Table 1-18. The following features are characteristic:

1. Extensive skeletal anomalies including radioulnar synostosis (Fig. 1-10).
2. Often extreme hypogenitalism with a hypoplastic, sometimes partial scrotum and complete cryptorchidism or incomplete descent of the testes (Fig. 1-11).
3. Defective prepubertal development of the seminiferous tubules (Fig. 1-12).
4. Characteristic dermatoglyphics in some subjects with a high frequency of simple arches.
5. Low grade mental deficiency.
6. Characteristic and similar facies (Fig. 1-13).

Maternal and paternal ages show little alteration from the normal (Table 1-19), the mean maternal age being 28.3 (29 cases) and the paternal age 30.1 (28 cases). Birth weight is often low and there is evidence that some of these babies are born postmaturely.

There is very little evidence available about the origin of the 49,XXXXY chromosome complement. Evidence from the Xg(a) blood groups in 24 families (Race and Sanger, 1969) indicates that in three families the origin of all four X chromosomes is maternal and the result

TABLE 1-17

Ref. No.	Age (years)	IQ[a]	Height (cm)	Span (cm)	Crown-pubis (cm)	Pubis-sole (cm)	Maternal age (years)
239/60	16	MD	175.0	175.0	86.5	89.0	20
71/60	20	MD	188.0	175.5	94.0	94.0	27
209/60	29	MD	181.5	171.5	84.0	95.5	40
73/60	29	MD	164.0	151.0	89.0	76.0	34
1	15	40–60	166.4	166.4	80.0	86.4	21
2[c]	55	54	184.2	179.1	86.4	97.8	37
3[c]	31	*Ca.* 30	174.0	172.7	85.1	88.9	38
2	14	60	161.9	162.6	74.3	87.6	20
HH/877961	22	49	170.5	164.0	77.2	93.0	38
JHH/178523	22	<20	175.0	177.0	80.8	94.0	27
Mean			174.1	169.5	83.7	90.2	30.2

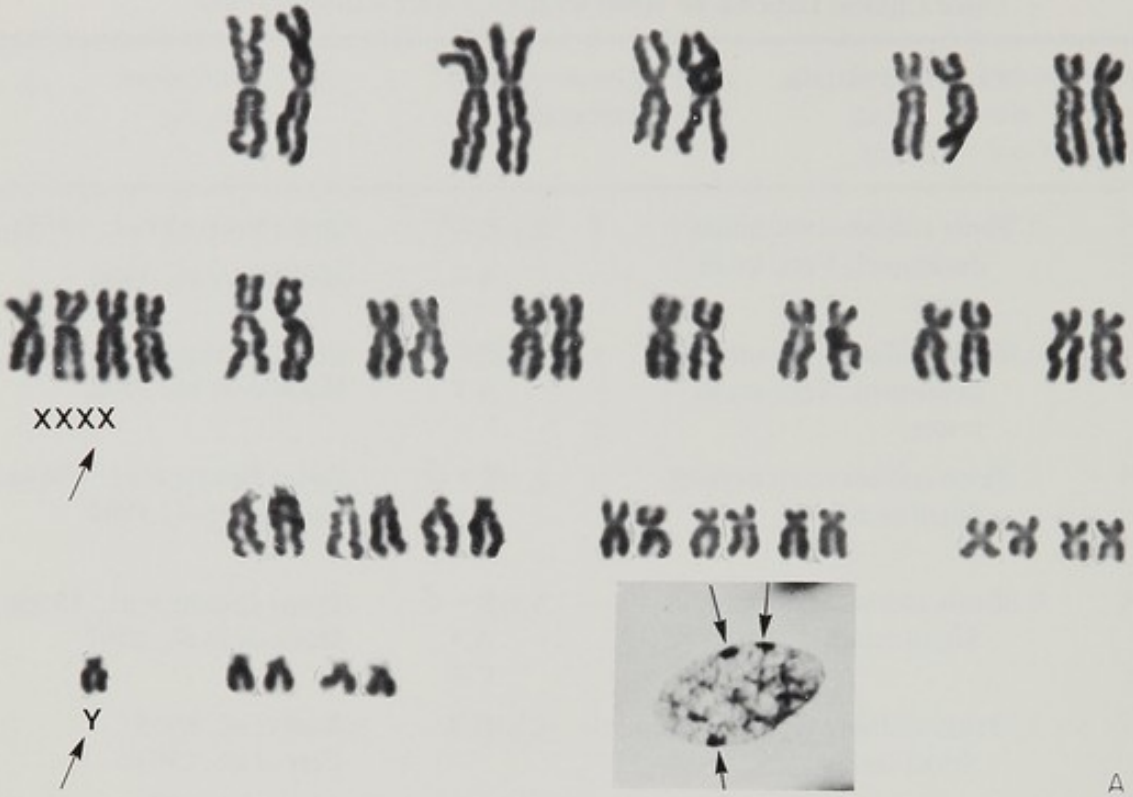
[a] Here MD stands for mental defective.
[b] See Footnote *a* Table 1-16 for definitions.
[c] Sex chromatin studies only.

of successive nondisjunction at meiosis I and II during oogenesis. Other possibilities are nondisjunction at meiosis I during oogenesis, which would result in an XX ovum and nondisjunction of the X chromosome at meiosis I and II and the Y chromosome at meiosis I, which would give rise to XXY sperm. Yet a further possibility is mitotic nondisjunc-

Some Clinical Data on 10 Males with 48,XXXY Chromosomes

Paternal age (years)	External genitalia	Gyne-comastia	Hair[b]	Reference
20	Penis and scrotum under developed. Very small testes.	±	P ± ♀ A –	Court Brown *et al.*, 1964a Maclean *et al.*, 1962
30	Penis and scrotum under-developed. Very small testes.	+	P ± ♂ A ± F –	Court Brown *et al.*, 1964a Maclean *et al.*, 1962
39	Penis and scrotum normal. Small testes.	–	P + ♂ A + F ±	Court Brown *et al.* 1964a Maclean *et al.*, 1962
34	Penis and scrotum normal. Small testes.	–	P + ♂ A + F ±	Court Brown *et al.*, 1964a Maclean *et al.*, 1962
41	Penis and scrotum normal. Small testes	–	N.K.	Barr *et al.*, 1959 Carr *et al.*, 1961b
37	Penis small. Testes very small.		P ?+♂ A F ±	Barr *et al.*, 1959
28	Penis normal. Testes normal.		P + ♂ F +	Barr *et al.*, 1959
23	Penis normal. Testes small.	±	N.K.	Barr *et al.*, 1959
52	Penis and scrotum normal. Testes small.	–	P ++ ♂ A ± F ±	Ferguson-Smith *et al.*, 1960b
31	Penis and scrotum small. Testes very small.	+	P + ♂ A + F –	Ferguson-Smith *et al.*, 1960b
33.5				

tion at the first cleavage division of both X chromosomes in an XXY zygote. This would result in a 49,XXXXY and 45,Y cell line, the latter probably being nonviable. The failure to find any parental age effect suggests that either the error is postzygotic or, if meiotic, that it affects both spermatogenesis and oogenesis equally (see also Volume I, Chapter 7).



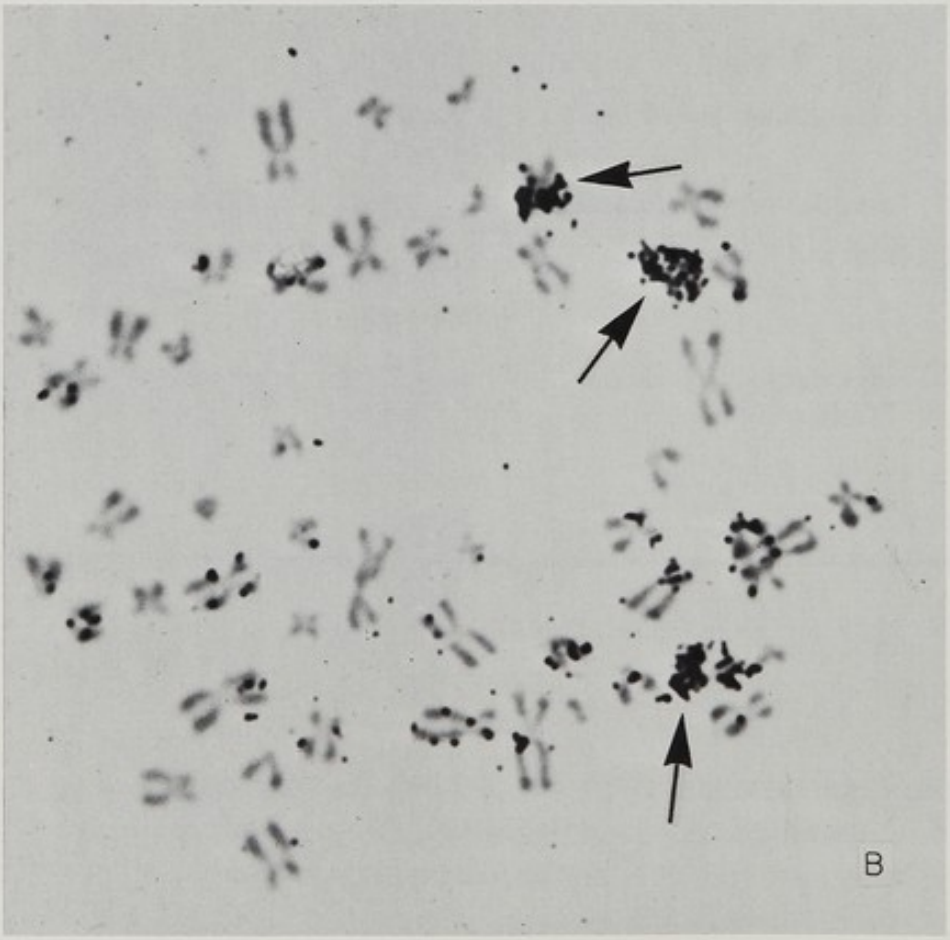


FIG. 1-9. A. Karyotype of male with triple sex chromatin masses (insert) and a 49, XXXXY chromosome complement (karyotype ×619). B. Metaphase plate showing three late-replicating X chromosomes on right (×2700). (B. By courtesy of Dr. F. Giannelli.)

Five mixoploid males with a 49,XXXXY cell line have been described, and these show an intermediate phenotype between the 48, XXXY males with Klinefelter's syndrome and the full 49,XXXXY syndrome (Table 1-20). Perhaps the most likely origin of these subjects is loss of one X chromosome during cleavage of an XXXXY zygote.

III. Chromatin-Negative Males with Two Y Chromosomes

A. *Phenotype*

Until 1965 only about a dozen 47,XYY males (Fig. 1-14) had been reported in the world literature (Table 1-21). Probably the first recorded case was that of a child with Sturge-Weber's syndrome with what was originally thought to be an additional G group autosome but which was subsequently identified as a Y chromosome (Hayward and Bower, 1960; Dent *et al.*, 1963). The phenotype associated with this chromosome constitution is relatively symptomless, the early cases being referred because of hypogonadism, abnormal external genitalia, Marfan's syndrome, occasional cryptorchidism, and various other nonspecific features (Table 1-21). More recently, a few individuals have been ascertained at both pediatric and adult psychiatric clinics because of behavioral problems and height. Two children were ascertained because they had Down's syndrome and proved to be double aneuploids (48,XYY,G+). The mean height of seven adults (Table 1-21) of whom only two were ascertained because of height is 191.5 cm. Among the children, the majority are tall, several having heights which fall above the ninety-fifth percentile for their age.

Interest in the effect of two Y chromosomes was aroused by the finding of a high proportion of 48,XXYY males in institutions for the criminally insane (Casey *et al.*, 1966a, 1968). Jacobs and her colleagues (1965, 1968) studied the chromosomes of 315 male patients in a Scottish maximum security hospital and among these they found nine 47,XYY males, six of whom were over 180 cm tall. It is clear from this and previous studies that the majority of these males are characterized by excessive height, and in more recent surveys a height of 180 cm and above has been one of the main selection criteria. The findings in five such surveys (Table 1-22) show that the frequency of a 47,XYY chromosome complement among tall criminal or psychopathic males is extremely high, varying from 3 to 24% depending on the type of population; this chromosome complement is found most frequently among mentally subnormal criminals. Recently, Court Brown *et al.* (1968) have reported a further

TABLE 1-18

Reference	IQ	Mongoloid slant	Epicanthal folds	Strabismus	Wide-set eyes	Shape of nose	Ears malformed
Fraccaro *et al.*, 1960a	Retarded	No	?+	No	+	Wide, flat, upturned	Too large
O.J. Miller *et al.*, 1961	21	+ Asym.	No	+	+	Flat	Abnormal
J.H. Fraser *et al.*, 1961	About 33	?	?	+	No	Normal	Normal
Turpin *et al.*, 1962a	Retarded	?	?	?	+	Flat bridge	Low set
Fraccaro *et al.*, 1962b	35	No	?	No	+	Wide bridge	?
Barr *et al.*, 1962b (1)	20	+ (Slight)	+	+	+	Wide, upturned	Normal
Barr *et al.*, 1962b (2)	About 60	+ (Slight)	?	+	+	Wide bridge	?
Pfeiffer, 1962	Retarded	?	+	+	+	?	?
De la Chapelle 1963	35	+ (Slight)	No	+	+	Wide, flat, upturned	Asymmetrical
Schade *et al.*, 1963	Severely retarded	+	+	Eyes abnormal	+	Wide, flat	Abnormal
R.W. Day *et al.*, 1963a	53	?	+	No	No	?	Malformed
Thuline unpublished Quoted by R. W. Day *et al.*, 1963a	45	?	?	?	?	?	?
Scherz and Roeckel, 1963	30	+	+	+	+	Wide, flat, upturned	Large well formed
Atkins *et al.*, 1963	Retarded	+ (Slight)	?	No	+	?	Abnormal

Clinical Data on 29 49,XXXXY Males [a]

Neck	Limitation of movement in elbow	Fifth finger	Hip or knee abnormalities	Feet abnormalities	Penis	Testes	Scrotum
Short	+	?	Normal	Abnormal toes	Very small	Very small +	Hypoplastic
Short	No	Normal	Genu valgum, coxa valga	Pes planus	Small	Very small	Hypoplastic
Normal	+	Curved	Coxa valga	Normal	Normal	Undescended	Hypoplastic
Short, webbed	?	Short, curved	Normal	Abnormal	Very small	Small +	Abnormal
Short	+	Short, curved	Genu valgum	Pes planus	Small	Undescended	Rudimentary
Normal	+ ?	Curved	Coxa valga	Abnormal, pes planus	Very small	Undescended	Normal
?	+	Normal	Coxa valga	?	Very small	? normal	Hypoplastic
?	?	Curved	? Normal	Deformed	Small	One undescended	Hypoplastic
Short	+	Curved	Coxa valga, genu valgum	Malformed toes, pes planus	Very small	Small	Hypoplastic
Short	+	Curved	Abnormal	Pes planus, abnormal toes	Small	Undescended	Very hypoplastic
Short	+	Short, curved	Normal	Pes planus, restricted dorsiflexion	Small	Normal +	Normal
?	+	?	Coxa valga	Normal	Low normal	Small +	Normal
?	+	Curved	Normal	Pes planus, restricted dorsiflexion	Small	Small +	Hypoplastic
Short, broad	No	Curved, short	Normal	Deformed toes	Small	Small +	Hypoplastic

TABLE 1-18 (cont'd)

Reference	IQ	Mongoloid slant	Epi-canthal folds	Strabismus	Wide-set eyes	Shape of nose	Ears malformed
Farquhar and Walker, 1964	About 50	+ (Slight)	+	+	? (Slight)	Wide bridge	Abnormal
Joseph *et al.*, 1964 (1)	40	+	+	?	+	Flat, wide, upturned	Mal-formed
Joseph *et al.*, 1964 (2)	50	+	+	No	+	Wide bridge	Normal
Blatch, 1964	60	+	+	No	++	?	?
Jancar, 1964 (1)	19	No	+ (Slight)	No	+	Wide	Simply formed
Jancar, 1964 (2)	23	No	+ (Slight)	No	+	Wide	Simply formed
Prader *et al.*, 1964	Severely retarded	?	?	?	No	?	Normal
F.J.W. Lewis *et al.*, 1964	Retarded	?	?	?	?	?	?
Sacrez *et al.*, 1965	Retarded	Anti-mong.	No	+	+	Flat bridge	Low set
Van Went *et al.*, 1965	Imbecile	?	+	?	+	Flat, wide	Malformed
Zaleski *et al.*, (1) 1966	21	+	+	+	+	Flat, wide	Asym-metrical
Zaleski *et al.*, (2) 1966	34	+	+	+	+	Flat, broad	Malformed
Zaleski *et al.*, (3) 1966	24	+	+	No	No	Broad, flat bridge	Malformed
Makino, 1966	30	+	?	+	+	Broad, flat	?
Atkins and Connelly, 1963	Retarded	?	+	?	?	Flat	Low set, small

[a] Modified from Zaleski *et al.*, (1966).

Neck	Limitation of movement in elbow	Fifth finger	Hip or knee abnormalities	Feet abnormalities	Penis	Testes	Scrotum
Normal	+	Curved	Coxa valga	Part syndactyly	Small	Very small	Hypoplastic
Short, slightly webbed	+	Curved	Normal	Normal	Small	Undescended	Abnormal
Short, webbed	+	Normal	Normal	Normal	Small	Undescended	Abnormal
?	No	Short, curved	Genu valgum	?	Normal	Normal	Normal
Short	+	Short, curved	Coxa valga, genu valgum	Right talipes varus, left pes planus	Small	Small	Hypoplastic
Normal	+	Curved, short	Genu valgum	Pes planus	Very small	Small	Rudimentary
?	+	Curved	Normal	Abnormal	Very small	One only and small	Hypoplastic
?	?	Curved	?	Deformed feet	Small	Absent	Hypoplastic and bifid
Short	+	Curved	?	No	Small	Small +	Hypoplastic
?	+	Curved	?	?	Small	Small +	Small
Normal	+	Short, curved	Coxa valga	Pes planus, malformed toes	Normal	Small +	Normal
Short, webbed	+	Short, curved	Coxa valga	Wide gap, I and II toes	Small	Small	Small
Short	+	Short, curved	Coxa valga	Wide gap, I and II toes	Normal	Small	Normal
Normal	+	Short, curved	?	?	Small	Very small	Normal
?	+	Short, curved	?	?	Small	Right normal, left undescended	Small

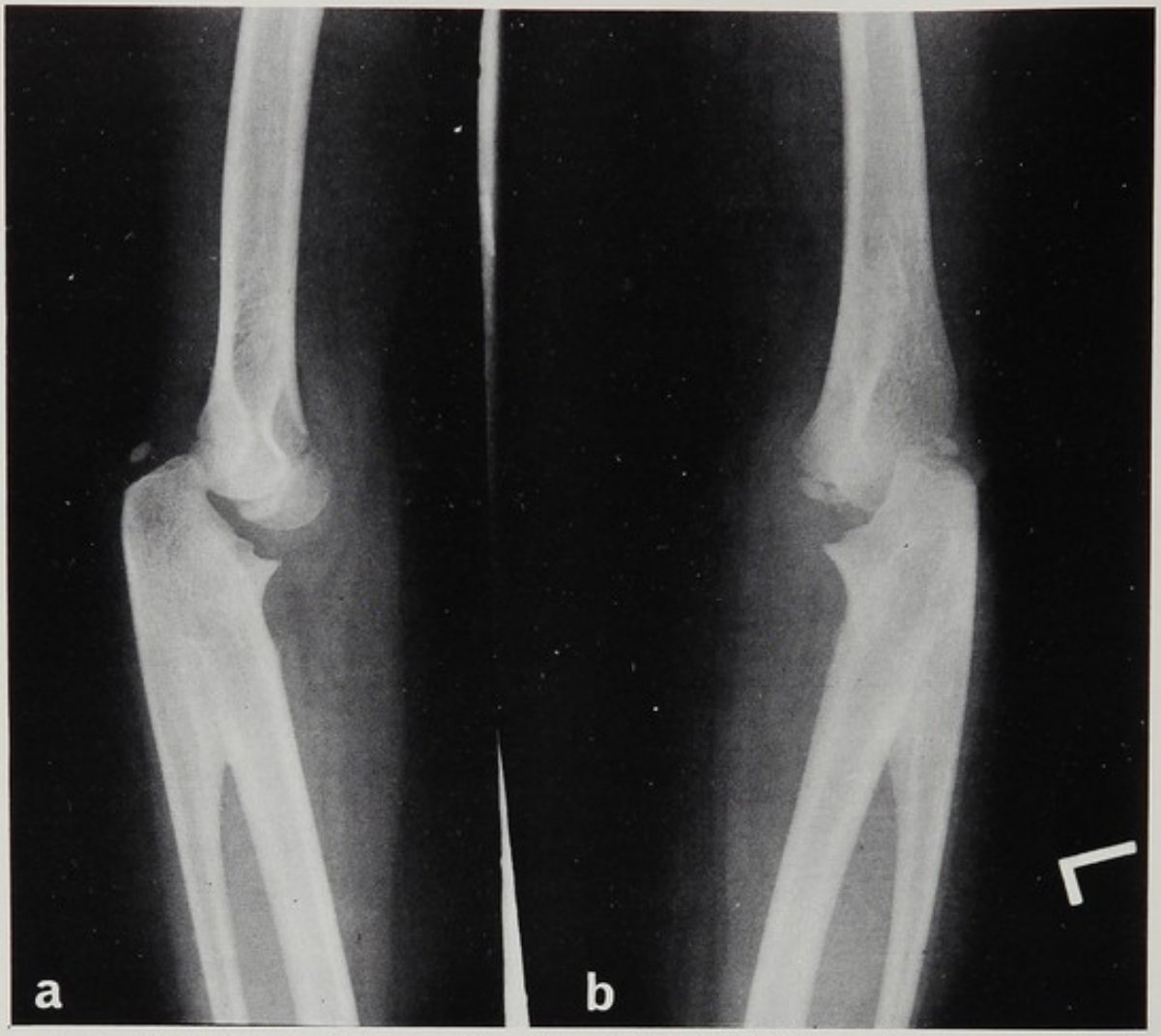


FIG. 1-10. X-ray of forearm of a child with 49,XXXXY sex chromosomes showing synostosis of the proximal portions of the radius and ulna. (a) right arm (b) left arm.

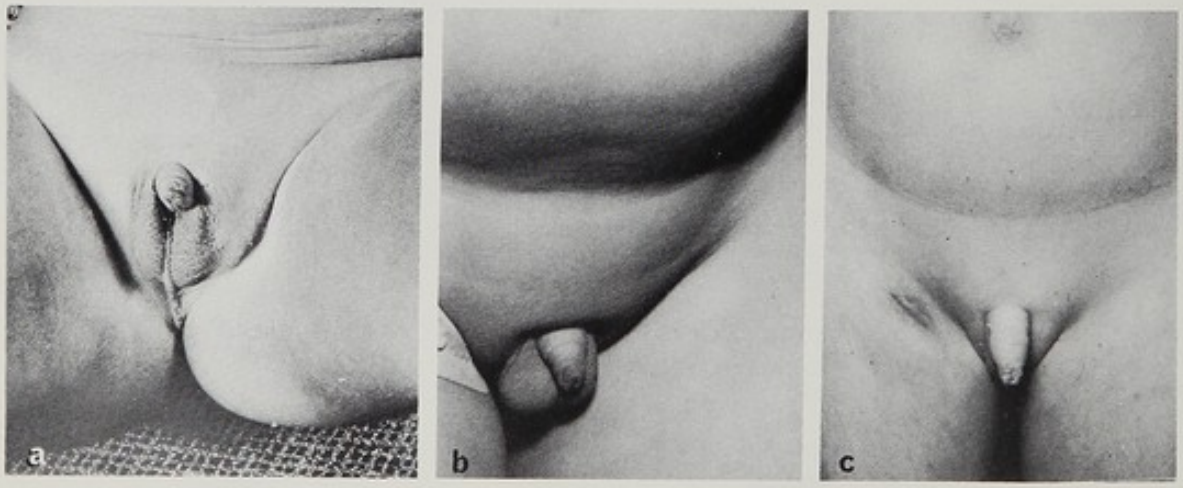


FIG. 1-11. External genitalia of three children with 49,XXXXY sex chromosomes showing extreme hypogenitalism in each case: (a) Rugose thickening of scrotum, undescended testes, (b) small penis and scrotum with testes, and (c) small penis and poorly developed scrotum. (Reproduced by permission of (a) Dr. I. Wickes, (b) Dr. M. Joseph, and (c) Dr. B. Gans.)

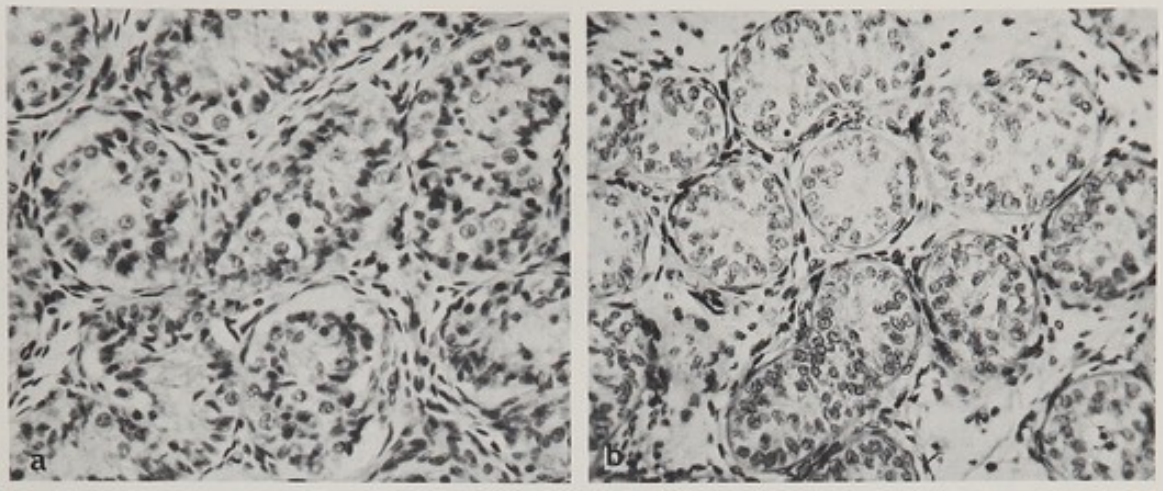


FIG. 1-12. (a) Normal testicular tissue (autopsy) from 6-month-old boy who died shortly after operation for umbilical hernia. Spermatogonia are present in 60% of tubular cross sections. Hematoxylin and eosin stain ×141. Reproduced from Barr *et al.*, 1962b.) (b) Testicular biopsy specimen from an infant with a 49,XXXXY chromosome complement showing normal appearance of interstitial tissue and tubular walls and only questionable reduction of tubular diameter. There is a significant lack of spermatogonia, cells that are probably degenerating spermatogonia being found in only 2% of tubular cross sections.

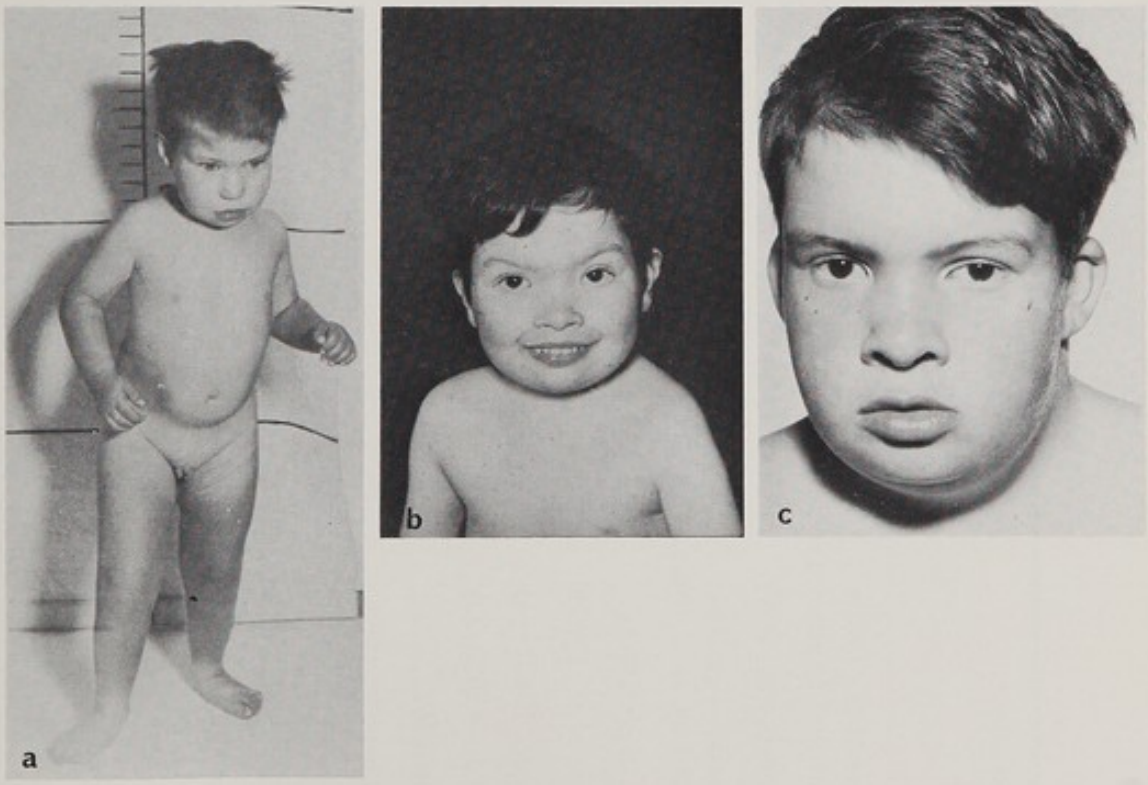


FIG. 1-13. Facies and physical appearance of three children with 49,XXXXY sex chromosomes: (a) age 4½ years, (b) age 5½ years, and (c) age 9 years. (Reproduced by permission of (a) Dr. I. Wickes, (b) Dr. M. Joseph, and (c) Dr. B. Gans.)

TABLE 1–19

Maternal and Paternal Ages and Other Data on Twenty-nine 49,XXXXY Males

Reference	Age of patient (years)	Maternal age (years)	Paternal age (years)	Height (cm)	Birth weight (gm)	Head circumference (cm)	Gestation
Fraccaro *et al.*, 1960a Fraccaro and Lindsten 1960	7	23	29	–	2400	–	Term
O.J. Miller *et al.*, 1961	21	23	32	164.0	–	–	?
J.H. Fraser *et al.*, 1961 Court Brown *et al.*, 1964a	8 6/12	22	24	107.0	–	–	?
Turpin *et al.*, 1962a	3 6/12	25	–	–	2460	–	Term
Fraccaro *et al.*, 1962b	12	26	29	147.3	3175	52.1	Term
Barr *et al.*, 1962b (1)	4 8/12	23	24	100.3	2566	48.3	Term
Barr *et al.*, 1962b (2)	4 7/12	38	38	66.0	3266	41.9	Term
Pfeiffer, 1962	4 9/12	20	23	69.0	–	–	?
De la Chapelle, 1963	18	18	25	163.0	–	–	? (49,XXXX, ?Yq-)
Shade *et al.*, 1963	24	28	27	178.0	3050	–	?
R.W. Day *et al.*, 1963a	4 6/12	29	32	106.0	2183	51.0	Term (breech)
Thuline, unpublished (quoted by R.W. Day), 1963a	19	43	49	179.0	–	–	–
Scherz and Roeckel, 1963	1 5/12	24	25	–	2360	–	43 weeks
Atkins *et al.*, 1963	1 9/12	39	23	76.0	1960	44.5	Term
Farquhar and Walker, 1964	4	25	25	96.5	–	–	Term abnormal birth

Joseph *et al.*, 1964							
(PRU 877)	5	32	32	95.0	2154	–	Term (toxemia)
(PRU 1582)	9	28	30	138.0	3288	–	41 weeks
Blatch, 1964	3	30	32	–	2381	47	40 weeks
Jancar, 1964 (1)	17	41	44	143.0	–	–	Term
(2)	17	26	27	164.0	–	–	Term
Prader *et al.*, 1964	1 6/12	35	36	–	2460	–	?
F.J.W. Lewis *et al.*, 1964,	35	26	26	188.0	–	53.3	?
Sacrez *et al.*, 1965	35 9/12	26	31	–	2010	31.5	?
Van Went *et al.*, 1965	14	40	36	–	–	–	?
Zaleski *et al.*, 1966 (1)	7 6/12	31	34	114.3	2040	49.8	34 weeks
(2)	7	22	26	127.0	2500	50	4 weeks premature
(3)	19 10/12	27	29	173.0	2950	–	Term breech
Makino *et al.*, 1964a							
Makino, 1966	12	21	25	142.0	–	–	?
Atkins and Conelly, 1963	2 9/12	29	31	–	3000	–	? (Postmature)
Mean		28.3(29)[a]	30.1(28)[a]		2567(18)[a]		

[a] Figures in parentheses are the numbers of subjects.

TABLE 1-20

Reference	Chromosome analysis	Age on exam. (years)	IQ	Mongoloid slant	Epicanthal folds	Strabismus	Wide-set eyes	Shape of nose
G. Anders *et al.*, 1960	48,XXXY/ 49,XXXXY/ 50,XXXXXY	8½	Severely retarded	No	+	+	No	Flat, broad
Lamy *et al.*, 1963	48,XXXY/ 49,XXXXY	2½	57	?	?	?	?	Broad bridge
Gilbert-Dreyfus, *et al.*, 1963	48,XXXY/ 49,XXXXY/ 50,XXXXYY	28	52	–	?	?	?	?
B. Turner *et al.*, 1963	48,XXXY/ 49,XXXXY	14	Retarded	+	?	+	? yes	Broad
Court Brown *et al.*, 1964a	48,XXXY/ 49,XXXXY	20	Retarded	?	?	?	?	?

[a] From Zaleski *et al.*, (1966).

fifteen 47,XYY males ascertained in various population groups (Table 1-23); 47% of these males were mentally subnormal, and the majority had been convicted for a variety of offenses on a number of different occasions. Despite reported behavioral difficulties a number of these men had managed to avoid conviction until later in life before conviction for petty offenses.

The physical characteristics for 31 47,XYY males ascertained in surveys (Table 1-24) shows that while the majority are of subnormal intelligence, a proportion are of average intelligence. The vast majority have a normal male habitus with normal sexual development; a few have nonspecific malformations of various types. These males are all tall although in this group the significance of this is largely obviated by selection. The mean parental ages do not differ significantly as between "survey selection" (Table 1-24) or "clinical selection," (Table 1-21) the mean maternal age being 28.9 (38 cases) while the mean paternal age is

Clinical Data on Five Mixoploids with a 49,XXXXY Cell Line[a]

Ears malformed	Neck	Limitation of movement in elbow	Fifth finger	Hip or knee abnormalities	Feet abnormalities	Penis	Testes	Scrotum
Simply formed	? Short	+	? Curved	Coxa valga	Pes planus	Normal	Undescended +	Hypoplastic
Low-set	?	? +	?	?	?	Small	Undescended	Hypoplastic
?	?	?	?	?	Club feet	Small	Very small	Near normal
Large asymmetrical	?	+	Curved	?	?	Small	Small	Hypoplastic
?	?	+	?	?	?	Normal	Small	Hypoplastic

31.3 (36 cases) years, which is not significantly different from the general population. There have been a few studies of approved school populations and other "junior criminals," and a relatively high frequency is found among boys tall for their age as well as among those commencing their criminal activities earlier than average (Table 1-25). In the general population, even among the tallest men and newborn boys (Table 1-26) the incidence is very low and possibly lies between 0.2 and 0.05%, but the lack of any rapid screening method makes these figures highly tentative (but see addendum to Volume I).

The behavioral difficulties and frequent criminal behavior of these males does, of course, pose serious social and forensic problems and at the time of writing at least two such cases are pending in the courts, one in the United States and one in France. The nine males identified in the Scottish maximum security prison have without doubt been the most completely studied psychologically (Price *et al.*, 1966; Price and What-

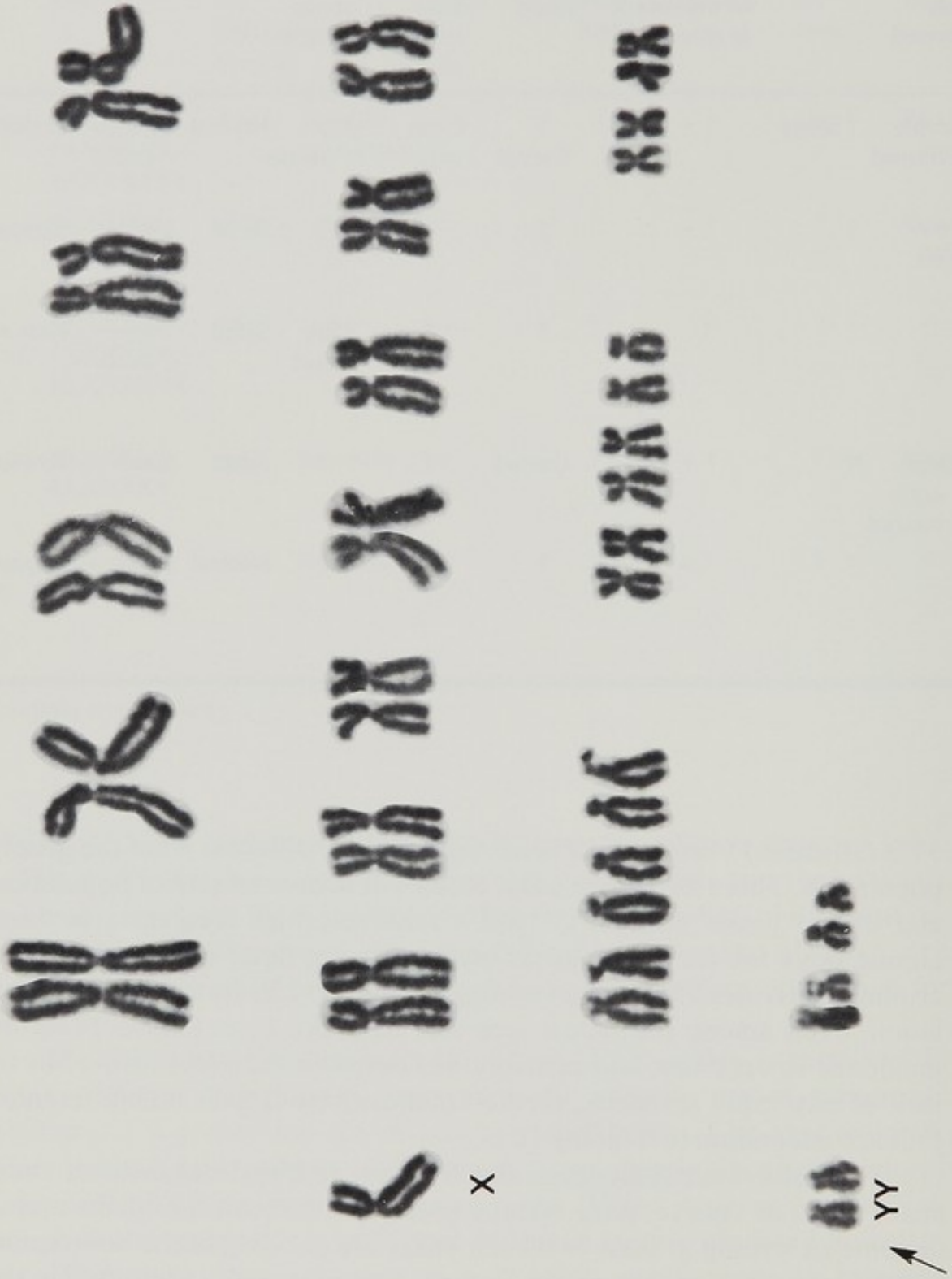


FIG. 1-14. Karyotype of a 47,XYY male (×907).

more, 1967; Hope *et al.*, 1967). These are all tall men with a mean height of 181.2 cm compared with the mean height of 170.7 cm for the 305 men with only one Y chromosome. All nine males suffer from a severe personality disorder of unknown cause; two are of normal and seven of subnormal intelligence. Their criminal behavior was characterized by the following features:

1. They displayed less violence against the person than did the control group. For instance, out of a total of 93 convictions accruing to these nine men, 81 were against property and only nine against the person, compared with 46 against the person and 132 against property for the control XY males.

2. They began their criminal activities on an average five years earlier than did the controls, the average age of the first conviction of the nine 47,XYY males being 13.1 years and the controls 18.0 years.

3. They had no significant family history of crime or mental illness. One out of 31 sibs of the 47,XYY males had one conviction compared with 139 convictions accruing to 12 out of 63 sibs of the 17 XY controls.

4. The criminal behavior of the 47,XYY males was more resistant to conventional forms of corrective training and treatment.

These data are limited, although it is suggested that the 47,XYY male suffers from considerable inherent psychosocial difficulties which make it difficult if not impossible for him to adjust to a normal social environment. These difficulties would seem to be even greater for the 47,XYY than for the 47,XXY male. These men seem to be impulsive and this, combined with their aggression, makes them liable to rather frequent conflict with authority so that many become incarcerated in special security institutions. However, not all these males reach such institutions and some drift along at the edge of society for many years before finally coming before the courts. At present we have little knowledge of the phenotype of those 47,XYY males who do not appear in one of the populations studied. There is little doubt that some are to be found in psychiatric or child guidance clinics, and it may be worth examining a series of tall and hard-to-manage boys (J. Cowie and Kahn, 1968).

B. *Origin*

The most likely origin of these males is paternal nondisjunction at meiosis II resulting in YY spermatozoa (see Volume I, Fig. 7-19). Al-

TABLE 1-21

Patient identification	Age (years)	Maternal age (years)	Paternal age (years)	Height[a] (cm)	Span (cm)	IQ	Birth rank/ sibship
T.S.	5/12	39	40	–	–	–	3/3
P.R.	7	43	47	–	–	Severely retarded	6/6
–	44	–	–	182.9	–	Average	–
G.K.	11 4/12	36	37	–	–	Average	3/6
–	7	–	–	–	–	Average	–
–	12	21	22	180.0(>95)	–	Average	1/3
–	15	19	23	161.0(<80)	–	Subnormal	–
–	3	32	–	–	–	Retarded	–
82/62	23	19	27	180.5	185.5	–	1/4
–	2 1/12	–	–	–	–	Slight retardation	–
–	9	–	–	–	–	Retarded	–
1	64	35	34	191.0	192	Low normal	3/3
–	24	–	–	Av.	–	Mentally retarded	–
–	8 7/12	23	26	144.8(>95)	–	95	–
–	14 9/12	27	24	164.0(>95)	–	Retarded	–

Data on 20 Clinically Ascertained 47,XYY Males

Sexual development	Physical abnormalities	Reference
Right testis undescended, penis abnormal.	Retarded behavior; abnormal right ear, fits.	Fraccaro *et al.*, 1962a
Testes undescended, penis normal.	Hypertelorism, fits, prominent ears.	Fraccaro *et al.*, 1962a
Normal. Two marriages. 7 children – first. 3 children – second. Last G+ D.S. 2 abnormal 5 ♂3 ♀	None	Hauschka *et al.*, 1962
? Normal	Marfan's syndrome CP/PS = 0.84. Tall.	Hustinx and Van Olphen, 1963
Hypospadias; small penis small testes in scrotum.	–	Milcu *et al.*, 1964a
Penis normal. Right testis scrotal; Left not palpable.	Obese	Sandberg *et al.*, 1963a
Normal adult	Normal male habitus	Ricci and Malacarne, 1964
–	Sturge-Weber's syndrome	Hayward and Bower, 1960; Dent *et al.*, 1963
Penis and scrotum under-developed; testes very small, ? Palpable.	Axilliary and pubic hair sparse ♂. Facial hair – gynecomastia – talipes equinovarus, high arched palate.	Court Brown *et al.*, 1964a
Penis normal; undescended testes.	Hypotonic, delayed osseous development.	Dunn *et al.*, 1961
Normal	Down's syndrome (48,XYY, G+,)	Verresen and Van den Berghe, 1965
Penis and scrotum normal, testes small, prostate normal.	Moderate gynecomastia	Balodimos *et al.*, 1966
Normal penis, scrotal testes, pubic hair ♂	Webbed neck	Kelly *et al.*, 1967
Normal	None; "difficult to manage child"	J. Cowie and Kahn, 1968.
Small penis, no pubic hair, small scrotum.	Skeletal anomalies	Kosenow and Pfeiffer, 1967

TABLE 1-21 (cont'd)

Patient identification	Age (years)	Maternal age (years)	Paternal age (years)	Height[a] (cm)	Span (cm)	IQ	Birth rank/ sibship
–	44	–	–	198.0	–	118	1/5
–	6/12	21	28	–	–	Down's syndrome	–
–	23	–	–	188.0	–	Normal	2/2
1	31	26	30	203.2	–	125	1/?
2	15	31	32	196.9	–	100	2/?
Mean		28.6 (13)	30.8 (12)	191.5 (7 adults)			

[a] In prepubertal subjects the height percentile for age is given in brackets.

ternatively, postzygotic nondisjunction in an XY zygote would give 45,X and 47,XYY cell lines and such mosaics have been found. Either selection in favor of the 47,XYY line or exclusion of the 45,X line from the embryo proper would result in an apparently "pure" 47,XYY zygote. An excellent review of our knowledge of the XYY male has been published recently (Court Brown, 1968).

IV. The Effect of Sex Chromosome Heterochromatin in the Male

The presence of additional sex chromosomes increases the amount of heterochromatin but not the amount of euchromatin in the cell (Hamerton, 1968b) (see Table 4-5). The phenotypic effects both on sex determination (Chapter 4) and on certain somatic characters must therefore be controlled through the heterochromatin. The main somatic characters involved are quantitative, such as stature and psychosocial development, and therefore perhaps open to control through heterochromatic blocks (Commoner, 1964).

A. *Stature*

Increase in sex chromosome heterochromatin affects the mean stature of each group of subjects with a particular abnormal chromo-

Sexual development	Physical abnormalities	Reference
Normal ♂	None	Leff and Scott, 1968
Normal infantile ♂	Radioulnar synostosis, clinodactyly, Down's syndrome 48,XYY, G+	Migeon, 1965a
? Normal	Normal	Matthews and Brooks, 1968
Normal	"Hard to manage"; no physical abnormality	Borgaonkar *et al.*, 1968
Normal	Behavioral problems; no criminality.	Borgaonkar *et al.*, 1968

some complement. Males who have a 46,XY chromosome complement are on the average shorter than those with 47,XXY or 48,XXXY, while the 47,XYY and 48,XXYY subjects are on the average taller than any of the above groups (Fig. 1-15). There is some evidence that the growth of males with additional X chromosomes may differ from those with two Y chromosomes. In general the presence of multiple X chromosomes leads to a greater excess of limb than trunk growth while the excess of Y chromosomes seems to result in a greater than usual size throughout childhood. These observations combined with those for women (Chapter 2) suggest that "controlling centers" for growth are present on the heterochromatic Y and probably the short arm of the heterochromatic X.

B. *Psychosocial Development*

We have already seen that sex chromosome abnormalities in the male lead to behavioral disturbances possibly resulting from difficulties of adjustment to normal adult life or perhaps in the case of the chromatin-positive male from postpubertal testicular atrophy (Hambert, 1966). This, however, cannot account for the effect of two Y chromosomes because the majority of these males apparently have normal testes and some are fertile although a few have hypogonadism (Court Brown, 1968).

TABLE 1–22

The Frequency of 47,XYY Males in Populations Mentally of Abnormal Criminals and Other Males Requiring Special Security Treatment

Reference	Ascertainment of population and selection criteria	Height (cm)	Total no. studied	No. 47,XYY	Proportion 47,XYY
Casey *et al.*, 1966b	Detained for antisocial acts.				
	Mentally subnormal	>182.9	50	12	0.24
	Mentally ill		50	4	0.08
	Intermediate sentence, criminals, England		24	2	0.08
Wiener *et al.*, 1968	H.M. Prison Pentridge, Melbourne	>182.9	34	4 (1 47,XYY/48,XYYY)	0.12
Nielsen, 1968	State Hospital and Psychiatric Ward, Denmark	>180	23	3	0.13
Nielsen *et al.*, 1968	Psychologically abnormal criminals, Denmark	>180	35	2	0.05
Jacobs *et al.*, 1965	Maximum Security Hospital, Scotland	Unselected	315	9	0.03
Jacobs *et al.*, 1968	Maximum Security Hospital, Scotland	>180	(28)[a]	(6)[a]	0.21

[a] Included in the unrelated group (Jacobs *et al.*, 1965).

TABLE 1–23

Ascertainment of fifteen 47,XYY Males[a]

Type of population	47,XYY	Proportion
Mentally subnormal males >178 cm	6	0.47
Mentally subnormal males (one hospital no height restriction)	1	
Male babies	1	0.53
Psychiatric clinic	1	
Mentally diseased males >183 cm	1	
All males referred for Borstal Training, Scotland, 12 months	1	
Young offenders institution >178 cm	1	
Epileptic males (no height)	1	
Prisoners in Scotland >178 cm	1	
Patients receiving intra-arterial thorotrast	1	
Total	15	

[a] Court Brown *et al.* (1968).

C. *The Action of Heterochromatin*

Hamerton (1968b) has suggested that abnormalities in the dose of sex-chromosome-derived heterochromatin affect both stature and psychosocial development. Testicular atrophy at puberty may also affect behavior in the multiple-XY males (Hambert, 1966; Maclean *et al.*, 1968). Both these somatic characteristics are usually thought to be controlled by a number of genetic factors interacting with the environment. They are, therefore, characteristics of a type which might be expected to be controlled through heterochromatin. Heterochromatin may act by controlling various cellular functions, perhaps by nucleotide sequestration (Commoner, 1964) or more likely by a close control of mRNA production at specific times and in specific cells. For instance, abnormal amounts or types of mRNA production in appropriate brain cells could result in abnormal behavioral responses. Similarly, abnormal cellular metabolism in appropriate growth centers could result in the abnormal growth seen in certain individuals with sex chromosome abnormalities.

TABLE 1-24

Patient No.	Age (years)	Maternal age (years)	Paternal age (years)	Height (cm)	Span (cm)	Pubis-sole (cm)	IQ[a]	Birth rank/ sibship
120/65	31	27	30	186	–	86.5	MS	2/5
122/65	32	32	35	175	172	86.0	MS	8/9
123/65	39	20	22	177	181	91.0	MS	1/5
132/65	17	23	30	183	178	89.0	Av	1/2
134/65	31	41	41	181	187	89.0	MS	5/5
141/65	28	23	22	186	188	97.0	MS	1/5
150/65	22	28	34	171	176	97.0	MS	4/7
152/65	28	32	37	184	191	87.0	Av	3/6
142/65	34	22	–	188	201	91.5	MS	2/4
76/66	17	30	30	169	–	–	86	–
290/67	0	25	23	–	–	–	–	–
289/67	13	29	36	202	–	–	–	–
255/67	16	24	16	189	–	–	av	–
341/67	17	32	33	199	–	–	MS	–
356/67	38	29	31	182	–	–	–	–
342/67	38	28	30	185	–	–	–	–
140/67	45	36	37	186	–	–	76	–
317/67	53	27	33	188	–	–	–	–
404/67	32	–	–	170	–	–	59	–
364/67	34	–	–	183	–	–	av	–
395/67	48	–	–	184	–	–	42	–
340/67	52	–	–	198	–	–	62	–
394/67	53	–	–	185	–	–	78	–
405/67	62	–	–	185	–	–	–	–
1	26	24	26	182	–	–	93	2/4
2	26	22	27	200	–	–	94	2/8
3	24	39	43	192	–	–	100	9/12
3	–	46	43	210	–	–	101	8/?
5	–	29	32	178	–	–	71	2/?
17	–	29	33	178	–	–	94	4/?
19	–	32	38	182	–	–	84	4/?
Mean		29.2 (25)[b]	31.8 (24)	185.3 (30)	184.3 (8)	90.4 (9)		

[a] Here MS stands for mentally subnormal, av stands for average.

[b] Figures in parentheses are the numbers of subjects.

Physical Characteristics of Thirty-one 47,XYY Males Ascertained in Surveys of Mentally Abnormal Criminals and Other "Hard to Manage" Males

Sexual development	Physical abnormalities	Convictions	Reference
Normal	Bilateral genu varum	12	Jacobs *et al.*, 1968
Normal	Acne, prognathism	14	Jacobs *et al.*, 1968
Normal	None	9	Jacobs *et al.*, 1968
Normal	Very obese	5	Jacobs *et al.*, 1968
Normal	None	1	Jacobs *et al.*, 1968
Normal	None	2	Jacobs *et al.*, 1968
Normal	None, obese	35	Jacobs *et al.*, 1968
Normal	None	7	Jacobs *et al.*, 1968
Normal	None	3	Jacobs *et al.*, 1968
Normal	Bilateral genu valgum	–	Court Brown *et al.*, 1968
Normal infantile	None	–	Court Brown *et al.*, 1968
?	?	–	Court Brown *et al.*, 1968
Normal	None	–	Court Brown *et al.*, 1968
Normal	Bilateral gynecomastia	–	Court Brown *et al.*, 1968
Normal	Myopia	–	Court Brown *et al.*, 1968
?	?	–	Court Brown *et al.*, 1968
Normal	None	–	Court Brown *et al.*, 1968
Normal	Varicose ulceration	–	Court Brown *et al.*, 1968
Normal	Congenital heart disease	–	Court Brown *et al.*, 1968
Normal	None	–	Court Brown *et al.*, 1968
Normal	Multiple facial sebaceous adenomata	–	Court Brown *et al.*, 1968
Normal	None	–	Court Brown *et al.*, 1968
Normal	None	–	Court Brown *et al.*, 1968
Normal	Previous varicose ulceration	–	Court Brown *et al.*, 1968
Normal	None	–	Nielsen, 1968
Normal	None	–	Nielsen, 1968
Normal	None	–	Nielsen, 1968
Normal	None	–	Wiener *et al.*, 1968
Normal	None	–	Wiener *et al.*, 1968
Normal	None	–	Wiener *et al.*, 1968
Normal	None	–	Wiener *et al.*, 1968

TABLE 1–25

Frequency of 47,XYY Males in Two Groups of "Junior Criminals"

Reference	Type of population and selection		No. studied	47,XYY	Proportion
Hunter, 1968	Approved school Age range 12–19 years	>90 P[a]	29	3	0.10
Kahn, 1968	Remand home	Random	200	1	0.005
		>75 P[a]	29	1	0.034
	Borstal Penal Institution	Random	100	–	–

[a] Here P stands for percentile for height.

The concept of controlling centers introduced into the cell by the heterochromatinization of some of the X chromosomes and the Y chromosome is discussed in more detail in Chapter 4. Abnormal dosage of these controlling centers could cause abnormal cellular metabolism to give the phenotypes seen.

TABLE 1–26

Frequency of 47,XYY Males in Various Control Groups

Type of population and selection	Total No. studied	No. 47,XYY	Incidence	Reference
Newborn males	3496	5	–	Court Brown *et al.*, 1968 Ratcliffe *et al.*, 1970
Newborn males	1066	4	–	Sergovich, *et al.*, 1969.
Newborn males	1931	0	–	Walzer *et al.*, 1969
Newborn males	2222	3	–	Lubs and Ruddle, 1970
Total newborn males	6785	12	1:700	
Mentally ill >182 cm	30	0	–	Casey *et al.*, 1966b
Normal males >182 cm	30	0	–	Casey *et al.*, 1966b
College basketball players, United States, 180–208 cm	36	0	–	Goodman *et al.*, 1968

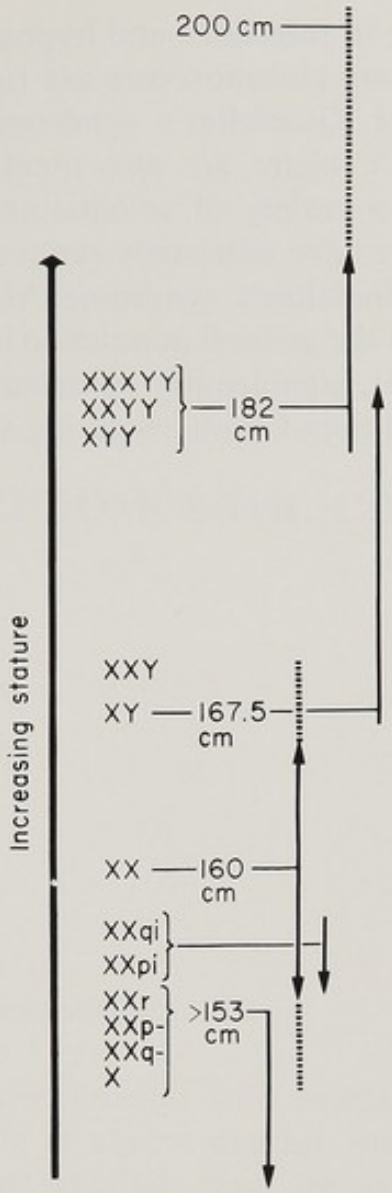


FIG. 1-15. Schematic diagram to show the effect of various aneuploid sex chromosome complements on stature.

V. Conclusions and Summary

In the present chapter the data which have become available on the abnormal sex chromosome complements in the male have been summarized and the phenotypic features of the major categories have been discussed. Chromatin-positive males with single masses and 47,XXY, 48,XXYY, or 46,XY/47,XXY sex chromosomes comprise the majority of patients with chromatin-positive Klinefelter's syndrome and make a

significant contribution to infertility and hypogonadism in the male. Patients with 48,XXXY sex chromosomes are rarer but may also be categorized as a variant of Klinefelter's syndrome with invariable mental retardation. 49,XXXXY males are also mentally retarded and form a distinctive group with a variety of somatic and skeletal anomalies and are often cryptorchid or have extremely reduced genitalia. These form a group distinct from Klinefelter's syndrome. Males with two Y chromosomes are infrequent in the general population and form an asymptomatic group. Others, however, significantly contribute to mentally subnormal and aggressive criminal populations requiring special security.

Chapter 2

ABNORMAL SEX CHROMOSOME COMPLEMENTS IN THE FEMALE

I. OVARIAN DYSGENESIS

A. *Classification and Nomenclature*

Postpubertal phenotypic females with ovarian dysgenesis have primary amenorrhea, infantile or absent ovaries, little or no pubic or axillary hair, infantile external genitalia, and are usually of short stature. This syndrome was described first in adult women by H. H. Turner (1938); previously Ullrich (1930) had drawn attention to a similar syndrome associated with other multiple anomalies and occurring both in boys and in girls. However, he did not observe the association between the syndrome he described and failure of secondary sexual differentiation, largely because he was looking at the condition in prepubertal children. Turner (1938) considered the skeletal and other anomalies including sexual infantilism to be those associated with pituitary deficiency; however, Sharpey-Schafer (1941) pointed out that it was probably the ovaries which were primarily defective and that pituitary function was normal. Endocrine investigations of these women revealed an increased output of pituitary gonadotrophins accompanied by low estrogen levels (Albright *et al.*, 1942; Varney *et al.*, 1942). Albright and his co-workers also obtained direct morphological evidence of ovarian maldevelopment, and it was considered that the high gonadotrophin levels accompanied by the low estrogen levels showed that there

was primary gonadal failure (Del Castillo *et al.*, 1947; L. Wilkins, 1957). L. Wilkins and Fleischmann (1944) further showed that this was the essential defect when they demonstrated that "streak gonads" devoid of ovarian follicles were found instead of normal ovaries. It has also been shown that streak gonads and the same hormonal defects are found in women with primary amenorrhea, lack of secondary sexual characteristics, and short stature, but they do not have the gross somatic malformations associated with Turner's syndrome (Albright *et al.*, 1942; Del Castillo *et al.*, 1947; Lisser *et al.*, 1947). The name *ovarian agenesis* was used to describe this syndrome and changed to *gonadal dysgenesis* in the light of the sex chromatin and chromosome findings.

The nomenclature associated with this syndrome is confusing in the extreme, and Hauser (1963a) listed no fewer than 26 synonyms. P. M. F. Bishop *et al.* (1960), Polani (1962), and Hauser (1963a) have distinguished the major clinical groups and the present clinical situation has been summarized clearly by Polani (1962) who distinguished two clinical groups of short women having clinical and hormonal evidence of ovarian maldevelopment:

1. Ovarian dysgenesis with webbing of the neck and other somatic anomalies ("Turner's syndrome in the female"). Other frequently associated anomalies are congenital heart defects, skeletal defects, renal anomalies, and more frequent intellectual subnormality.

2. Ovarian dysgenesis without webbing of the neck. Associated severe or obvious somatic malformations are less common in this group.

Polani further distinguished three distinct clinical variants which are of interest.

1. Pure gonadal dysgenesis. This is a group of women with evidence of primary gonadal failure and without either short stature, webbing of the neck, or other somatic anomalies. In fact some of these females may be tall and of eunuchoid proportions. The etiology of this group, some of whom may have normal male chromosomes and others normal female chromosomes, may be different from the other groups (see Section II, below.)

2. Gonadal dysgenesis with phallic enlargement (Grumbach *et al.*, 1955; Greenblatt *et al.*, 1956). Attention to this condition was first drawn by Gordan *et al.* (1955) though cases had previously been described by Meyer (1925) and Pich (1937-1938). The internal and external genitalia are similar to those in ovarian dysgenesis. Apart from the phallic enlargement the gonadal streaks contain clumps of Leydig cells. Other somatic anomalies are infrequent, and the patients are invariably chromatin negative.

3. Gonadal dysgenesis with male pseudohermaphroditism. These

are present as male pseudohermaphrodites with ambiguous external genitalia (Grumbach *et al.*, 1955; Grumbach and Barr, 1958). Usually one gonad is a testis and the other shows a structure identical to the gonadal streaks seen in ovarian dysgenesis.

Hauser (1963a) considered the characteristics of gonadal dysgenesis to be

> . . . *the absence of germ cells* and the development of female external and internal genital organs (tubes, uterus, vagina, etc.). The gonads are usually represented by remnants of tissue, e.g., ovarian stroma, rete structures, and hilus cells that do not contain any germ cells (follicles).

Small stature and other somatic anomalies (cubitus valgus, webbed neck, coarctation of the aorta, etc.) are not invariably present. Gonadotrophin output is usually increased. Hauser concluded by distinguishing three classes of gonadal dysgenesis based on chromosomal sex. These are XX, XO, and XY gonadal dysgenesis. In view of recent findings which will be discussed in this chapter, such a classification is clearly invalid, and there are many different sex chromosome complements associated with ovarian dysgenesis. Furthermore, any valid classification must be based on the phenotype and not on the chromosome findings. Two categories of ovarian dysgenesis will therefore be recognized (Polani, 1961, 1962).

1. Ovarian dysgenesis with short stature and a variety of other somatic anomalies which will be considered to be synonymous with *Turner's syndrome in the female.*

2. Ovarian dysgenesis with short stature but without other somatic anomalies.

In the two variants pure gonadal dysgenesis and gonadal dysgenesis with male pseudohermaphroditism, the adjective "gonadal" will be retained since there may be some doubt as to the primary gonadal type.

There is yet a further category which can be distinguished; these have many of the somatic anomalies associated with Turner's syndrome such as webbing of the neck, cubitus valgus, and coarctation of the aorta; but they lack evidence of primary gonadal failure, have a normal menstrual cycle, and normal external and internal genitalia. They are also chromatin-positive and usually have a normal female chromosome complement. The name *Ullrich's syndrome in the female* may be used to describe this condition which can be distinguished from chromatin-positive ovarian dysgenesis with webbing of the neck, solely because there is no evidence of primary ovarian maldevelopment in Ullrich's syndrome.

Polani (1962) also included those males who have webbing of the neck in this classification as *Ullrich's syndrome in the male* if gonadal, genital, and secondary sexual development are normal. However, if go-

nadal, genital, or secondary sexual development are abnormal then these can be said to have *Turner's syndrome in the male*.

The possible abnormalities include hypospadias, unilateral or bilateral failure of testis descent (especially if the descended testis in unilateral examples is particularly small after puberty), and postpubertal evidence of testicular involvement, e.g., small size or failure of endocrine or exocrine functions with absent or grossly impaired spermatogenesis.

The various interrelationships between Turner's syndrome (males and females) and Ullrich's syndrome (males and females) and ovarian dysgenesis without webbing of the neck are shown in Fig. 2-1.

B. *Clinical and Etiological Features of Ovarian Dysgenesis*

Clinical and etiological features of ovarian dysgenesis have been reviewed in detail on several occasions (Fig. 2-2) (Lisser *et al.*, 1947;

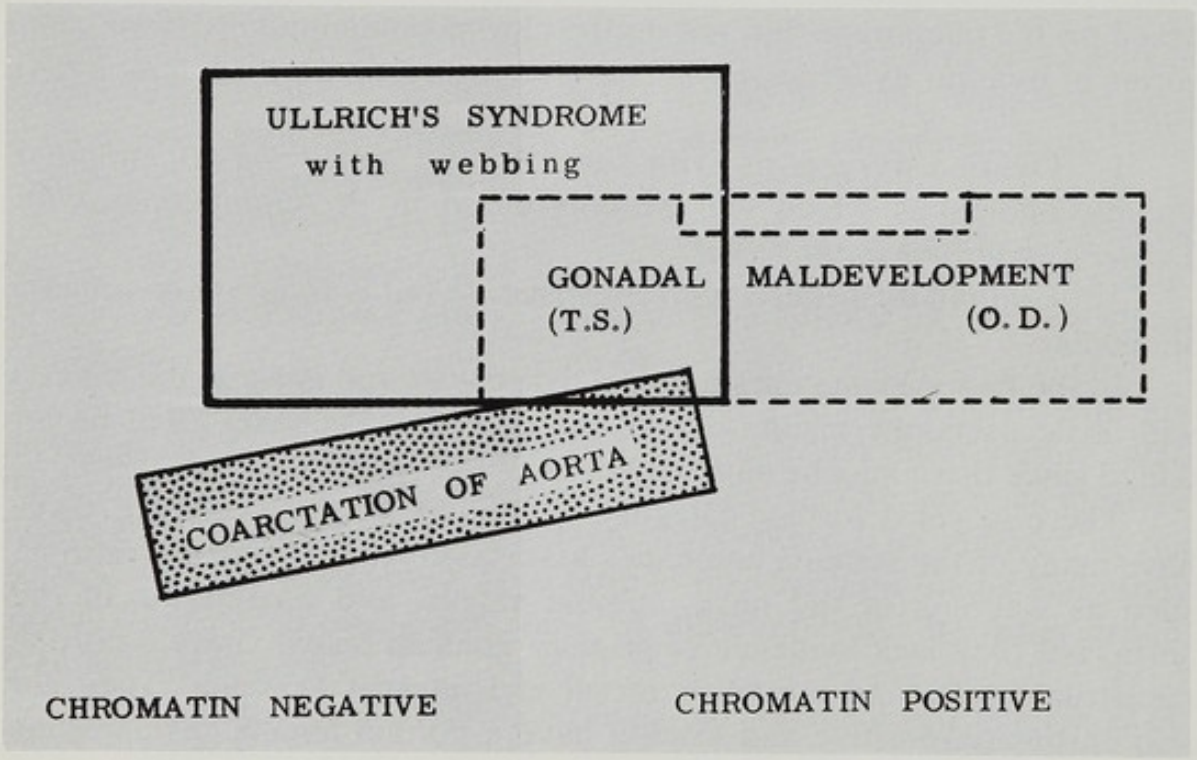


FIG. 2-1. Interrelation of Turner's syndrome (♂ and ♀), Ullrich's syndrome (♂ and ♀), and gonadal dysgenesis. Patients with webbing of the neck have either Turner's syndrome (if the gonads are maldeveloped) or Ullrich's syndrome (if there is no evidence of gonadal maldevelopment). The relative frequency of chromatin-positive and chromatin-negative findings in relation to the different phenotypes is indicated by shading as well as the high frequency of coarctation of the aorta in chromatin-negative Turner's syndrome (T. S.) compared to chromatin-positive ovarian dysgenesis (O.D.). (Modified from Polani, 1962.)

Grumbach *et al.*, 1955; Hoffenberg and Jackson, 1957a,b; Grumbach and Barr, 1958; Haddad and Wilkins, 1959; P. M. F. Bishop *et al.*, 1960; Hauser, 1963a; Polani, 1961, 1962; Levin, 1962).

1. Abnormalities of Sexual Development

Primary amenorrhea is a universal feature of ovarian dysgenesis at puberty, although a few cases of intermittent or even, exceptionally, more regular menstruation have been reported (Hoffenberg *et al.*, 1957; Bahner *et al.*, 1960; Court Brown *et al.*, 1964a). Breast development is usually slight with widely spaced nipples and hypoplastic areolae. These abnormalities occur particularly in girls with "shield" or "funnel" chests. Sexual hair is usually scant and may be absent, and the external genitalia are infantile. The labia majora are neither pigmented nor prominent, and the labia minora may not be apparent. The clitoris is usually normal, although it may occasionally be enlarged (see Fig. 2-2).

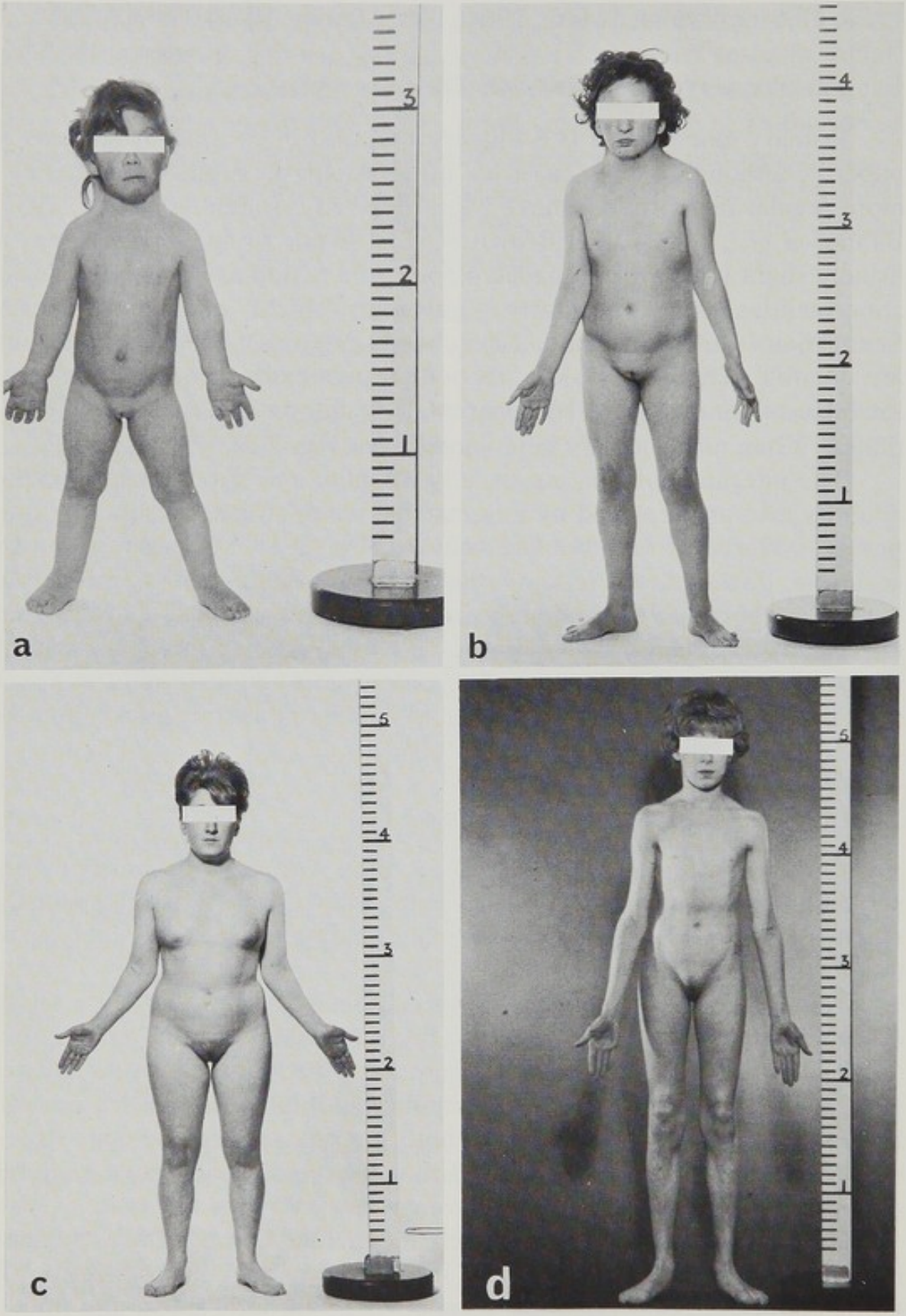
The internal genitalia are usually infantile and hypoplastic, and the adult ovaries are replaced by long narrow white streaks which are composed of ovarian stroma but lack follicles (Fig. 2-3). Up to three months gestation, however, the fetal ovaries contain germ cells in normal numbers (Carr *et al.*, 1968) and some are still present at birth (Gordon and O'Neill, 1969; Polani, 1967) (Fig. 2-3). However, by puberty these have all, or almost all, disappeared. The output of 17-ketosteroids is lower than normal in about half the cases, while the gonadotrophin output is often markedly increased.

2. Stature and Skeletal Anomalies

Girls with ovarian dysgenesis are often ascertained because of their short stature which is usually less than 4 ft 9 in. (144 cm), especially when there are other associated somatic anomalies such as webbing of the neck (Fig. 2-2).

Haddad and Wilkins (1959) have demonstrated that there is a slight delay in epiphyseal formation and closure, while Acheson and Zampa (1961) have shown that skeletal maturation ceases at the time of expected puberty when failure of postpubertal epiphyseal closure occurs. Polani (1961) has pointed out that both the coarser and the finer structure of the bones is abnormal and that the whole pattern of skeletal growth is grossly affected for any given age.

Skeletal anomalies are often seen and include micrognathia, changes in the spine resembling those seen in Scheuermann's disease, fusion of the cervical vertebrae as in the Klippel-feil syndrome, shield and funnel chest, android shape to the pelvis, cubitus valgus, and other limb de-


a
b
c
d

formities such as knock-knees in a proportion of the cases (Fig. 2-2). Polani (1961) has pointed out that these somatic anomalies are more common in patients with webbing of the neck as compared to those without that malformation. An abnormal structure of the hands, however, is found equally frequently in both variants of the syndrome and is obvious in about one in every four patients. These may consist of digital anomalies (camptodactyly and syndactyly) or what has been termed *brachymetacarpalism*. This results from premature fusion of the metacarpal epiphyses with consequent shortening of the metacarpals and is particularly seen on the ulnar side (Kosowicz, 1959; Van der Werff Ten Bosch, 1959; Hortling *et al.*, 1960); this can also be seen in subjects with normally functioning ovaries. Severe osteoporosis occurs in a proportion of affected girls and may involve the lower femoral epiphyses and the carpal and tarsal bones; if the vertebrae are affected, collapse may result which usually involves the cervical, lumbar, and coccygeal vertebrae (Hoffenberg and Jackson, 1957b; Kosowicz, 1959).

3. Birth Weight and Signs in the Newborn

The birth weight of patients with ovarian dysgenesis is often low and may come within the range of prematurity [5.5 lb (2495 gm)] (Polani, 1961). The lower birth weights are usually found in the more malformed girls, particularly in those who are subsequently shown to have a webbed neck. Many newborn babies who are subsequently found to have ovarian dysgenesis have an unexplained peripheral lymphedema at birth. P. M. F. Bishop *et al.* (1960) obtained a history of edema in 45 out of 126 patients (35.7%) under the age of 16 and four out of 120 (3.3%) over 16, while in the series reported by Lindsten (1963) it was present in nine out of 57 (16%) patients. Three examples of webbing of the neck in the newborn have been reported (Schneck *et al.*, 1962; Frøland *et al.*, 1963a) all of which showed marked lymphedema. Polani (1962) considered the occurrence of an unexplained peripheral lymph-

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Fig. 2-2. Clinical features of patients with various types of ovarian dysgenesis. (a) Turner's syndrome 45,X—age 4 years. Note gross webbing of the neck, abnormal facies, and short stature; Pru 137/2424 (b) Turner's syndrome 45,X—age 14 years. Note webbing of the neck, short stature, cubitus valgus, and absence of secondary sexual characteristics; Pru 2723/4783 (c) ovarian dysgenesis 45,X—age 22 years. Note absence of somatic malformation, short stature, and absence of secondary sexual characteristics; Pru 270/91 (d) pure gonadal dysgenesis—age 17 years. Normal stature, absence of secondary sexual characteristics, and XY sex chromosomes Pru 76/2687. (Reproduced by permission of (a) Dr. M. C. Joseph and Professor P. E. Polani, (b) Dr. P. M. F. Bishop and Professor P. E. Polani, (c) Dr. P. M. F. Bishop and Professor P. E. Polani, and (d) Professor P. E. Polani.

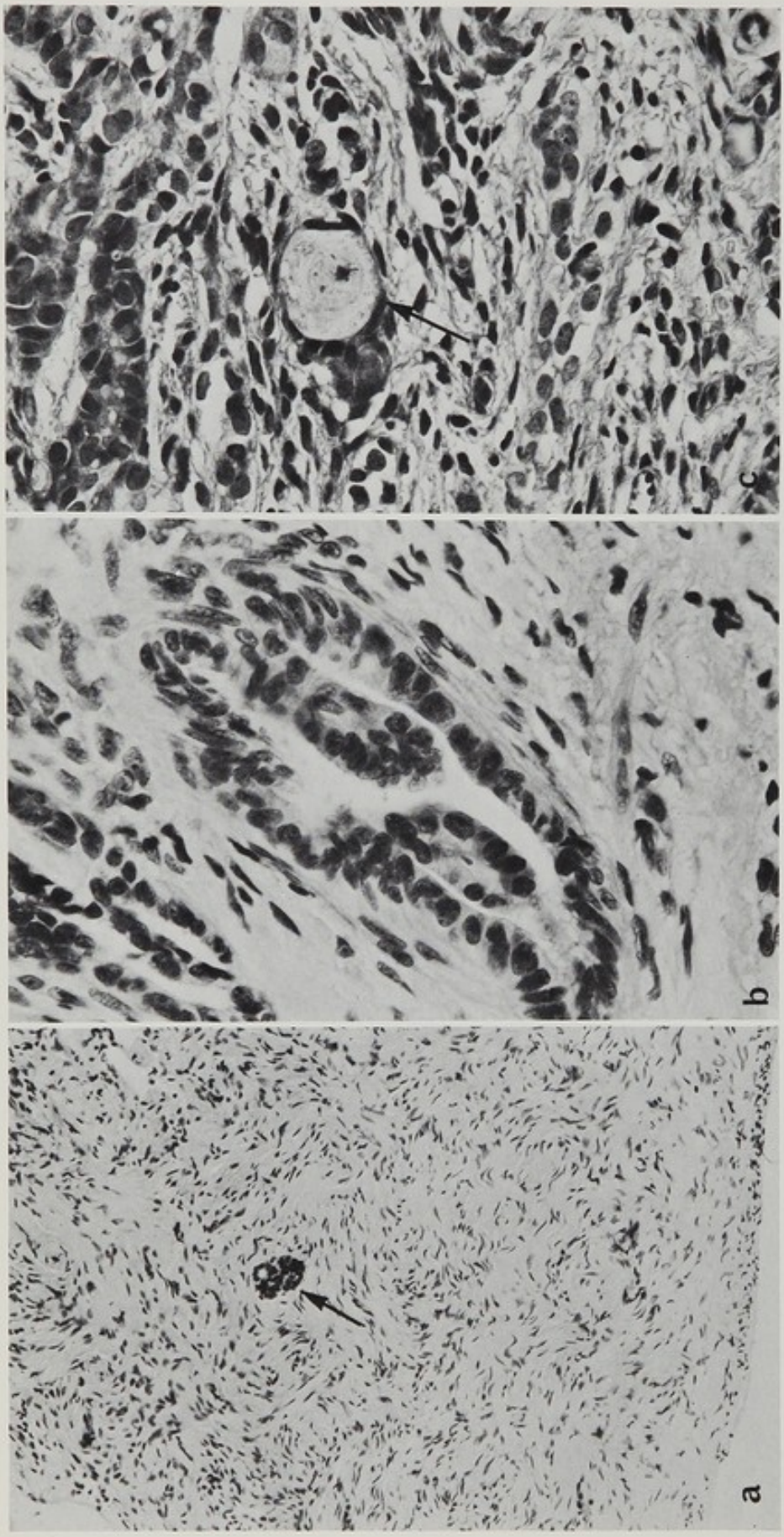


FIG. 2-3. (a) Histological section from ovarian streak from a patient with 45,X/46,XY sex chromosomes. Note the probable remnant of a mesonephric duct. (b) Higher power showing possible mesonephric remnant. (c) Oocyte in the ovary of a patient with Turner's syndrome and a 45,X chromosome complement at the age of 6 months. (All hematoxylin and eosin stain. (a) ×54; (b) and (c) ×538.) (Reproduced by permission of Professor P. E. Polani.)

edema in the newborn to be strongly suggestive of ovarian dysgenesis and indicative that a sex chromatin examination should be carried out. Neck webbing may also occur in the newborn, although it is more usual to find a redundant fold of skin at the back of the neck; either is indicative of possible ovarian dysgenesis. Benson *et al.* (1965) have studied six patients with primary lymphedema and clinical evidence of ovarian dysgenesis: five were 45,X and one was 46,XY and was subsequently found to have testicular feminization. Evidence of hypoplasia or aplasia of the primary lymphatic vessels of the legs was detected in all these patients.

Gordon and O'Neill (1969) have recently described 10 children who showed Turner's infantile phenotype within the first six months of life. Nine of these had edema of the feet and seven loose neck folds. Four had a peculiar facies consisting of a large mouth, squashed nose, a small chin, and skin folds below the lower eyelids (Fig. 2-4). Eight of these babies were 45,X, one 45,X/46,XXqi, and in one the chromosome complement was not known.

4. Other Somatic Anomalies

Webbing of the neck is characteristic of as many as 50% of patients with ovarian dysgenesis. Some girls may, however, have an unduly short wide neck without webbing; and in others occasional webbing of the fingers and axillae may also be seen (Haddad and Wilkins, 1959; P. M. F. Bishop *et al.*, 1960; Albright *et al.*, 1942; Hoffenburg and Jackson, 1957a,b).

Some patients with ovarian dysgenesis have peculiar facies, and there is an increased frequency of congenital heart disease and renal anomalies. Also, there are frequently an excessive number of pigmented nevi (Zampa, 1961, quoted by Polani, 1962). The most important form of congenital heart disease is coarctation of the aorta, which may be found in as many as one-third of the chromatin-negative patients and which may also occur in girls with Ullrich's syndrome (Albright *et al.*, 1942; Lisser *et al.*, 1947; Hoffenberg and Jackson, 1957a,b; Haddad and Wilkins, 1959; P. M. F. Bishop *et al.*, 1960). Other types of congenital heart disease are less common in ovarian dysgenesis but have been observed in patients with webbing of the neck and normal ovarian function. Evidence of systolic and diastolic hypertension could be found equally in patients with and without webbing of the neck who did not have coarctation of the aorta (Haddad and Wilkins, 1959).

A fairly high frequency of renal anomalies such as horseshoe kidney and double ureter are observed and may occur in as many as one in four patients, while lesser anomalies are even more common. The most fre-

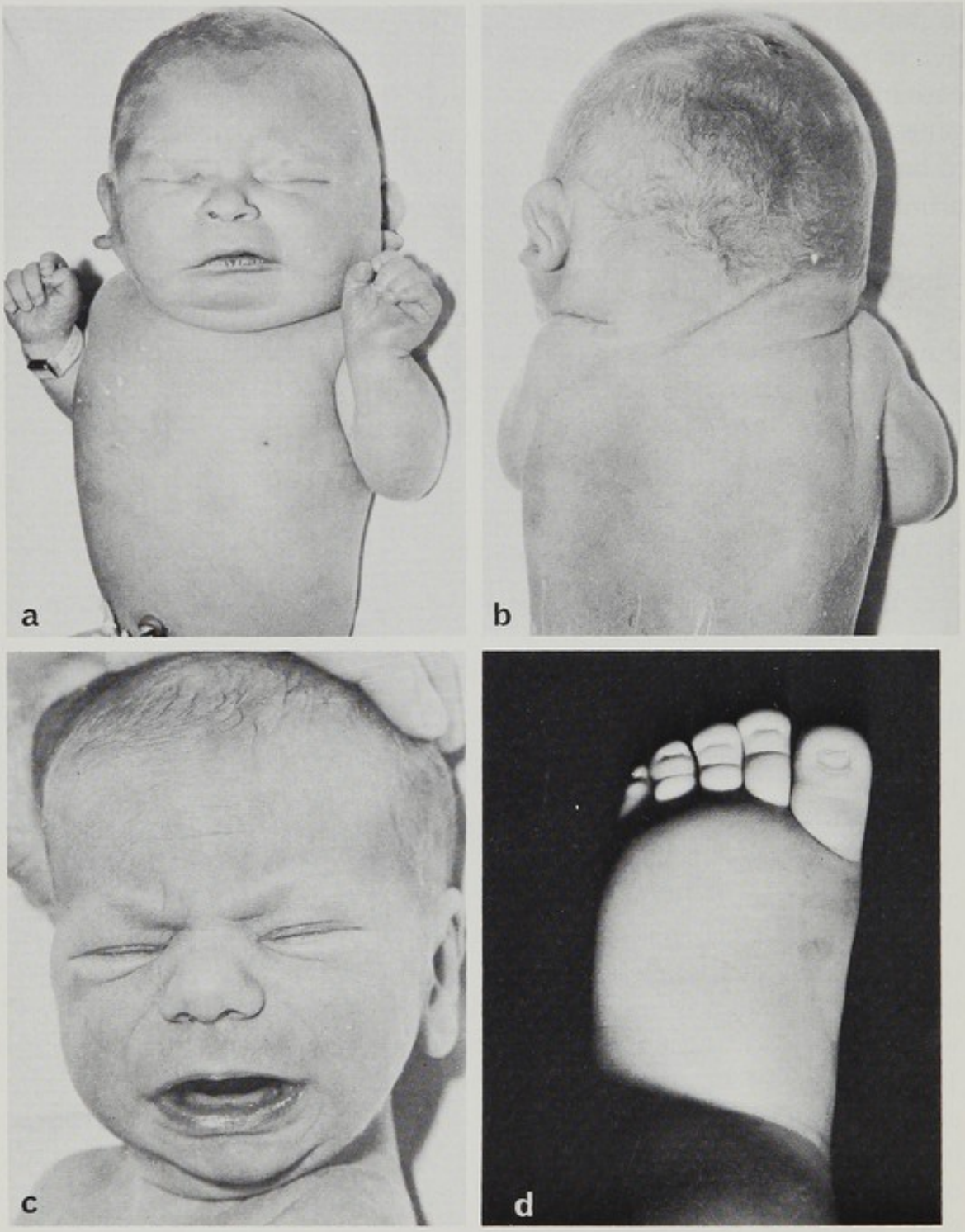


FIG. 2-4. Features of Turner's syndrome in the newborn. Note abnormal facies consisting of large mouth and squashed flat nose, short broad neck with loose skin folds, low hair line, and edema of the feet. (From Gordon and O'Neill, 1969. Reprinted from the *British Medical Journal* by permission of the authors and editor.)

quent renal malformation observed in chromatin-negative patients with a webbed neck was a horseshoe kidney (Meyer, 1925; P. M. F. Bishop *et al.*, 1960; Hortling, 1955).

5. Metabolic Disorders and Autoimmunity in Turner's Syndrome

Fraccaro *et al.* (1960b) have shown that the level of circulating human growth hormones (HGH) is as high as in acromegaly in spite of the short stature, and Polani (1961) has suggested that this might indicate a target organ failure. However, Escamilla *et al.* (1960) and Forbes *et al.* (1962) have suggested that these patients do show some slight response to human growth hormone. Almqvist *et al.* (1963) have studied linear growth, sulfation factor (SF) activity, and chromosome constitution in 22 patients. They found a retarded growth rate with a decreased SF activity in one subject, normal SF activity in nine subjects, and increased SF activity in 12 subjects, while the mean serum SF activity was increased in all age groups. They suggested that the pituitary growth hormone in ovarian dysgenesis does not stimulate growth in the usual manner.

Lindsten *et al.* (1967) studied 14 patients with Turner's syndrome with a normal intravenous glucose tolerance test and showed that the plasma insulin response to prolonged glucose infusion was in most instances delayed and diminished. The fasting plasma HGH level was elevated, and hyperglycemia induced a paradoxical increase in plasma HGH in most of the patients. The HGH response to hypoglycemia was normal. In this study the authors found no increase in the frequency of diabetes mellitus among the relatives of patients with Turner's syndrome in contrast to the findings of Engel and Forbes (1965) and Andreani (quoted by Lindsten *et al.*, 1967). This could be owing to the fact that Lindsten's patients were younger than those studied previously. Lindsten and his colleagues also showed an increased HGH response to hyperglycemia after estrogen replacement, while at the same time the insulin response was reduced further. They argued that in the light of the known diabetogenic effect of HGH in man:

> It is tempting to suggest that some relation exists between the elevated fasting values for HGH and its paradoxical reaction to hyperglycaemia on the one hand, and the abnormal insulin response to hyperglycaemia and hyperplasia of the pancreatic islets on the other.

They consider that the paradoxical HGH response in patients with Turner's syndrome perhaps represents abnormal hypothalamic function resulting from the chromosome abnormality. Recently, Donaldson *et al.*

(1968) studied growth hormone secretion before and after insulin hypoglycemia in 14 patients with Turner's syndrome (eight—45,X; three—45,X/46,XX; one—45,X/46,XXstr, and two—46,XXstr) and 12 normal female controls using a radioimmunological assay technique and taking a 50% fall in blood glucose as an adequate stimulation for HGH secretion. Out of the 12 controls, two showed less than a 50% fall in blood glucose but had a good HGH response and only one had a poor HGH response to adequate hypoglycemia; four patients with Turner's syndrome had less than a 50% fall in glucose, but the HGH response was good. The magnitude of the HGH response was variable in Turner's syndrome, but some response was present with adequate hypoglycemia in all patients. Human growth hormone response was slower in Turner's syndrome than in controls, a peak being reached after 60 min in controls and 90 min in Turner's syndrome. The authors concluded that some factor other than HGH deficiency was responsible for poor growth in Turner's syndrome. They considered that the chromosome abnormality might be affecting the growth potential of the tissues directly (see Hamerton, 1968b, and Section V below).

Williams *et al.* (1964) and Engel and Forbes (1965) have suggested that patients with ovarian dysgenesis appear to be prematurely aged and more frequently have a degenerative disorder characteristic of aging, such as hypertension. There appeared to be a significant increase in various metabolic disorders such as diabetes mellitus, clinical or histological thyroiditis, and circulating antibodies to thyroglobulin in the group of patients studied by these authors. They suggested that patients with an isochromosome may have a predilection for diabetes mellitus and clinical thyroiditis, and that ". . . this association is not readily accorded with the hypothesis that the abnormal chromosome was uniformly inactivated early in embryonic life." Finally, they found that thyroid autoimmunity is more common in relatives of patients with ovarian dysgenesis than in the general population.

Recently, Doniach *et al.* (1968) have analyzed the thyroid antibodies in a series of 88 patients with ovarian dysgenesis and an abnormal chromosome complement and thirty nine 46,XX controls who had either pure gonadal dysgenesis or Ullrich's syndrome (Table 2-1). Their results are summarized in Fig. 2-5. Increased levels of thyroid antibodies compared to 46,XX controls were found in the 45,X group, the group of mixoploids with chromosomes of normal structure, and the group of mixoploids with structurally abnormal chromosomes, the highest levels being found in the latter group (Fig. 2-6). Although the significance of these findings is not clear at present, there does seem to be no doubt that patients with ovarian dysgenesis and abnormal sex chromo-

TABLE 2–1

Sex Chromosome Findings in 134 Patients in Whom Thyroid Antibodies Were Studied [a]

Probands with XX sex chromosomes		No. of cases
Pure gonadal dysgenesis		11
Ullrich's syndrome		28
		39
	Aneuploid Subjects:	
XO		52
XO/XX and similar XO/XY and similar	Mosaics, structurally normal sex chromosomes	13
XO/XXqi XO/other abnormal Xs XO/abnormal Ys or ? Ys	Mosaics, structurally abnormal sex chromosomes	23
Others		7
		95

[a] After Doniach *et al.*, (1968).

somes are particularly prone to develop thyroid autoantibodies and further that different chromosome subgroups differ in their propensities to antibody production. Fialkow (1964, 1966) and Vallotton and Forbes (1967) have shown that a higher proportion of the probands' parents with abnormal chromosomes have antibodies than age-matched controls, and it has been suggested that the autoimmune disturbance of these parents is expressed not only in the production of antibodies but also in the chromosomally abnormal children who inherit their parents' tendency to disturbed immune tolerance. Doniach *et al.* (1968) were unable to show increased antibodies in relation to age among the parents of their patients and conclude as follows: "The nature of a hypothetical relationship between the immune disorder in the parents and the chromosome anomaly in the offspring . . . has so far no firm factual basis."

6. Intellectual Impairment

Haddad and Wilkins (1959) and Polani (1960) found a general degree of slight intellectual impairment, particularly in the more grossly malformed subjects and especially in those patients with webbing of the neck. In general, however, there does not seem to be an increase in the frequency of ovarian dysgenesis among severe mental defectives such as occurs in chromatin-positive 47,XXY males and 47,XXX females

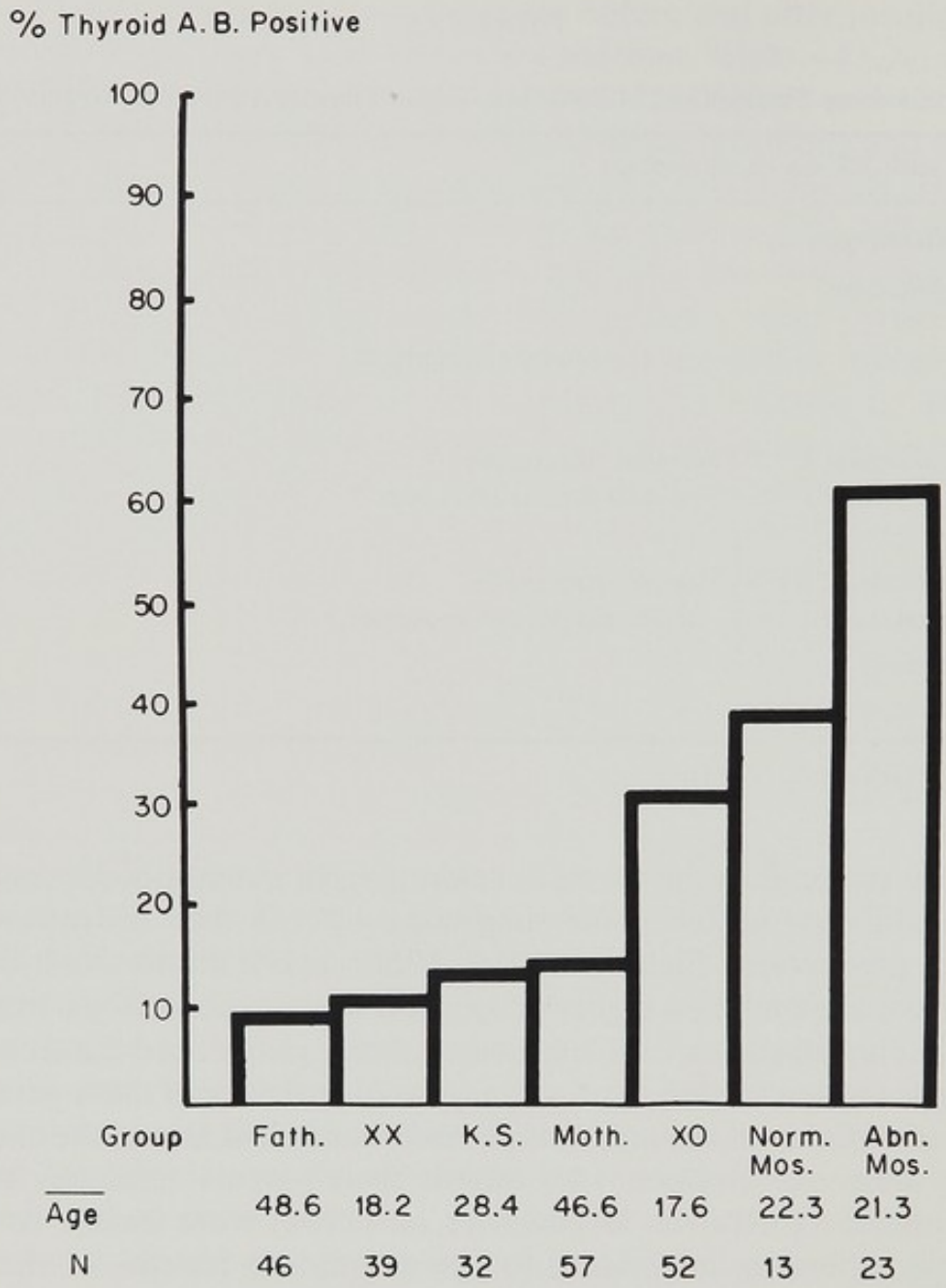


FIG. 2-5. Histogram showing per cent patients tested with various chromosome complements who were positive for thyroid autoantibodies. Abbreviations: Fath., father's; K.S., Klinefelter's syndrome; XX, patients with O.D.; Moth., mother's; XO, Turner's syndrome with 45,X chromosomes; Norm. Mos., mixoploids with structurally normal sex chromosomes; and Abn. Mos., mixoploid subjects with structurally abnormal sex chromosomes. (Reproduced from Doniach *et al.*, 1968.)

(Chapter 1 and below). Hamerton *et al.* (1962) found one chromatin-positive case of ovarian dysgenesis among 196 female defectives who did not have Down's syndrome, while Maclean *et al.* (1962) found only one chromatin-negative girl with a 45,X chromosome complement in 1907 mental defective females, but in the same series they found seven 47,XXX

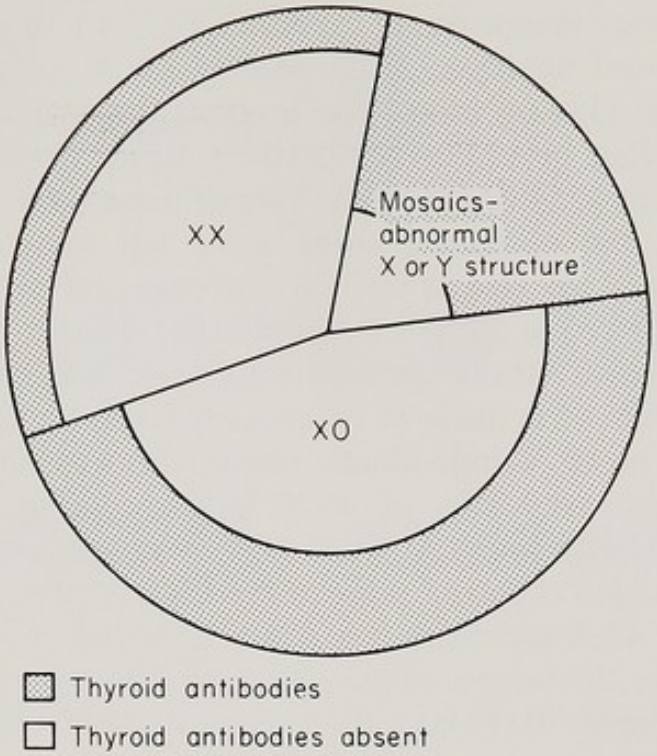


FIG. 2-6. A diagrammatic comparison between three groups of patients who showed statistically significant differences in the proportions of patients in which thyroid autoantibodies were found. The size of the slices are proportionate to the number of patients in each group. (Reproduced from Doniach *et al.*, 1968.)

females. De la Chapelle (1963) found three 45,X, one 45,X/46,XX?–, and one 45,X/46,XXqi females in a series of 1256 mental defectives. Maclean *et al.* (1968) have summarized the sex chromatin and chromosome findings in 9249 mental defectives from 12 different series, and out of this total four are 45,X, two 45,X/46,XXqi, one 45,X/46,XXr, one 45,X/46,XX?–, and one 45,X/46,XY. In a similar mental hospital series these authors studied 7207 women and failed to find a single chromatin-negative female or female with abnormal-sized sex chromatin.

7. INCIDENCE

It is difficult to obtain a satisfactory figure for the true incidence of ovarian dysgenesis in the general population. The frequency of chromatin-negative female infants given in sex chromatin surveys of the newborn should be treated with some reserve in view of the reported suppression of sex chromatin during the neonatal period among normal females (D. M. Smith *et al.*, 1962a; A. I. Taylor, 1963), unless these are confirmed to be 45,X by chromosome studies.

Court Brown *et al.* (1964a) estimated the frequency of chromatin-negative female infants to be 0.37/1000 live female births, a consider-

ably lower frequency than is found for either 47,XXY or 47,XXX. K. L. Moore (1959) found no negative females in 1804 consecutive female births; Bergemann (1962a) found one in 1838 (0.54/1000); Maclean *et al.* (1964) found four in 10,000 (0.40/1000), while Taylor and Moores (1967) found five in 4754 (0.11/1000). Two of these were 46,XY and the chromosomes of the remaining three were not known. Taylor and Moores summarized the results from six surveys and reported 10 chromatin-negative females in 22,068 female births, an over-all incidence of 0.45/1000; since two of these are known to be 46,XY, the frequency of 45,X and 45,X/46,XX? is likely to be about 0.4/1000 female births. The lower frequency of 45,X individuals among the newborn may be explained by an increased loss of 45,X fetuses during gestation (see Chapter 9). Carr (1965) found 11 45,X fetuses in a series of 200 spontaneous abortions which occurred prior to the 154th day of gestation. This high frequency of 45,X abortuses has also been found in other series and seems to comprise the largest single group of chromosomally abnormal abortuses (see Chapter 9) (Polani, 1966; Geneva Conference, 1966).

C. *Chromosome Studies in Ovarian Dysgenesis*

The discovery in 1956 that well over half of the patients with ovarian dysgenesis were chromatin-negative led to considerable speculation as to their chromosome complement. Polani *et al.* (1956) suggested that chromatin-negative patients might have a 45,X chromosome complement, while Danon and Sachs (1957) suggested that some cases might show sex chromosome mosaicism. Both these predictions have been confirmed; Ford *et al.* (1959c) showed that a 14-year-old chromatin-negative girl with features of ovarian dysgenesis had a 45,X chromosome complement and three other 45,X girls were reported by Fraccaro *et al.* (1960c) (Fig. 2-7). Also, in 1959, Ford reported on three chromatin-positive girls with 45,X/46,XX mixoploidy (Ford, 1961) and other examples of 45,X/46,XX were soon reported (Fraccaro *et al.*, 1960b; Sandberg *et al.*, 1960a). The first example of 45,X/47,XXX mixoploidy was reported by Jacobs *et al.* (1960a), and although the first patient with this mixoploidy did not have ovarian dysgenesis, the second did (Jacobs *et al.*, 1961). In the same year the first cases of ovarian dysgenesis with a deleted X chromosome and with an X-isochromosome (Xqi) were reported (Jacobs *et al.*, 1960a; Fraccaro *et al.*, 1960d). By 1961 several other chromosome complements had been reported including 45,X/46,XY and 45,X/47,XYY mixoploids, as well as patients with various structural abnormalities of one X who were in some cases also mixoploids (Fig. 2-8).

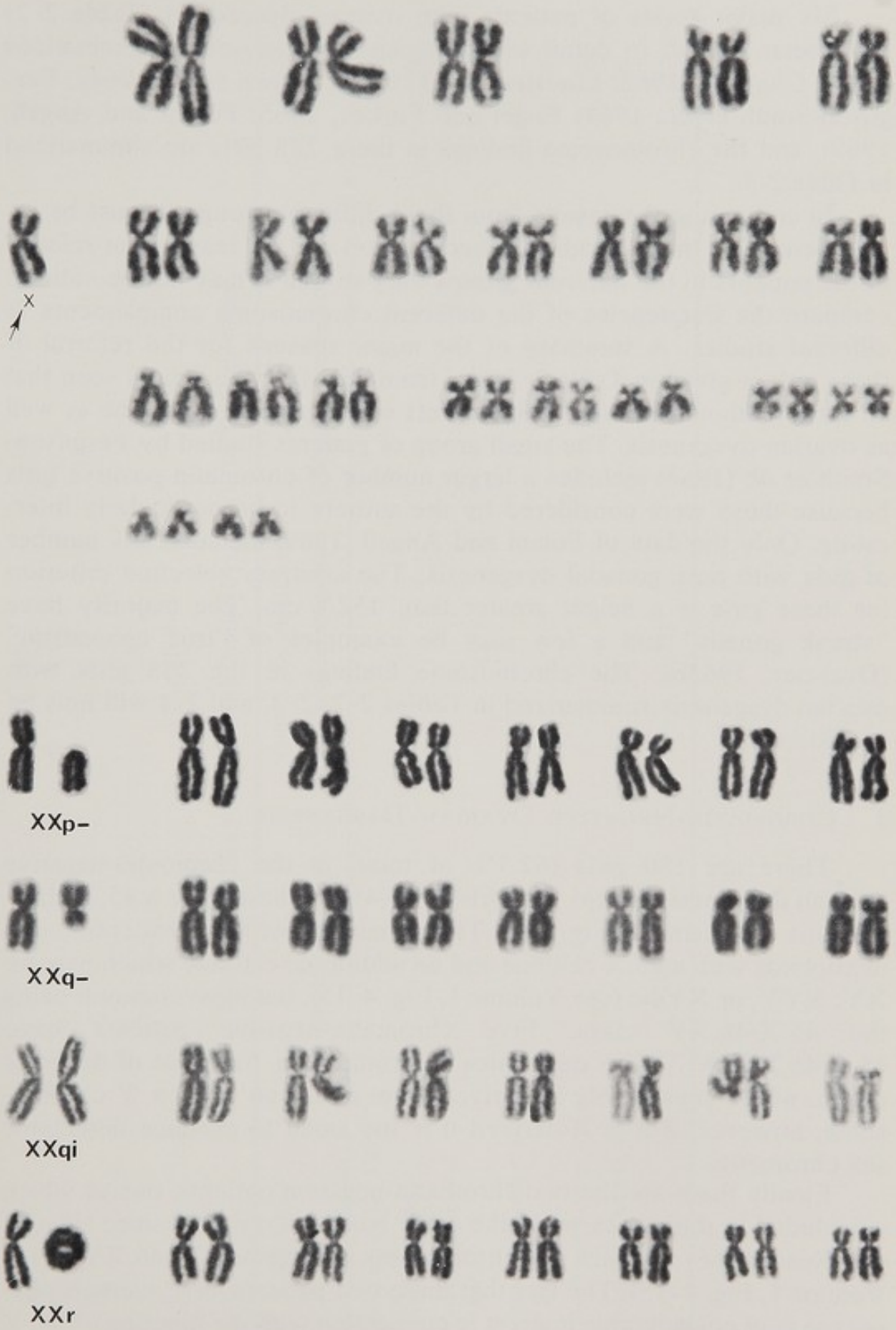


FIG. 2-8. Partial karyotypes of the X+6-12 group from four patients with ovarian dysgenesis and a structurally abnormal X chromosome (aceto-orcein ×666).

Six major series of patients with ovarian dysgenesis (Table 2-2) have been studied in detail with extensive chromosome examinations (De la Chapelle, 1962; Lindsten, 1963; Court Brown *et al.*, 1964a; Ferguson-Smith *et al.*, 1964; Engel and Forbes, 1965; Polani and Angell, 1969), and the chromosome findings in these 288 girls are summarized in Table 2-3.

In comparing the results from these different groups it must be remembered that the methods of ascertainment and the reasons for referral of the patients in the different groups vary so that it may not be valid to compare the frequencies of the different chromosome complements in different studies. A summary of the major reasons for the referral of these girls is given in Table 2-4, and from this it can be clearly seen that all surveys should include both patients with Turner's syndrome as well as ovarian dysgenesis. The small group of patients studied by Ferguson-Smith *et al.* (1964) includes a larger number of chromatin-positive girls because these were considered by the authors to be particularly interesting. Only the data of Polani and Angell (1969) included any number of girls with pure gonadal dysgenesis. The arbitrary selection criterion for these girls is a height greater than 152.4 cm. The majority have "streak gonads" and a few may be examples of "true agonadism" (Overzier, 1963b). The chromosome findings in the 288 girls with ovarian dysgenesis summarized in Tables 2-2, 2-3, and 2-4 will now be considered.

1. Chromatin-Negative Ovarian Dysgenesis

There are 180 girls (62.5% of total) in the chromatin-negative ovarian dysgenesis group; 161 girls or 89.4% of these have a 45,X chromosome complement (Fig. 2-7). The remainder, with one exception, are mixoploids with a 45,X cell line and an additional cell line which may be XY, XYY, or XYdic (see Volume I, Fig. 4-15), the most common being the 45,X/46,XY class. Five chromatin-negative patients have 45,X/46,X,fra+* (*fra+ designates a chromosome fragment of doubtful origin, which presumably is derived from either an X or a Y chromosome; however, if it is X-derived it is too small to produce detectable sex chromatin).

Finally there are the two chromatin-negative patients, one of which is included in this series while the other has been reported since (Jacobs and Ross, 1966) in which the chromosome complement is 46,XYqi (see Volume I, Fig. 4-15). The fact that these two patients have a female phenotype is of considerable interest in connection with the function of the Y

TABLE 2–2

Clinical Distribution of Patients with Ovarian Dysgensis in the Different Series

Reference	Number of patients with			Total
	Ovarian dysgenesis	pure gonadal dysgenesis	Secondary amenorrhea	
De la Chapelle, 1962	21	1	1	23
Lindsten, 1963	57	–	–	57
Court Brown *et al.*, 1964a	61	3(2?)	4	68(2?)
Ferguson-Smith *et al.*, 1964	25	4	–	29
Engel and Forbes, 1965	32	4	–	36
Polani and Angell, 1964–	92	28	–	120
Total	288	40(2?)	5	333(2?)

TABLE 2–3

Chromosome Findings in 288 Patients with Ovarian Dysgenesis

Chromosome constitution		No. of patients	Percent	Mixoploid (%)
Chromatin negative 180 (62.5%)	45,X	161	89.4	10.0
	45,X/46,XYdic	2	7.2	
	45,X/47,XYY	2		
	45,X/46,XY	9		
	45,X/46,Xfra+[a]	5	2.8	
	46,XYqi	1	0.6	
Chromatin positive 108 (37.5%)	46,XXqi	12	11.1	81.5
	46,XX	4	3.7	
	46,XXpi or q– / 46,XXp–	4	3.7	
	45,X/46,XXqi / 45,X/46,XXqi/47,XXqiXqi	38	35.2	
	45,X/46,XX	20	18.5	
	45,X/47,XXX	15	13.9	
	45,X/46,XXstr [b]	15	13.9	

[a] Here fra stands for minute fragment of doubtful origin.
[b] Here str stands for structurally altered X chromosome.

(see Chapter 4, this volume). The excess of 45,X/46,XY mixoploids over the 45,X/47,XYY and 45,X/46,XY dic suggests that these are generally formed by the loss of the Y chromosome from one blastomere of a 46,XY zygote rather than by non-disjunction and inclusion of the Y in the other cell line. The 45,X/47,XYY and 45,X/46,XY dic mixoploids have presumably originated from a 46,XY zygote with non-disjunction of the Y at an early cleavage division. At least one of these subjects may also have a minor XY cell line. The 46,XY dic line may have arisen at the same time as the nondisjunctional event by equal chromatid exchange with sister union between the short arms of a single Y (Fig. 2-9) or by chromosome breakage and an homologous translocation between the two Y chromosomes in a 47,XYY cell. There are two other 45,X/46,XYdic subjects reported (McIlree *et al.*, 1966) who both have a male phenotype. In these individuals the 46,XYdic is the major cell line, while in the two girls referred to above the major cell line is 45,X (Table 2-5). Thus it is becoming clear that in those subjects who have a 45,X as well as a cell

line containing a Y chromosome, the proportions of the two lines and the tissues in which they occur are of extreme importance in determining the phenotype (see also Chapter 3); and in several of these subjects, where more than one tissue has been sampled, there is evidence that the proportions of the two cell lines vary between different tissues. Examination of Table 2-6 suggests that where the phenotype is ovarian dysgenesis then the 46,XY cell line may predominate in the blood while the 45,X cell line predominates in skin and presumably gonad. In the true hermaphrodites (see Table 3-5) with this chromosome complement in which different tissues have been studied there is far less evidence of a predominant cell line in different tissues.

TABLE 2–4

Reasons for the Referral of 288 Patients with Ovarian Dysgenesis in the Six Surveys

Reference	Reason for selection
De la Chapelle, 1962	Clinical classification of gonadal dysgenesis. Short stature, ovarian malfunction, raised urinary gonadotrophins. Low estrogen. Blood culture only.
Lindsten, 1963	Short stature. Symptoms of ovarian dysgenesis, ovarian malfunction. Variable somatic malformations. Blood and skin culture.
Court Brown *et al.*, 1964a	Primary amenorrhea. Growth retardation. Features of ovarian dysgenesis. Newborn survey general population and mentally deficient survey. Rare secondary amenorrhea. Mainly blood culture.
Ferguson-Smith *et al.*, 1964	Clinical features of Turner's syndrome. Excess of chromatin-positive patients owing to selection. Two selected on sex chromatin only. Blood culture.
Engel and Forbes, 1965	Selected because of congenitally defective ovaries as shown by: (1) direct observation, (2) history of primary amenorrhea, (3) absent sex development, (4) raised urinary gonadotrophins, and (5) classical clinical Turner's syndrome. Blood culture – skin rare.
Polani and Angell, 1969	(1) Primary amenorrhea and evidence of ovarian malformation, (2) short stature, and (3) somatic signs of Turner's syndrome, pure gonadal dysgenesis survey. Blood and skin culture and gonad culture where possible. Ovarian malformation and normal stature.

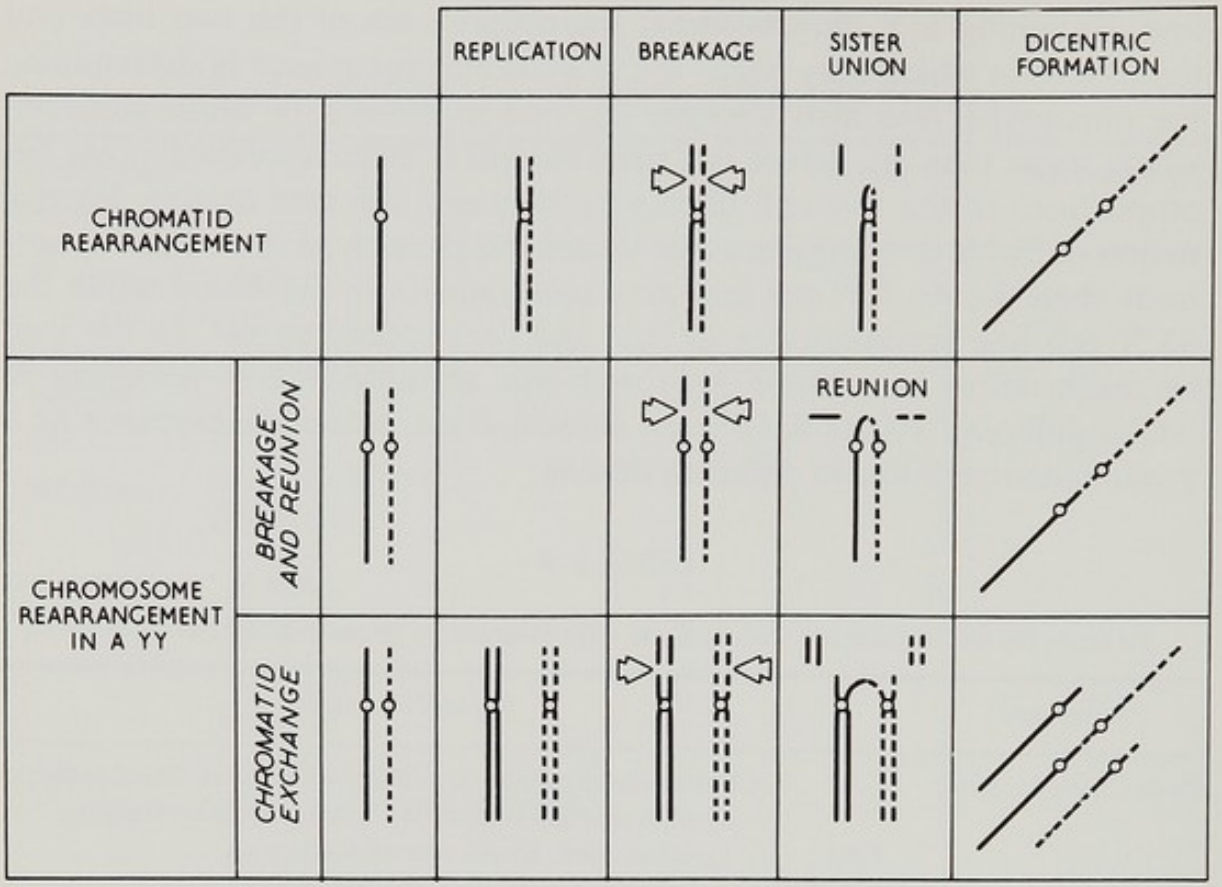


FIG. 2-9. Schematic diagram to show the origin of a dicentric Y chromosome by either chromatid or chromosome rearrangement.

2. CHROMATIN-POSITIVE OVARIAN DYSGENESIS

The chromatin-positive ovarian dysgenesis group comprises 108 out of the 288 girls (37.5%) and a far wider range of chromosome complements are found.

a. NONMIXOPLOID GROUP. This is a small group of 20 girls (18.5%), four of whom have an apparently normal chromosome complement, while the remainder have 46,XXstr (Xstr stands for structurally altered X chromosome). The largest number of girls in this group are 46,XXqi (Fig. 2-8). The isochromosome is a long, equal-armed metacentric chromosome which resembles a No. 3 in size and morphology and is invariably late replicating. The sex chromatin in these girls is larger than normal (see Volume I, Chapter 6). If these 12 definitely have only one cell line, then the isochromosome must have been formed during meiosis (see Volume I, Chapter 8, Section II, C). Other structurally abnormal X chromosomes usually resemble chromosomes of the 13-20 groups; in three instances it is a metacentric or submetacentric and is probably either an Xpi or an Xq−; in one girl it is acrocentric and is

TABLE 2–5

Proportion of XYqdic Cells in some 45,X/46,XYqdic Patients in Relation to Their Phenotype[a]

Case No.	Age (years)	Tissue[b]	No. of cells	Proportion XYqdic	External genitalia	Gonads	Reference
1	24	B	114	0.88	Normal male	Testes Azoospermia	McIlree *et al.*, 1966
2	–	–	–	XO<XYqdic	Ambiguous Enlarged clitoris	Inguinal testes with immature tubules	Jacobs (quoted by McIlree *et al.*, 1966)
3	14	B	46	0.61	Infantile female	Bilateral streaks (testicular tissue observed in right streak)	Polani and Angell (quoted by Court Brown, 1967)
		S	56	0.04			
		G	77	0.13			
4	35	B	31	0.39	Infantile female	Bilateral streaks	Polani and Angell (quoted by Court Brown, 1967)
		S	45	0.00			
		G	24	0.00			
5	13	B	150	0.69	Small phallus bifid scrotum; perineal urethra	Right testis inguinal; left streak abdominal	Ferrier *et al.*, 1968
		S	120	0.03			
6	—	B	91	0.04	Small phallus; perineal urethra	Uterus and Fallopian tubes; testes abdominal	Boschetti *et al.*, 1968
		S	75	0.03			

[a] See also Table 4 – 3.
[b] B, Blood; S. Skin; G. Gonad.

TABLE 2–6

Proportion of 46,XY cells in Some Patients with Ovarian Dysgenesis and 45,X/46,XY Mixoploidy [a]

Ref. No.	Proportion XY cells		Reference
	Blood	Skin	
111/61	0.70	0.03	Court Brown *et al.*, 1964a
65/62	0.18	0.03	Court Brown *et al.*, 1964a
10/59	0.84	0.07	Court Brown *et al.*, 1964a
170/60	0.86	0.00	Court Brown *et al.*, 1964a
200/60	0.59	Not done	Court Brown *et al.*, 1964a
PRU 67/ MC 270439	0.62	0.28 (skin) 0.38 (right gonad) 0.20 (left gonad)	Polani and Angell, 1970
PRU 2655/ VM 171143	0.53	0.00 (right gonad) 0.11 (left gonad)	Polani and Angell, 1970
PRU 2909/ RT 210749	0.63	0.21	Polani and Angell, 1970

[a] See also Table 11 – 3.

probably an Xp– (Fig. 2-8). The abnormal X in each case is late replicating and the sex chromatin mass smaller than normal.

b. MIXOPLOID GROUP. The remaining 88 girls (81.5%) in the chromatin-positive group are all mixoploids. Twenty of these (32.4%) are 45,X/46,XX and a further fifteen 45,X/47,XXX, a few of whom have in addition a possible 46,XX cell line. These have arisen either by loss of one X at a cleavage division or by nondisjunction and inclusion of the one X in the wrong cell giving a 47,XXX cell line. The remaining 53 (49.1%) chromatin-positive girls all have an Xstr in one cell line while the other is 45,X. Thirty-eight of these are 45,X/46,XXqi with, in a very few subjects, an occasional cell with 47,XXqi,Xqi. Of the remaining 15 girls, seven have an Xq–, three an Xp–, and five an Xr.

The frequency of mixoploidy in the two groups is of considerable interest. In the chromatin-negative group the 45,X karyotype accounts for about 90% of the affected girls while mixoploids represent approximately 10%. In contrast, over 80% of the chromatin-positive females are mixoploid and under 20% pure line with a structurally abnormal X chromosome. All the mixoploids which have been reported have a 45,X cell line and all of these must have resulted from a nondisjunctional type of error in an early cleavage division. Russell (1963) has suggested that the

majority of 45,X zygotes in mice result from a postfertilization error, and the lack of any pronounced parental age effect tends to support this idea for man. The relatively low frequency of mixoploids with a 46,XY, 46,XYdic, or 47,XYY cell line compared to the high frequency of subjects in which the second cell line has an X and an Xstr suggests that there is a greater chance that the second X, if it undergoes nondisjunction, will be included in a daughter nucleus and, perhaps as a result of the mitotic error, may also misdivide to give an isochromosome. If the Y undergoes nondisjunction, perhaps it is usually completely eliminated, thus resulting in a pure 45,X zygote. If this is so it might be expected that a higher proportion of 45,X subjects would be X^M rather than X^P. On this assumption the majority of 45,X zygotes should originate by loss of the Y from an XY zygote, while the mixoploids result from X chromosome nondisjunction in an XX zygote combined with structural change. Thus both one X and the Y seem to be at risk during early cleavage, and it is possible that this is always the paternally derived sex chromosome. An extension of this hypothesis might account for the high frequency of 45,X zygotes which spontaneously abort, if we assume that these are largely X^P and as a result at greater risk than X^M zygotes.

3. Source of the X Chromosome in Chromatin-Negative and Chromatin-Positive Ovarian Dysgenesis

Recently, Race and Sanger (1968, 1969) have summarized the Xg groups in 253 families with ovarian dysgenesis (Table 2-7). In 195 families with 45,X probands the single X is maternal in 64 (33%), paternal in 3 (1%), and undisclosed in 128 (66%). However, it is clear from an examination of this table that the matings which can demonstrate a maternal origin are far more common than those which can show a paternal origin. G. R. Fraser (1963) provided the necessary formulas to estimate the true proportion of maternal and paternal X chromosomes, and by applying these to the 195 families Race and Sanger estimated that 74% are X^M and 26% X^P. This is contrary to the suggestion by Lindsten *et al.* (1963a) that the X^P was as likely to contribute to the 45,X state as the X^M. It also, perhaps, lends weight to the suggestion made above that either the paternal sex chromosome or an X^P fetus is more at risk of loss. If so, the majority of 45,X abortuses should be X^P rather than X^M.

An attempt has also been made to trace the parental origin of the structurally abnormal X in some chromatin-positive females with a 46,XXqi chromosome complement. Lindsten *et al.* (1963b) have analyzed the Xg(a) data on two informative families with 46,XXqi and have concluded that in both the isochromosome is paternally derived. In six

TABLE 2–7

Xg Groups of Parents of Northern European Patients with Ovarian Dysgenesis and 45,X;46,XXqi and 45,X/46,XXqi Chromosome Complements[a]

Xg groups of Father	Mother	Turner	Source of the normal X	XXqi XO		XXqi XO/XXqi		Combined	
				Obs.	Proportion	Obs.	Proportion	Obs.	Proportion
+	+	+	Undisclosed	96	0.49	30	0.52	126	0.50
–	+	+	Maternal	39	0.20	6	0.10	45	0.18
+	–	+	Paternal	3	0.01	1	0.02	4	0.01
+	+	–	Maternal	19	0.10	6	0.10	25	0.10
–	+	–	Undisclosed	21	0.11	9	0.15	30	0.12
+	–	–	Maternal	6	0.03	1	0.02	7	0.03
–	–	–	Undisclosed	11	0.06	5	0.09	16	0.06
Total				195		58		253	

[a] From Race and Sanger (1969).

other families the Xqi was paternal, provided that it was either genetically inactive or the Xg(a) locus was situated on the short arm of the X. Recent studies by Polani and his colleagues (quoted by Race and Sanger, 1969) on a family with a 46,XXq–,Xg(a–) proband who is the daughter of Xg(a+) parents suggest that the Xg locus, if it is not inactivated, should be located on the long arm. These contradictory conclusions can only be reconciled if it is assumed that the Xg locus is always inactivated when it is carried on an abnormal X chromosome.

Race and Sanger (1969) have summarized the Xg data on 58 families with a 46,XXqi or 45,X/46,XXqi proband and find the Xqi to be paternal in 13 and maternal in one, while its origin is undisclosed in 45 families (Table 2-7).

The lack of any increase in maternal age at the birth of patients with ovarian dysgenesis (Table 2-8) (Alberman and Polani, 1967) and the evidence that most 39,X mice and 45,X human females carry a maternal X chromosome suggest that the majority of 45,X zygotes result from a postzygotic error with loss of the paternal sex chromosome or that most 45,X^p zygotes abort (see above).

The evidence about the origin of the isochromosome is even more difficult to evaluate. The frequency of 45,X/46,XXqi mixoploidy suggests that a high proportion of isochromosomes arise at an early cleavage division rather than during spermatogenesis (see Volume I, Chapter 8, Section II, C). However, as Polani (1962) has pointed out, it

is possible for misdivision of the centromere to occur during gametogenesis, forming an unstable telocentric chromosome which does not become stabilized by forming an isochromosome until the first cleavage division when a mixoploid is formed (see Volume I, Chapter 8, Section II, C). The nonmixoploids presumably result from centromere misdivision of an X chromosome during meiosis. Therefore, we have evidence that the single X in the 45,X state is usually matroclinous and that this condition probably results either from the loss of the paternal sex chromosome during an early cleavage division or from abortion of $45,X^P$ fetuses. The frequency of the different types of mixoploids suggests that either the original zygote is more frequently XX than XY or that when the Y chromosome is lost it is usually completely excluded from the

TABLE 2–8

The Maternal and Paternal Ages in Females with Ovarian Dysgenesis and Various Chromosome Complements [a]

Chromosome constitution	Mean paternal age ± S.E [b]	Mean maternal age ± S.E. [b]	Comment
45,X	32.08 ± 0.72 (59)	27.78 ± 0.78 (64)	Webbed neck
	31.39 ± 0.85 (59)	28.19 ± 0.68 (59)	No webbing
	31.00 ± 1.39 (32)	26.10 ± 0.73 (38)	Webbing not known
45,X/46,XX	30.69 ± 0.97 (26)	28.72 ± 0.88 (29)	–
45,X/47,XXX	26.17 (6)	24.83 (6)	–
45,X/46,XX/47,XXX	29.83 (6)	26.17 (6)	–
45,X/46,XXfra [c]	37.21 (14)	30.60 (15)	–
45,X/46,XXqi	34.83 ± 1.22 (29)	29.06 ± 1.01 (31)	–
45,X/46,XY	31.07 (14)	26.93 (14)	–
45,X/46,XX del [d]	28.50 (6)	23.83 (6)	–
46,XXpi	27.00 (3)	22.67 (3)	–
46,XXqi	32.50 (18)	29.44 (18)	–
Control			
General population [e]			
England 1935	30.9 ± 0.6	28.6 ± 0.7	
1958	32.2	28.7	

[a] Alberman and Polani, 1967

[b] Standard error calculated only for groups over 20.

[c] Here fra stands for any type of X chromosome fragment.

[d] Here del stands for deletion.

[e] Registrar General's data.

zygote and only rarely included in one of the other cell lines; on the other hand, when the X chromosome is excluded from one cell line it is either as a result of structural change or it may equally likely be included in the other cell line and only relatively infrequently is it completely excluded (45,X/46,XX). The available evidence is that an isochromosome is more frequently patroclinous than matroclinous.

D. *Correlation of Clinical and Cytogenetic Findings in Ovarian Dysgenesis*

There is no clear-cut clinical distinction between the different cytogenetic groups which by definition all show evidence of primary gonadal maldevelopment. Lindsten (1963) has compared the degree of somatic malformation, physical growth, and intelligence between the 45,X group and patients with other chromosome constitutions. He found some evidence that the 45,X group may have a higher degree of somatic malformation and a lower mean IQ than the other cytogenetic groups although a clear-cut distinction is difficult to obtain.

Engel and Forbes (1965) have analyzed the clinical and cytogenetic data from 32 patients with primary gonadal malfunction and concluded that the somatic anomalies are spread equally over all groups with a chromosome anomaly but are not found in tall, eunuchoid females with primary gonadal failure but without any cytogenetic abnormality. Certain clinical features, notably coarctation of the aorta and webbing of the neck, were found almost exclusively in 45,X subjects, while other clinical features found almost exclusively in this group included strabismus, abnormal external ears, blue sclerai, funnel chest, and congenital lymphedema.

The group of 96 patients studied by Polani and Angell (1969) can be divided into 38 girls with evidence of ovarian malfunction, short stature, webbed neck, and several of the other classic features of Turner's syndrome, and 54 girls who have evidence of ovarian malfunction and short stature only and no associated anomalies. The cytogenetic picture in these two groups was clearly quite different (Table 2-9): 37 of the 38 girls with Turner's syndrome are chromatin negative and 34 of these were 45,X. Among the girls with fewer somatic malformations 26 are chromatin negative and 28 chromatin positive; 22 of the chromatin-negative girls are 45,X, while 25 out of the 28 chromatin-positive girls are mixoploid as compared to a complete absence of chromatin-positive mixoploids among the girls with Turner's syndrome proper. From this we can conclude that while the chromosome complements do not correspond to any strict clinical grouping, the majority of girls with complete

TABLE 2–9

Cytogenetic Findings in Turner's Syndrome (*sensu stricto*), Ovarian Dysgenesis and Pure Gonadal Dysgenesis [a]

Classification	Chromatin-negative			Chromatin-positive			Total
	XO	XY	Mixo-ploid	XX	XXqi XXstr	Mixo-ploid	
Turner's syndrome	34	–	3	–	1	–	38
Ovarian dysgenesis	22	–	4	–	3	25	54
Pure gonadal dysgenesis	–	5	3	15	1	4	28
Total	56	5	10	15	5	29	120

[a] Polani and Angell, 1969.

Turner's syndrome are 45,X, while fewer girls with ovarian dysgenesis have this chromosome complement and a higher proportion are mixoploid and chromatin-positive.

The clinical features of twenty five 45,X subjects have been analyzed by Lemli and Smith (1963). These patients are invariably of short stature, and other common somatic anomalies involve virtually every part of the body. These somatic anomalies are, however, not confined to 45,X patients but as we have seen occur less commonly in conjunction with other chromosome complements. The most striking feature about the chromosome findings in ovarian dysgenesis is their extreme variability. At least 15 different sex chromosome abnormalities have been reported (see Table 2-3), and these can best be understood when considered in relation to the basic chromosome abnormality associated with ovarian dysgenesis, which is clearly the 45,X state, to the theories of sex determination discussed in Chapter 4, and to the effect of X chromosome inactivation (Volume I, Chapter 6).

Evidence has already been presented (Volume I, Chapter 6, Section IV) which shows that a morphologically abnormal X chromosome, when present, invariably becomes functionally heterochromatic, late replicating and forms the sex chromatin, and is presumably genetically inert. If this is so, then all females have an effective 45,X chromosome constitution from the time at which sex chromatin is first seen in embryogenesis (about 16 days gestation); the differences relating to the amount of sex-chromosome-derived heterochromatin present in the cells, which

must therefore be affecting the phenotype and cannot be entirely without influence. (See Section V, below; see also Chapters 1 and 4.)

II. Pure Gonadal Dysgenesis

This group includes not only those girls with true agonadism (Overzier, 1963b) but also all girls with evidence of primary ovarian malfunction whose height is over 152 cm (See Fig. 2-2). There are 40 girls in this group among the patients with ovarian malfunction whom we have been discussing (Table 2-10). 28 of these are chromatin-positive and 12 are chromatin-negative. Twenty-one of the 28 chromatin-positive patients have an apparently normal female chromosome complement (46,XX), one has an X isochromosome, and six are mixoploids. Nine of the chromatin-negative patients have a 46,XY chromosome complement and three are 45,X/46,XY (see Table 2-10). The two most interesting groups here are clearly those with normal chromosomes, who comprise 75% of tall girls with ovarian dysgenesis. The remainder with abnormal chromosomes may simply consist of a few girls with ovarian dysgenesis who are of normal or nearly normal height and who lack any other somatic anomalies. Generally, both the XX and XY groups are tall and of eunuchoid appearance; they have primary amenorrhea and lack of secondary sexual characteristics. They usually have gonadal streaks, although even these may be absent. The internal genitalia are generally infantile and consist of Fallopian tubes and a small uterus (Table 2-11).

This phenotype can be explained by a primary failure of gonadal development early in embryonic life which results in fetal castration and

TABLE 2–10

Chromosome Findings in 40 Patients with Pure Gonadal Dysgenesis

Chromosome analysis	No. of patients	Proportion
46,XX	21	0.53
46,XY	9	0.23
45,X/46,XX	2	0.12
45,X/46,XY	3	
46,XXqi	1	0.03
45,X/46,XXstr	4	0.10
Total	40	1.01

hence a complete absence of the usual hormonal environment which determines the sexual phenotype. Jost (1953, 1961) has shown that early fetal castration in rabbits caused the fetus to develop into a female irrespective of the genotype.

There is some evidence of a genetic basis for XY pure gonadal dysgenesis. There are two reports of XY gonadal dysgenesis in sisters (Cohen and Shaw, 1965; Brøgger and Strand, 1965) and one report in twins (Frasier *et al.*, 1964). Recently, Barr *et al.* (1967) have reported two sisters, one with pure gonadal dysgenesis and one with male pseudohermaphroditism, and finally Sternberg *et al.* (1968) have reported a family in which the propositus, a maternal cousin, and a maternal aunt all have XY gonadal dysgenesis (Fig. 2-10). These reports suggest the presence of a gene which causes the primary sex cords in the medulla to degenerate so that a testis fails to develop in an XY fetus. In the absence of testicular development no fetal androgens will be produced; this will lead to a failure of development of the Wolffian ducts, persistence of the Müllerian ducts, and in the absence of androgens the development of a female phenotype. These "women" should be tall since they have male growth control centers. If we assume that the same gene is involved in XY male pseudohermaphroditism—and this seems likely in the family reported by Barr *et al.* (1967)—then the different phenotypes can be accounted for by variations in penetrance and expressivity, a lower penetrance leading to poor testicular development, but some androgen production and hence a more masculinized and truly intersexual phenotype (see also Chapters 3 and 4).

The cause of XX gonadal dysgenesis may be genetic or environmental leading to a blockage of gonadal development. The result of this may be either a complete absence of gonads or the development of streak gonads. These girls should be of normal female stature since they have a full complement of female growth controlling centers on the X chromosomes.

III. Turner's and Ullrich's Syndrome in the Male

There are a few reports of males who have some of the developmental anomalies seen in Turner's syndrome, in particular webbing of the neck and short stature (Polani, 1962). These boys may have normal gonadal, genital, and secondary sexual development before puberty (Ullrich's syndrome in the male). However, more frequently, prepubertal development is abnormal and some affected boys may have hypospadias, unilateral or bilateral failure of testis descent. Those testes which do descend are small, especially after puberty; other postpubertal

TABLE 2–11

Clinical Findings in 20 Patients with 46,XY Pure Gonadal Dysgenesis [a]

Age	Height (cm)	Clitoral enlargement	Gonads	Somatic anomalies	Comments
19	169	–	Not palpable	None	–
26	167	–	Left absent; right dysgenetic	None	Sertoli cells lining occasional tubules, right gonad
28	171	–	Not palpable	Left kidney small and rotated	–
20	–	? +	Atrophic white ridges	–	Culdoscopy
36	175	+	Streaks	None	Gonadal stroma and Leydig cells
19	171	+	Tumors	None	Right gonocytoma III; left dysgenetic (? seminiferous tubules).
21	172	–	Streaks	None	–
6 (twins)	Normal	–	Streaks	None	Bilateral gonadoblastoma
6 (twins)	Normal	–	Streaks	None	Right gonadoblastoma. Nests of immature germ and Sertoli cells
17	166	–	Streaks	None	–
17	169	–	Very small	None	–
21 (sisters)	156	+	Left measured 7 mm	Short fourth and fifth metacarpals	Right gonadoblastoma

27 (sisters)	168	–	Streaks	None	Right gonadoblastoma
17	156	–	Absent	Minor	–
12	155	–	Left streak	None	Right gonadoblastoma
21	168	–	None found	Slight webbing on left side of neck	–
18	164	–	Ovary	None	Bilateral dysgerminoma
27	–	–	Right streak	Virilism	Left dysgerminoma
22	169	+	Streaks	None	–
33	174	–	Right streak; left bean-sized	None	Y chromosome deleted. Some hyalinized tubules in gonad

[a] From Barr *et al.*, (1967).

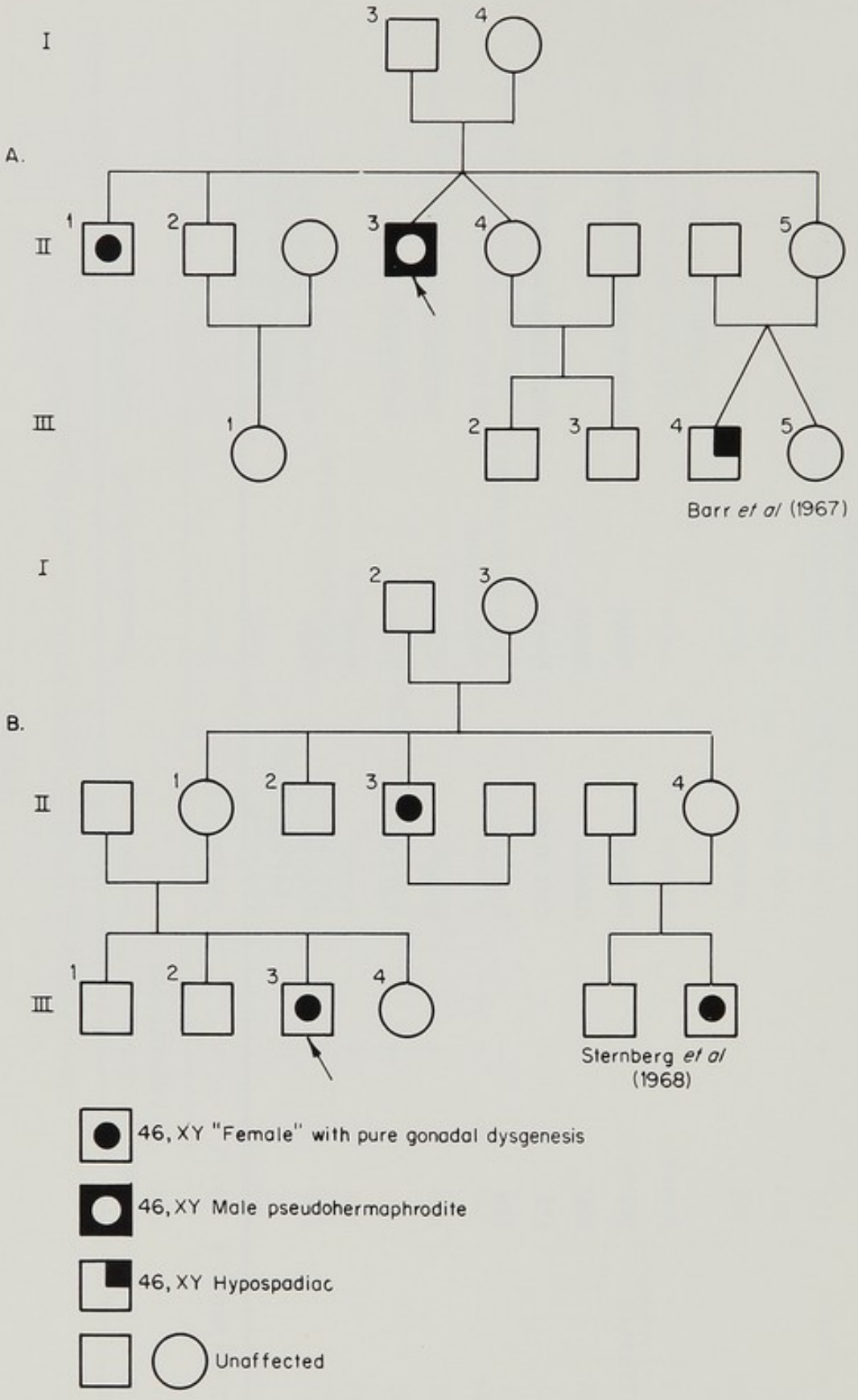


FIG. 2-10. Pedigrees of two families in which females with pure gonadal dysgenesis and in one case male pseudohermaphroditism and a male with hypospadias occur together. (see also Fig. 11-6 (a) From Barr *et al.*, 1967; and (b) from Stenberg *et al.*, 1968).

testicular abnormalities include an abnormal histological picture and a failure of endocrine or exocrine testicular function. When such gonadal failure or maldevelopment is found the eponym *Turner's syndrome in the male* is valid.

Polani (1962) reviewed 17 cases and pointed out the clinical difficulties of this classification, especially before puberty. He concluded that there is some considerable doubt as to whether a strict parallel can be drawn between females with ovarian dysgenesis and males with gonadal dysgenesis unless both testicular failure and similar somatic anomalies are observed.

Chromosome studies have been carried out on 13 patients, and a normal male chromosome complement (46,XY) was found in all of them (Court Brown *et al.*, 1960; Fraccaro *et al.*, 1961; E. H. Y. Chu *et al.*, 1961; Steiker *et al.*, 1961; Polani, 1962; De Gennes *et al.*, 1963; Caron *et al.*, 1964; Gustavson *et al.*, 1964a). One of the patients of Gustavson *et al.* (1964a) had an elongated Y chromosome, but since this was also found in his normal father, as well as in other members of the general population who show no clinical symptoms, it is probably not significant (Volume I, Chapter 4).

Polani (1962) suggested that one of the mentally deficient patients described by Ferguson-Smith *et al.* (1960b) who had small testes and webbing of the neck could be classified as a case of male Turner's syndrome. This boy had a 48,XXXY chromosome complement.

IV. X Chromosome Polysomy in the Human Female

The discovery of the 45,X and 47,XXY conditions in 1958 suggested the possibility that polysomic-X females should also occur. The first report (Jacobs *et al.*, 1959a, 1960a) described two 47,XXX women, one with secondary and the other with primary amenorrhea, but who otherwise lacked any distinctive clinical features. A considerable number of 47,XXX females have been reported since then. The clinical findings are variable, and there is no distinctive phenotype. Because of this, most 47,XXX females have been ascertained during sex chromatin surveys of various population groups.

A. *Sex Chromatin and Chromosomes*

1. Nonmixoploid Females with Two Sex Chromatin Masses

Well over 70 females have now been reported with double sex chromatin (Fig. 2-11) and who have been shown to have a 47,XXX chromo-

some complement (Fig. 2-11) (Jacobs *et al.*, 1959a, 1960a,b; De Carli *et al.*, 1960; J. H. Fraser *et al.*, 1960; Sandberg *et al.*, 1960b; J. E. S. Stewart and Sanderson, 1960; Hamerton *et al.*, 1962; Maclean *et al.*, 1961, 1962, 1968; R. W. Day *et al.*, 1963b, 1964; Court Brown *et al.*, 1964a; Taylor and Moores, 1967; J. M. Anders *et al.*, 1968). This additional chromosome is interpreted as an X chromosome because of the presence of two sex chromatin bodies, two late-replicating X chromosomes (Fig. 2-11) compared with one in 46,XX and none in 45,X females. Finally, the extreme variability of the phenotype and the lack of any major congenital malformations suggest that the additional chromosome is an X chromosome and not an autosome, as has been suggested (De Carli *et al.*, 1960; Sandberg *et al.*, 1960b).

2. Nonmixoploid Females with More Than Two Sex Chromatin Masses in the Interphase Nucleus

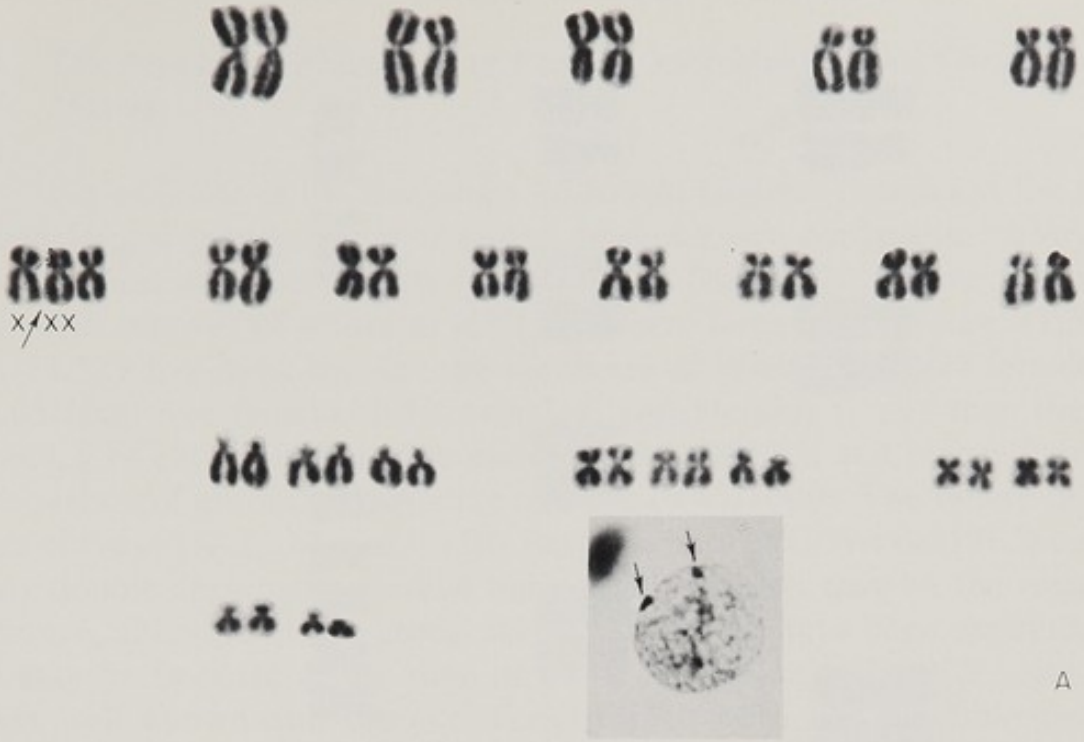
Five patients have been reported, all of whom are mentally defective, who have three sex chromatin masses in some interphase nuclei. Chromosome studies revealed a 48,XXXX chromosome complement (Fig. 2-12) with 18 chromosomes in the X+ 6-12 group and four presumptive X chromosomes, three of which showed late DNA synthesis (Carr *et al.*, 1961c; R. W. Day *et al.*, 1964; De Grouchy *et al.*, 1968a; Lejeune and Abonyi, 1968; Di Cagno and Francheschini, 1968).

3. Mixoploid Females with Double Sex Chromatin Masses

Four women with double sex chromatin masses have been reported who proved to be mixoploid 46,XX/47,XXX, and two further women with normal menstruation were found to have 45,X/47,XXX chromosomes (Maclean *et al.*, 1962, 1968; Court Brown *et al.*, 1964a). Three of these were mentally deficient, two were schizophrenics, and one suffered from depression.

Bergemann (1962a,b) has reported two unrelated families (Fig. 2-13) each with Down's syndrome probands. In the first family there are three 47,XXX/48,XXXX mixoploid females, two of whom are fertile and one of whom is prepubertal. There is one female with 46,XX/47,XXX/48,XXXX mixoploidy. In the second family, the mother was 48,XXXX, and there was one sib with Down's syndrome. These families supply further evidence that there may be some genetic control over nondisjunction (see Volume I, Chapter 7).

Fig. 2-11. A. Karyotype of double chromatin-positive female with a 47,XXX chromosome complement (×694). Inset—sex chromatin. B. ^{3}H-thymidine-labeled metaphase with two late-replicating X chromosomes (×1800). (B. Reproduced by courtesy of Dr. F. Giannelli.)



A



B

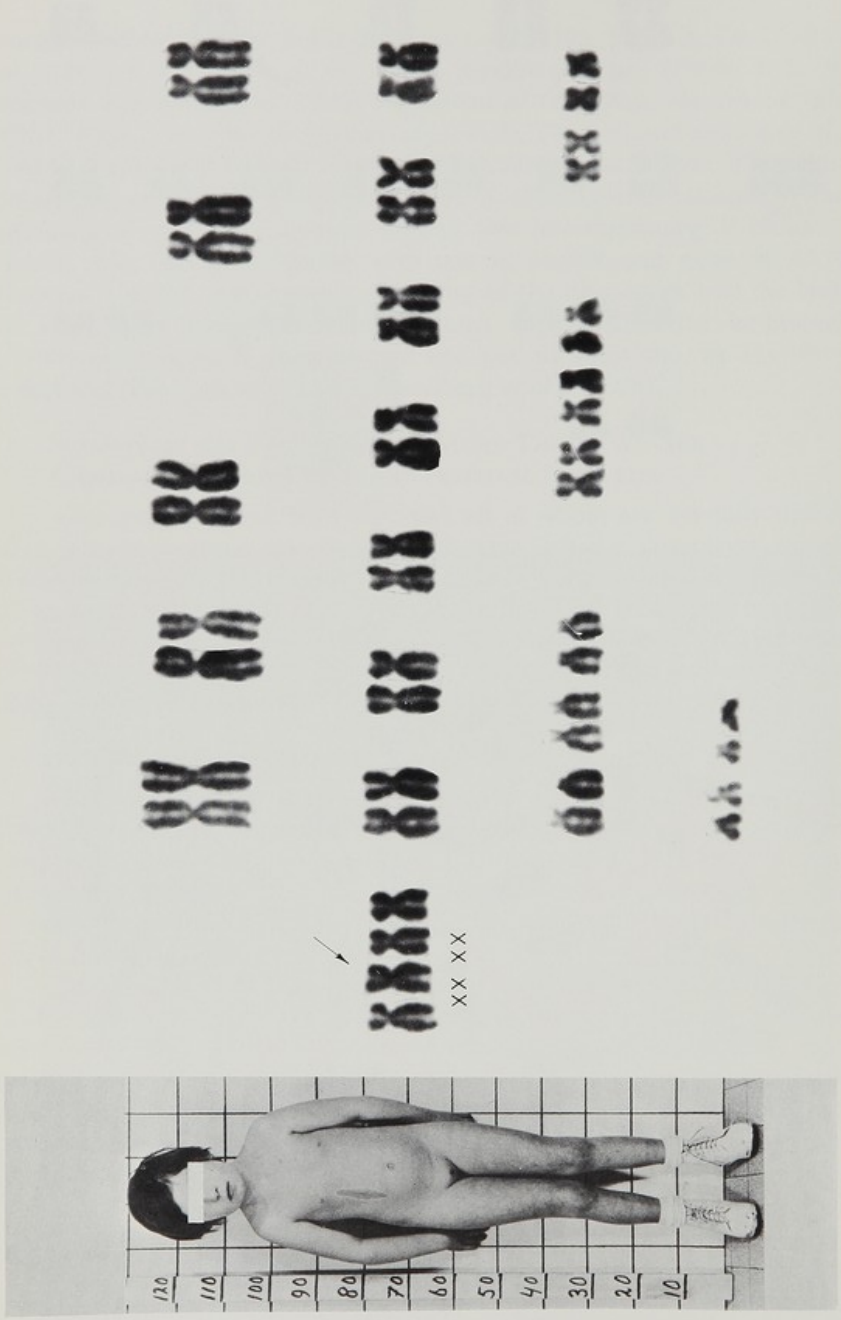


FIG. 2-12. Phenotype and karyotype of a 6½-year-old patient with a 48,XXXX chromosome complement. (Reproduced with permission of Dr. J. De Grouchy *et al.*, 1968a, and editor of *Ann. Genet.*)

B. *The Population Frequency of Females with Multiple Sex Chromatin Masses*

An estimate of the frequency of double positive females in the newborn female population is obtained from six sex chromatin surveys of populations of newborn girls (Table 2-12). These have shown 15 double positive females of whom at least nine have been shown to be 47,XXX in 23,229 live-born females, an incidence of double positive females of 0.65/1000 live female births, which is considerably lower than the frequency of chromatin-positive males (2.13/1000) but still higher than the frequency of chromatin-negative females (0.45/1000). The failure of earlier surveys (K. L. Moore, 1959; Bergemann, 1961; Wiesli, 1962) to find any double chromatin-positive babies in 5108 girls may be the result of chance, although in this group about three might have been expected, or it may be because at the time of these surveys the 47,XXX state was less well known and the occasional female with some double masses might have been missed. There have been no reports of subjects with more than two masses in the general population, so that the frequency of 48,XXXX females is much less at birth.

It is of interest to compare the frequency of 47,XXX females in the general population with the frequency among mentally defective or psychotic females (Table 2-12).

Twenty-one 47,XXX females have been found among 5308 institutionalized mentally defective females, an incidence of 3.95/1000, compared with three 47,XXX females among 857 psychotic patients, the majority of whom were schizophrenic, an incidence of 3.58/1000. The frequency of 48,XXXX females is very much lower; Carr *et al.* (1961c) found two such females in a population of mental defectives, while R. W. Day *et al.* (1964) found one 48,XXXX female among 1088 mentally defective subjects. In the same population, Day and his colleagues found three triplo-X females, giving a frequency of 48,XXXX females of about one-third the frequency of 47,XXX females in this type of population or about 0.81/1000 mentally defective females.

C. *Anamnestic Data*

1. Parental Age and Parity

Both the maternal and paternal ages at the birth of 47,XXX females are increased. The mean maternal age of thirty eight 47,XXX female subjects collected from the literature is 32.8, while the paternal age is 36.5 years (35 cases) compared to a mean maternal age for the general population of 28.7 and a paternal age of 32.2 years (Registrar General). The in-

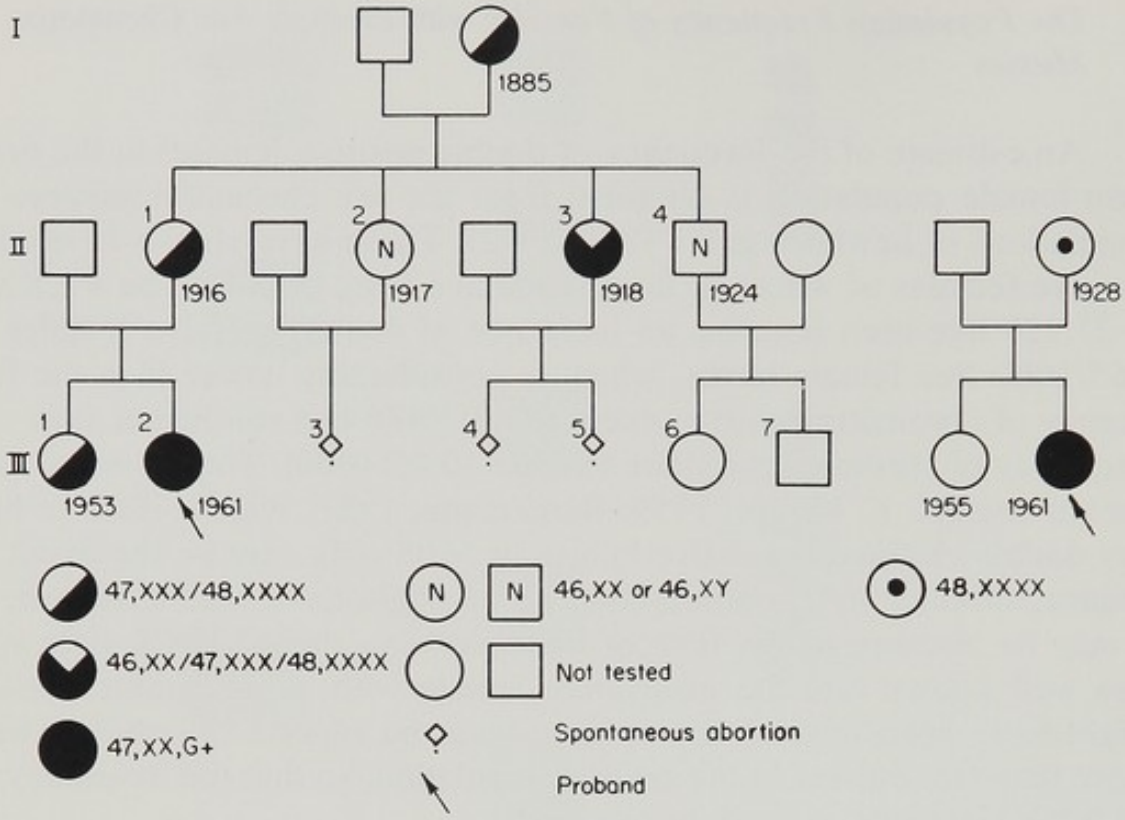


FIG. 2-13. Pedigrees of two families reported by Bergemann (1962a) containing several subjects with various different chromosome complements.

crease in maternal age in this group is clearly not so great as that found in Down's syndrome, but it is similar to the level of increase found in patients with Klinefelter's syndrome and considerably greater than that found in any of the classes of ovarian dysgenesis (Alberman and Polani, 1967).

There is also some evidence of an effect of parity similar to that observed for 47, XXY males (see Chapter 1). Analysis of the sibships of twenty six 47,XXX females (Court Brown *et al.*, 1964a) shows that 15 were last and four one from last, while of the remaining seven, two were in the early and five in the latter half of the sibship. In the present data there is no way of separating the effect of maternal age from that of parity which are, of course, related.

2. SIBSHIP CONCENTRATIONS AND ASSOCIATIONS

Apart from the families reported by Bergemann (see above) there is very little evidence of any genetic predisposition to nondisjunction, but this may result from the relative infrequency of family studies. There are a few examples of double aneuploids (48,XXX,G+ and 48,XXX,E+; see also Chapters 5 and 6), and there seems little doubt that the

TABLE 2–12

Incidence of Females with Two Sex Chromatin Bodies in Three Populations

Type of population	No. of females	Double positive females	Per cent	Increase over A	Reference
Newborn (A)	23,229	15	0.065	–	Taylor and Moores, 1967
Mental defective (B) institutions	9,249	43	0.46	Sevenfold	Maclean *et al.*, 1968
Mental hospitals (C)	7,207	17	0.24	Fourfold	Maclean *et al.*, 1968

47,XXX,E+ is much more common than would be expected by chance, occurring with a frequency of about 3.5% of E+ females (Taylor, 1968a).

In contrast to this relatively high frequency of 48,XXX,18+ double trisomics the frequency of 48,XXX,21+ trisomics is much lower, and there are very few reports of this chromosome complement among children with Down's syndrome (see also Chapter 5). Three 48,XXX,21+ trisomic girls have, however, been reported (R. W. Day *et al.*, 1964; Vignetti *et al.*, 1965; Taylor, 1968) and all have typical features of Down's syndrome without any additional phenotypic abnormalities. The expected chance frequency among the newborn of 48,XXX,E+ or D+ is about one in five million, and it is about one in one million for 48,XXX, G+. The finding of three 48,XXX,18+ females among 89 E+ females gives a frequency of about one double trisomic female per 100,000 female births, a fiftyfold increase over expectation. 48,XXX,21+ females are very rare, and there are no data on the population incidence. It is, however, likely to be lower than the observed incidence of XXX,E+ double trisomy.

The relatively high frequency of XXX,18+, XXY,18+, and XXY,21+ and the lower frequency of the XXX,21+ double aneuploids provide further evidence of genetic control of nondisjunction and also provide some evidence that the association between different chromosomes is nonrandom; thus, while 18-trisomy may be equally associated with XXX or XXY sex chromosomes, 21-trisomy seems more likely to be associated with XXY sex chromosome complements.

3. Menstruation and Fertility

Nine of the 33 cases summarized by Court Brown *et al.* (1964a) were prepubertal and 24 postpubertal; of these, 14 menstruated regularly, three irregularly, and one had primary and one secondary amenorrhea; no data were available for five cases. Four triplo-X females are known to have produced children (J. H. Fraser *et al.*, 1960; J. S. S. Stewart and Sanderson, 1960; Barr, 1963). These four women have produced 12 boys and 5 girls, all of whom are phenotypically normal and have normal sex chromatin. This finding is unexpected since with random disjunction a triplo-X female should produce 50% unbalanced disomic ova so that half their sons should have XXY sex chromosomes and half their daughters should be triplo-X females. Perhaps the most reasonable explanation for this discrepancy is some form of directed segregation during oogenesis so that the disomic chromosome complement is regularly included in one of the polar bodies.

4. The Xg Blood Group in 47,XXX Females

Out of twenty six 47,XXX females, 25 were Xg(a+) which is compatible with an ultra-female distribution but by no means conclusive. This suggests that nondisjunction during oogenesis is the usual, but perhaps not the only, cause of the aneuploid condition. Both parents of ten 47,XXX females were grouped, but Xg cannot give direct evidence of the source of the additional X in these families (Race and Sanger, 1969). Two 48,XXXX females have been grouped and one complete family (Fig. 2-14); the proband is Xg(a—), the father Xg(a+), and the mother Xg(a—) (De Grouchy *et al.*, 1968a). Assuming that (1) there is no question of incorrrect paternity and that (2) one Xg^a will produce a positive reaction in the face of three Xg genes, then the father will not have contributed any sex chromosomes to his 48,XXXX daughter and all four X chromosomes are X^M. This could be owing to loss of the paternal sex chromosome during an early cleavage division or to the fertilization of an XXXX ovum resulting from successive maternal nondisjunction by a nullisomic sperm.

5. Clinical and Psychiatric Findings

There are no distinctive somatic findings in these women such as are found in girls with Turner's syndrome, and the vast majority have no congenital malformations; the nine females ascertained during sex chromatin surveys of the newborn are all considered to be normal females (Court Brown *et al.*, 1964a). One mentally deficient 47,XXX girl reported by Hamerton *et al.* (1962) was found to be a microcephalic spastic diplegic, but there is nothing to connect this phenotype with the chromosome findings. The majority of these females were located during the course of sex chromatin surveys either of the newborn population or of institutes for the mentally handicapped, and there is some evidence that a proportion of these females suffer from some form or other of mental disturbance. Out of 24 postpubertal cases in the Edinburgh series (Court Brown *et al.*, 1964a), 22 were located in institutions for the mentally handicapped. Of these, two were classed as feebleminded, five were schizophrenic, and six had some other form of psychosis. No diagnosis was given in nine cases. The incidence in this type of population is between three and four per thousand compared with less than one per thousand in the newborn general population, and it has been suggested that some triplo-X females may develop a variety of psychoses and as a result they may have postpubertal behavioural problems.

Kidd *et al.* (1963) carried out a detailed psychiatric investigation of twenty two 47,XXX patients. Eleven were classed as mentally subnormal

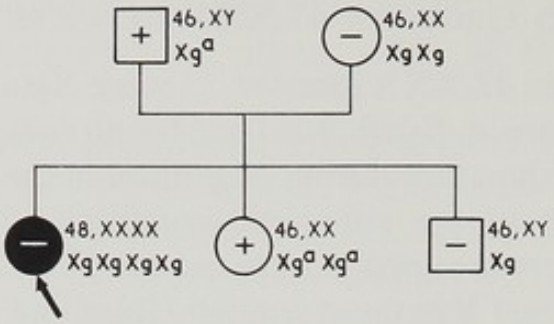


FIG. 2-14. Pedigree of family reported by De Grouchy *et al.* (1968a). The Xg blood groups show that all four X chromosomes in the proband are maternal in origin.

or severely subnormal (IQ < 69), while the remaining 11 had a normal IQ but were psychotic (Table 2-13). The majority seem to suffer from behavioral disturbances; for instance, 77% of triplo-X females have interpersonal difficulties compared with only 52% of the controls, while 81% of the triplo-X females showed social withdrawal compared with 59% of the controls. Other prominent features of the 47,XXX patients were psychomotor retardation, poverty of speech, persecutory ideas, and ideas of reference. The major psychiatric diagnosis was shown to be schizophrenia and paraphrenia (seven cases) while mental subnormality with psychoses accounted for four cases. The diagnosis of patients who were not mentally subnormal was typical of the mental hospital population in which they were observed. This was not so, however, for the mentally subnormal group in whom the most outstanding feature was a superimposed psychosis. In institutions primary subnormality (feeblemindedness) normally accounts for 80% of the patients; however, only two (16%) 47,XXX females were diagnosed to have this condition. It can be concluded from this survey that genetically predisposed mental subnormality is not a primary feature of the triplo-X state. However, the proportion of psychotic triplo-X patients was found to be surprisingly high and significantly in excess of that found among controls. Thus it is clear from these data that a proportion of triplo-X females are mentally subnormal, psychotic, or both, and eventually become institutionalized. This seems to be a feature of certain sex chromosome abnormalities since similar findings are reported among chromatin-positive males with Klinefelter's syndrome. This, however, is perhaps more understandable since these males are infertile and have postpubertal testicular atrophy. They are also frequently feminized and their antisocial and psychotic behavior might be thought to result from their sexual inadequacy, in particular from their testicular atrophy. However, the majority of 47,XXX females are relatively normal and may be fertile, and this applies also to the 47,XYY males. A number of them are married and have had children; abnormal sexual development cannot therefore account for the

TABLE 2–13

Psychiatric Findings in twenty two 47,XXX Females[a]

IQ	Diagnosis	No. of 47,XXX patients	Controls	
<69	Primary subnormality	2	51	
Subnormality or severe subnormality	Subnormality with psychosis	4	2	
	Postencephalitic state	3		
	Epilepsy	1		
	Epilepsy with psychosis	1	2	
>70	Schizophrenia	4	18	
Normal IQ range	Paraphrenia	3	4	
	Affective disorder, depression	1	5	
	Affective disorder, depression with arteriosclerotic features	1	3	Paranoid state
	Organic brain disease with psychosis	1	2	Presenile dementia
	Personality disorder, cyclothymia	1	1	Chronic alcoholism
Total		22	88	

[a] From Kidd *et al.*, (1963).

TABLE 2-14

Reference	Age at exam. (years)	Maternal age (years)	Paternal age (years)	Height[a] (cm)	Span (cm)	Weight (kg)	IQ
Carr *et al.*, 1961c	12.5	21	19	158.8 (>75P)	152.4	50.8 (>90P)	30
Carr *et al.*, 1961c	32	41	39	163.2	163.8	48.1	50
Lejeune and Abonyi, 1968	14	31	38	156 (>50 <75P)	–	60.0 (<90P)	Retarded
De Grouchy *et al.*, 1968a	6.5	26	27	125 (>90P)	–	25 (>75P)	50
Di Cagno and Francheschini, 1968	4.6	25	31	103.5 (<50P)	–	16.6 (<50P)	Retarded
Mean		28.8	30.9				

[a] P = percentile for height

[b] P = Pubic; A = Axillary

mental subnormality and psychosocial difficulties observed. Hamerton (1968b) has postulated that this may result from the abnormal amounts of sex-chromosome-derived heterochromatin which are present in these cells and which might affect developmental pathways in the cells of the brain, hence leading to mental impairment.

6. 48,XXXX Females

Five cases of 48,XXXX females have been reported (Carr *et al.*, 1961c; R. W. Day *et al.*, 1964; De Grouchy *et al.*, 1968a; Lejeune and Abonyi, 1968; Di Cagno and Francheschini, 1968). All these patients are physically normal with normal menstruation in the postpubertal cases. They are all severely mentally retarded with IQ's of 50 or less. There were no striking clinical findings; three of the girls are, however, tall for their age (> 75P) (Table 2-14).

D. *The Origin of the Chromosome Abnormality*

The incidence of 47,XXX females is about 1/1000 live-born females compared to about 1 in 450 for chromatin-positive males. However, in both conditions there is a similar increase in maternal age at birth and

Clinical Findings in Five Patients with 48,XXXX Chromosome Complement

Age of menarche (years)	Menstruation	External genitalia	Breasts	Hair[b]	Somatic malformations	Behavior
12.25	Normal	Small clitoris; otherwise normal	Normal for age	P± A−	Strabismus	Passive and withdrawn retarded speech
12.25	Normal	Normal	Small	P+ ♀ A±	Enlarged thyroid	Personality better than expected on IQ
10.5	Normal anovular cycle	Small clitoris	Normal	P± ♀	Hypertelorism; abnormal facies	–
–	–	Normal	–	–	None	–
–	–	Normal	–	–	Abnormal facies of Down's syndrome type	–

the majority of births occur late in the sibship. Xg blood groups show an ultra-female distribution which also suggests a maternal origin of the X chromosomes. It seems most likely therefore that the origin of most 47,XXX zygotes is the fertilization of an XX ovum by an X sperm. If so, this could account for the higher frequency of the 47,XXY compared with the 47,XXX state. The 47,XXY zygote is formed most commonly by the fertilization of an XX ovum by a Y-bearing sperm but also more rarely by an X ovum being fertilized by an XY sperm. The 47,XXX zygote is likely to be formed very largely by the fertilization of an XX ovum by an X-bearing sperm, and only very rarely, if at all, by the fertilization of an X ovum by an XX sperm. This would require nondisjunction at meiosis II in the male, which may be less common. Thus there are two routes taken in the formation of a 47,XXY zygote and only one certain route for the formation of a 47,XXX zygote; the former is thus likely to be the more common.

The 48,XXXX state has been shown to result from successive meiotic nondisjunction during oogenesis in at least one case (see above). Other routes include maternal nondisjunction at both divisions with loss of one X to give an XXX ovum which is fertilized by an X-bearing sperm or an XX ovum fertilized by an XX sperm.

V. The Effect of Sex Chromosome Heterochromatin in the Female

The loss or gain of X chromosomes in the female affects the amount of heterochromatin in the cell and not the amount of euchromatin, exactly as it does in the male (see Chapter 1, Section IV) except that it is derived from the X chromosomes entirely.

The effect of loss of one X in the 45,X or of part of one X in the 46,XXstr state has been discussed in some detail and results in a sterile girl who is usually of short stature and may have other developmental abnormalities. Her sterility results from ovarian malfunction and absence of germ cells at puberty. It has already been stated, however, that this absence of germ cells results from a failure of development of a functional ovary rather than from a failure of migration of germ cells from the yolk sac to the genital ridge.

Stature and psychosocial development are also affected by X chromosome abnormalities in the female, and it seems likely that centers controlling growth may be situated on the short arm of the X chromosome and mediated only when this X chromosome becomes heterochromatic. Absence of these centers as in the 45,X and some 46,XXstr states leads to abnormal growth, possibly as a result of failure of the peripheral target tissues to respond to growth hormone which has been shown to be present in normal amounts.

Psychosocial development is less affected by the loss of one X or by an abnormal X chromosome than it is by an excess of X chromosomes; additional X chromosomes, however, appear to have very little effect on fertility or on stature in females, which is in contrast to the effect of additional X chromosomes when associated with a Y chromosome in the male (Chapters 1 and 4). Thus we may conclude that abnormal amounts of sex chromosome heterochromatin affects stature and mental development (see also Chapters 1 and 4, and Hamerton, 1968b) and that the phenotypic abnormalities seen in ovarian dysgenesis can be related to imbalance in the amount of heterochromatin present in the cell, causing initially primary gonadal failure. This leads to abnormal estrogen secretion and hence infantile genitalia. Somatic abnormalities may result from insensitivity of target tissues to normal stimuli such as HGH.

Chapter 3

THE SEX CHROMOSOMES AND INTERSEXUALITY IN MAN

I. Introduction and Terminology

The terms *intersex* and *intersexuality* have been used in a wide variety of senses. They have been and still are used to describe not only cases of mixed internal or ambiguous external genitalia of various origins but also to describe cases where the primary error is chromosomal, the genitalia male or female, and the gonads either testes, ovaries, or gonadal streaks. In this context both Klinefelter's syndrome and ovarian dysgenesis have been described incorrectly as intersexes.

Polani (1962) has suggested that the term *intersex* should be restricted to those patients with ambiguous external genitalia. The basic types of urinogenital system found in various classes of intersexes are shown in Fig. 3-1. They range from the purely female to the purely male type with various intermediate states. In this classification the terms *hermaphrodite* and *pseudohermaphrodite* are dictated solely by gonadal structure; if both ovarian and testicular structures are present in the same individual such a person is known as a *true hermaphrodite*, irrespective of whether both gonads are functional, i.e., produce mature gametes. If, however, gonads of only one type are seen, the patient is called a *male* or *female pseudohermaphrodite*, depending on whether the gonads are testes or ovaries, respectively. Thus an intersex with ambiguous but predominantly female external genitalia and a female phenotype, with testes, is a male pseudohermaphrodite (testicular intersex),



FIG. 3-1. The basic types of urogenital system ranging from the "purely female" to the "purely male." A wide variety of these basic types is found in both true and pseudohermaphroditism and the exact appearance depends on the strength and time of onset of inductive activity. I "Purely female"; II common external orifice; III urogenital sinus; IV internal urogenital sinus; and V "purely male" form. In intersexual conditions this may or may not be associated with a uterus. (From Overzier, 1963d.)

while an individual with ovaries but masculinized external genitalia and perhaps a virilized phenotype is a female pseudohermaphrodite (ovarian intersex).

II. Clinical Classification and Diagnosis

Polani (1962) has pointed out that if the meaning of the term *intersex* is restricted to "individuals with ambiguous external genitalia" a few patients with normal genitalia will be excluded such as the fully masculinized and rare girl with adrenocortical hyperplasia, who should be included, and some patients will be included who strictly should not be; in this category comes the rare patient with testicular feminization and partly virilized external genitalia. Polani (1962) also discussed the meaning of "ambiguous external genitalia" and considered that some difficulties of assignment might arise at the extreme ends of the scale. However, he felt that these slight ambiguities were greatly outweighed by having clear-cut definitions of the various terms which will be used. Sex chromatin studies have greatly assisted in the clinical evaluation of intersexes in recent years, and with the exception of the mixed ovotesticular intersexes (true hermaphrodites) the sex chromatin usually corresponds to the gonadal sex.

L. Wilkins (1960) has summarized the problems involved in the differential diagnosis of individuals with ambiguous external genitalia (Table 3-1), and the classification given below which has been adapted from Polani (1962) will be used here.

1. Ovarian Intersexes (chromatin-positive female pseudohermaphrodites with virilized external genitalia) (Fig. 3-2).

(a) *Androgenic*

- (*i*) Fetal source. Congenital virilizing adrenal hyperplasia [several clinical types (Jailer and Holub, 1960)].
- (*ii*) Maternal source
  - (*a*) iatrogenic
  - (*b*) virilizing ovarian tumors

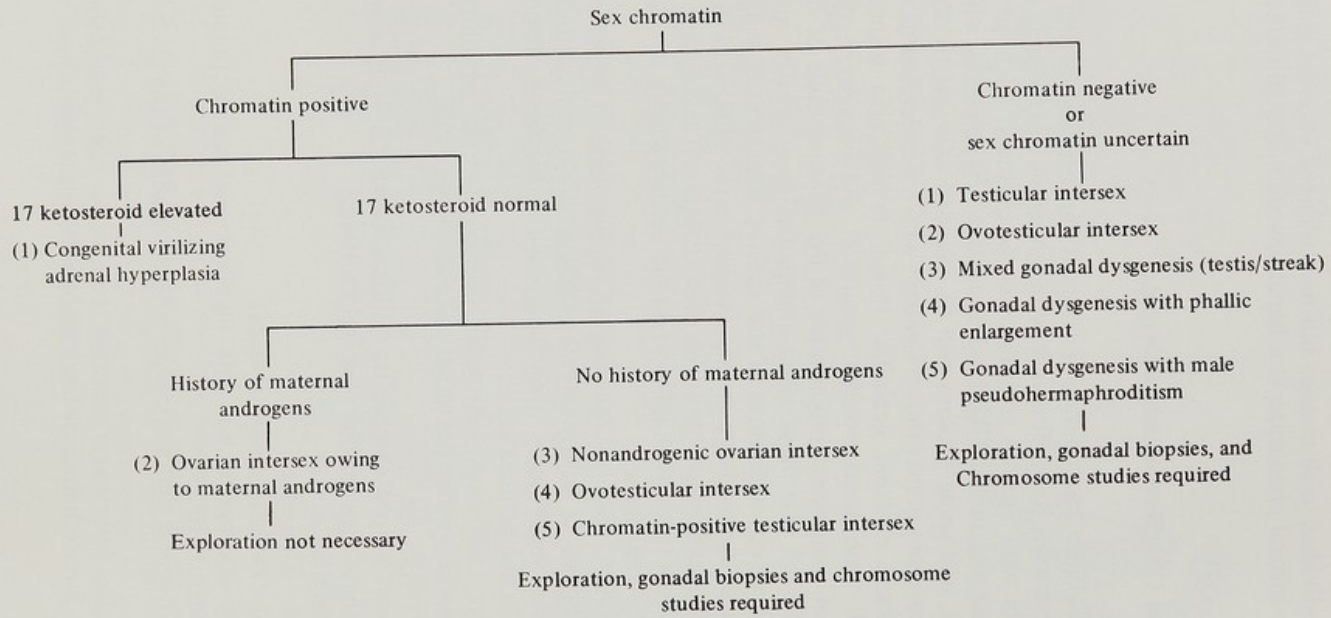
(b) Possibly androgenic but with undetermined source [clinically resembling (a) (*ii*)].

(c) Nonandrogenic and associated with anomalies of the genitourinary tract.

2. Testicular Intersexes (chromatin-negative male pseudohermaphrodites, but excluding the testicular feminization syndrome).

TABLE 3–1

Differential Diagnosis of the Patient with Ambiguous External Genitalia [a]



[a] Modified from L. Wilkins (1960) and Polani (1962).

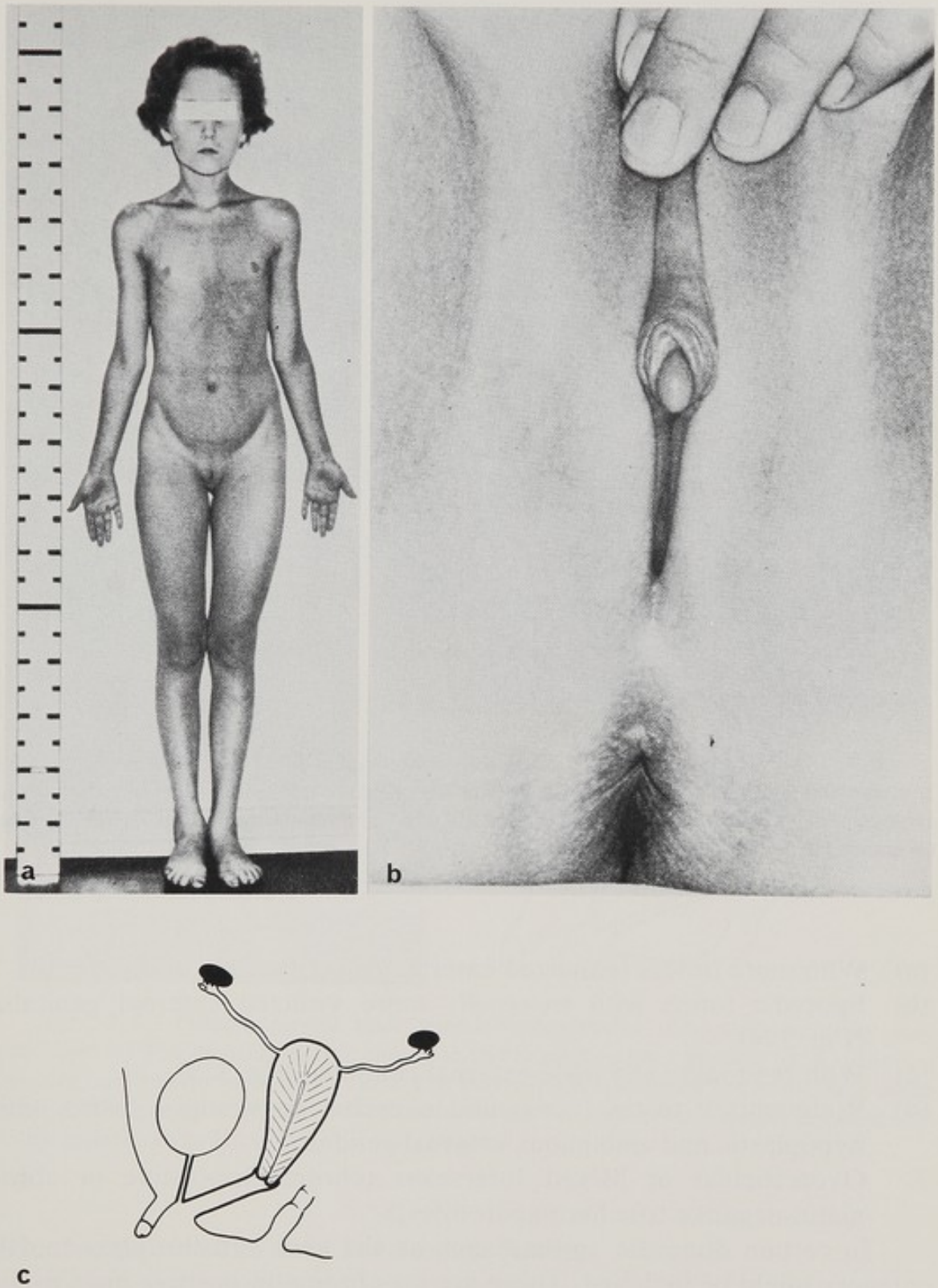


FIG. 3-2. Twelve-year-old female pseudohermaphrodite: (a) a large phallus with prepuce is present, (b) the remaining genitalia were normal (type II), and (c) internal arrangement of the genitalia. (From Overzier, 1963d.)

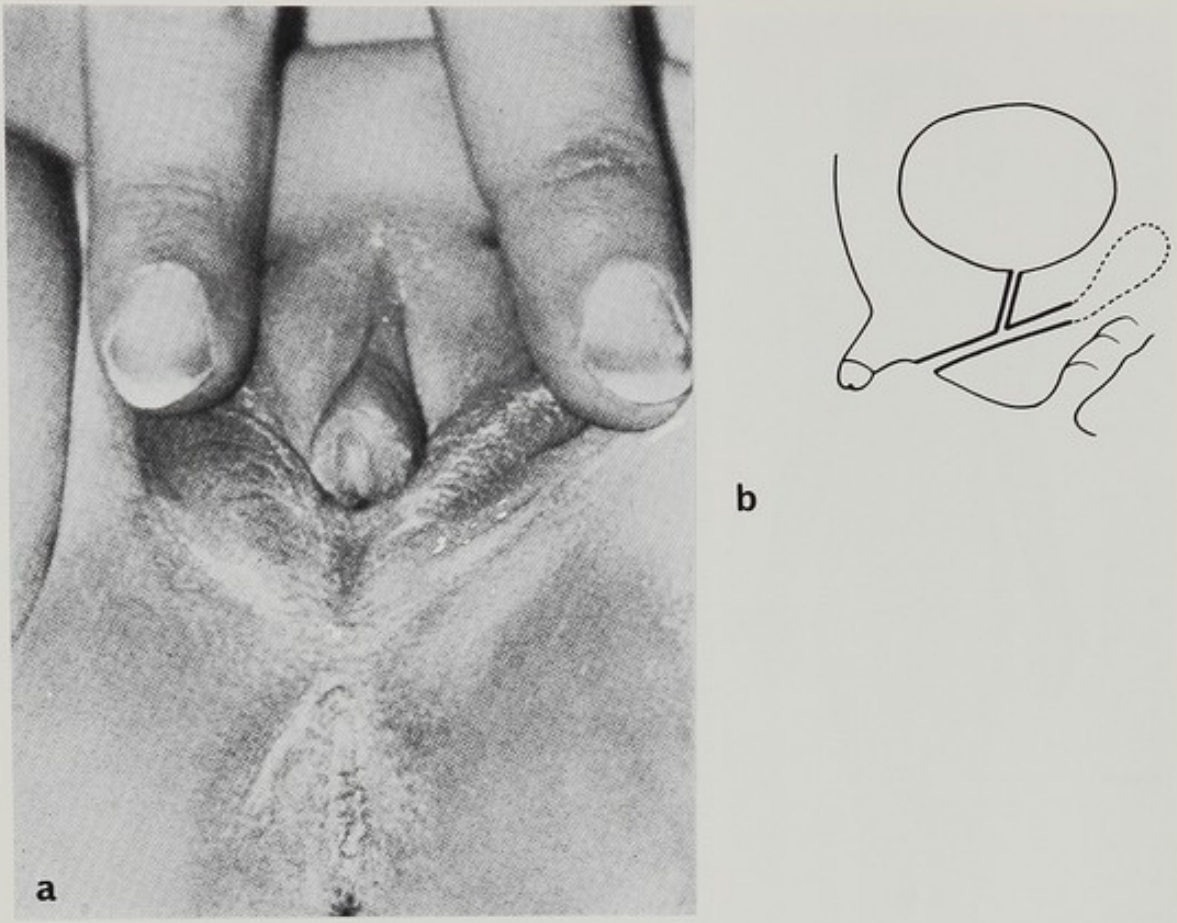


FIG. 3-3. Chromatin-negative male pseudohermaphrodite: (a) with large phallus with prepuce and glans with a dimple beneath which is orifice of urogenital sinus and (b) internal arrangement of genitalia (type III). Gonads intra-abdominal presumed testes. (From Overzier, 1963d.)

(a) With more or less feminized external genitalia (Fig. 3-3).
(b) Sporadic forms with externally more virilized external genitalia (Fig. 3-4).
(c) With predominantly male external genitalia (Fig. 3-5).
(d) Rudimentary testes (congenital anorchia or vestigial testes with hypoplastic and ambiguous external genitalia).

3. Ovotesticular or Mixed Intersexes (chromatin-positive or chromatin-negative true hermaphrodites).

In certain domestic species such as the goat and the pig a fourth category might be included. These are the chromatin-positive male pseudohermaphrodites. These have a genetic etiology; the gonads are testes and the external genitalia are virilized to a greater or lesser extent. These form the exception to the rule that the chromosomal sex invariably corresponds to the gonadal sex (see above).

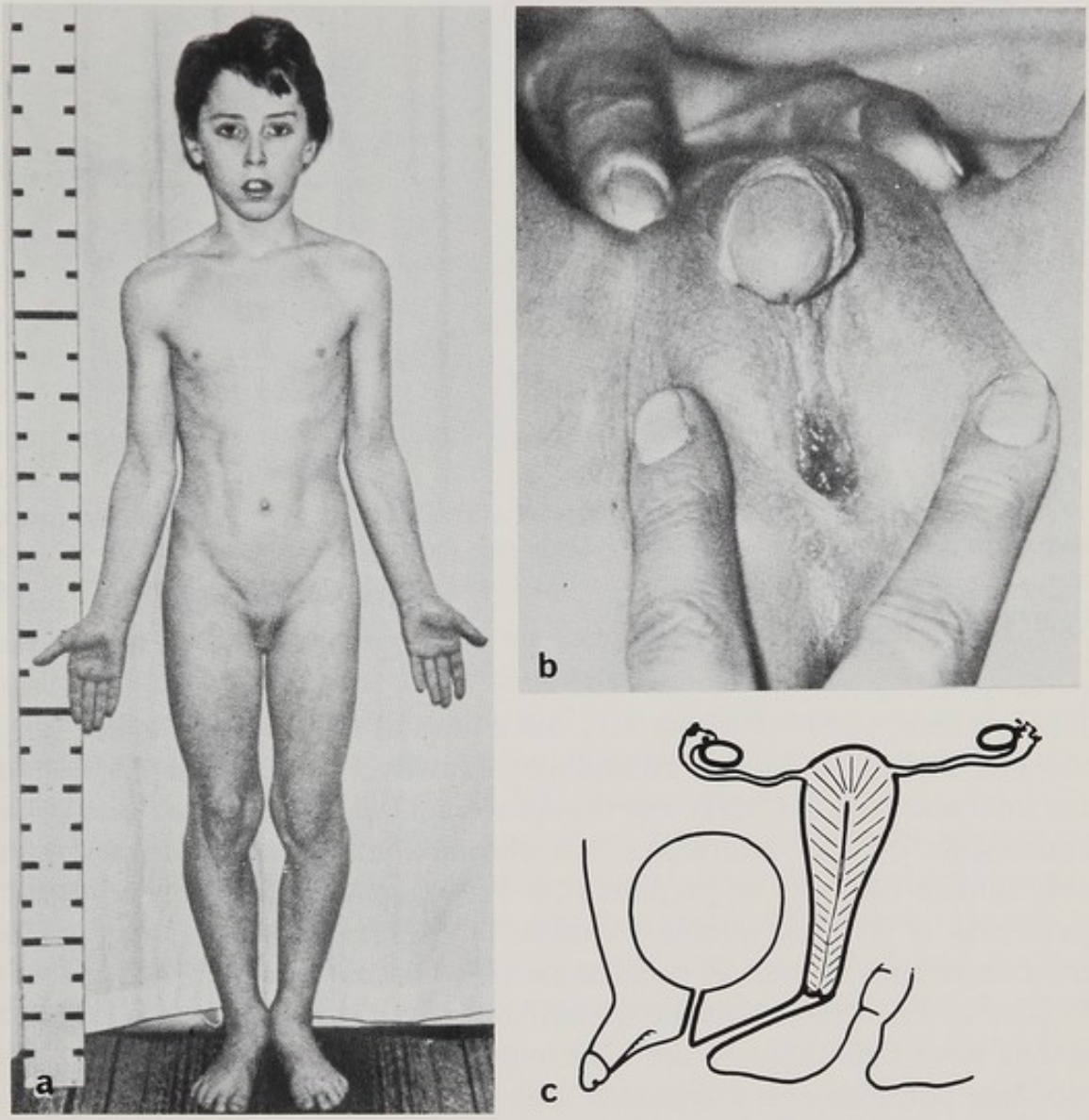


FIG. 3-4. Fifteen-year-old male pseudohermaphrodite. Chromatin-negative male physique: (a) The genitalia appear male with penile phallus; (b) a glans at tip, a redundant prepuce, and scrotum-like empty labia. The external urethral orifice lies at the base of the phallus. The gonads are intra-abdominal testes, and (c) shows the arrangement of the internal genitalia (type II). (From Overzier, 1963d.)

III. Sex Chromatin and Chromosome Studies

A. *Ovarian Intersexes*

The chromosome findings in human intersexuality cut completely across the clinical classification, there being for instance no single chromosome finding in true hermaphrodites or in male or female pseudoher-

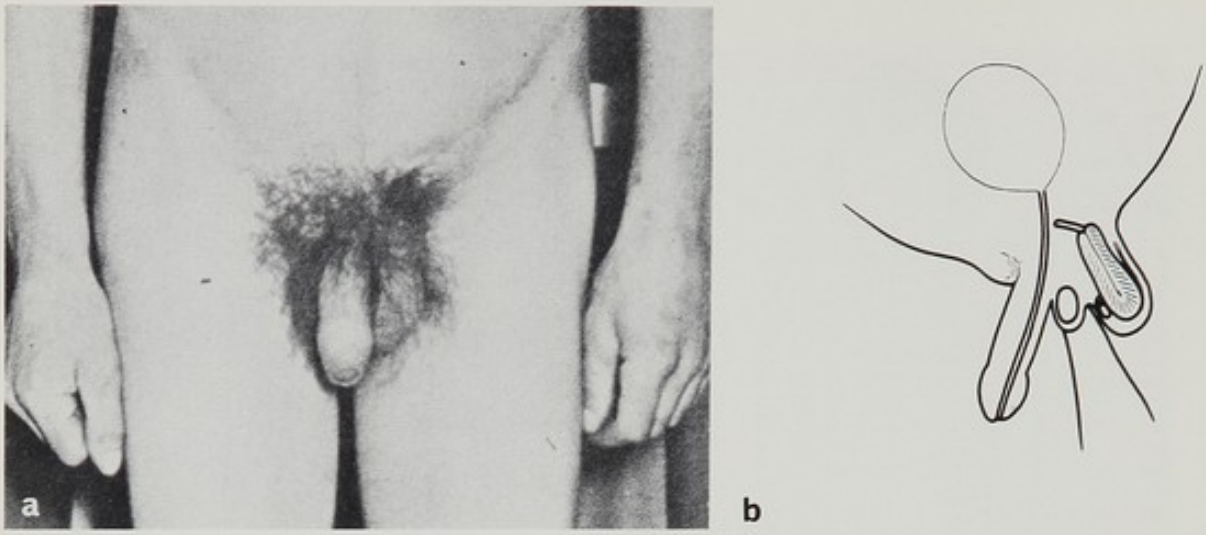


FIG. 3-5. (a) Male pseudohermaphrodite with normal external genitalia with penile urethra (type V). (b) The left side of the scrotum included an inguinal hernia containing uterus tube and right gonad (an atrophic testis). The left testis was scrotal and normal. (From Overzier, 1963d.)

maphrodites, some of whom may have normal male or female sex chromosomes while some are mixoploids. However, where the etiology of the intersex state is clearly not chromosomal but environmental as in the androgenic ovarian intersexes, the chromosome constitution is invariably female (46,XX) as predicted by Polani (1962). The nonandrogenic examples of ovarian intersexes often have a variety of urinary genital tract anomalies as well as renal anomalies (Franks and Northcutt, 1963; Ferrier *et al.*, 1964), and the majority of these subjects whose chromosomes have been studied are also found to have a normal female chromosome complement. Carpentier and Potter (1959) have suggested the term *specific female pseudohermaphroditism* where there is a disturbance of the genital system only; this includes all the androgenic intersexes, while the term nonspecific is applied to cases of female pseudohermaphroditism with associated anomalies.

B. *Testicular Intersexes*

These are usually chromatin-negative and have masculinized external genitalia and often female internal genitalia. The gonads are by definition testes, and the phenotype is usually that of a virilized female. The chromosome findings in these subjects are more variable and can arbitrarily be divided into two groups.

1. Chromatin-Negative Nonmixoploids

Two chromatin-negative male pseudohermaphrodites (Atkins and Engel, 1962; Bottura and Ferrari, 1962) have been reported. They were both Negro phenotypic females with phallic enlargement, one 13 and the other 9 years old. Both patients had a small uterus and the Fallopian tubes were prepubertal in size; no abdominal gonads were found at laparotomy. A tunica vaginalis enveloping an immature testis was found in the left labium, and no vasa or epididymis was seen, but in other respects the testis was "grossly normal" but lacked recognizable germ cells. The Sertoli cells were well developed in some tubules. No gonad was found in the right labium but simply a pea-sized nodule of fat. A very similar picture was seen in the second patient in which a gonad was found on the left side only. This was also a testis with tubules lined exclusively by Sertoli cells and containing no germ cells. Chromosome studies in one instance on bone marrow and the other on blood and skin failed to reveal a Y chromosome with certainty in either case, each patient having a 45,X chromosome complement.

Alexander and Ferguson-Smith (1961) studied eight cases of male pseudohermaphroditism with varying degrees of anomalous sex differentiation. All were found to have 46,XY chromosomes. Four of these subjects had bilateral testes which varied in development from normal to rudimentary, while four subjects with gonadal dysgenesis and male pseudohermaphroditism had a testis or rudimentary testis on one side and a streak or absent gonad on the other. Case 1 in this group had normal female genitalia and was an example of testicular feminization (see below), while the remaining seven cases all had ambiguous masculinized external genitalia and female internal genitalia. Ferrier *et al.* (1964) studied a newborn infant with ambiguous external genitalia and some of the characteristic features of Patau's syndrome. The child was chromatin negative with a 46,XY chromosome complement. No autosomal anomaly was found. Bradbury and Bunge (1960) reported a chromatin-negative male pseudohermaphrodite with ambiguous external genitalia and well-developed uterus and Fallopian tubes, a testis on one side, and a streak gonad on the other. The laparotomy findings in the girl reported by Bottura and Ferrari (1962) were very similar, but no gonad was found on the left side, while on the right in the position normally occupied by the ovary, a white almond-like structure, about 1 by 3 cm in size was found, which on histological examination was seen to be an immature testis.

A further example of a 45,X male pseudohermaphrodite with testes was reported by Bloise *et al.* (1960). In this case the phenotype was

male, the external genitalia rudimentary, and the testes immature. No ovarian or streak tissue was found. However, only 20 bone marrow cells were studied and the failure to find a Y chromosome with these low numbers of cells cannot be taken as conclusive, particularly when the proportions of cells with different chromosome constitutions can vary from tissue to tissue (see Table 2-5). The most likely explanation of the findings of 45,X chromosomes in patients with intersexuality is that they are further examples of 45,X/46,XY mixoploidy (Hirschhorn *et al.*, 1960b).

Boczkowksi and Teter (1965) have reported two sibs and a cousin with ambiguous external genitalia and rudimentary testes, all of whom were 46,XY. Three members of generation II died in the perinatal period (Fig. 3-6). Other families of this type have already been discussed (see Chapter 2, Section II) and this condition may well be found to have a genetic etiology.

2. Chromatin-Negative Mixoploid Subjects

a. The 45,X/46,XY Intersexes. The variability of the 45,X/46,XY state has already been referred to in Chapter 2 in relation to subjects with ovarian dysgenesis. This variability is presumably

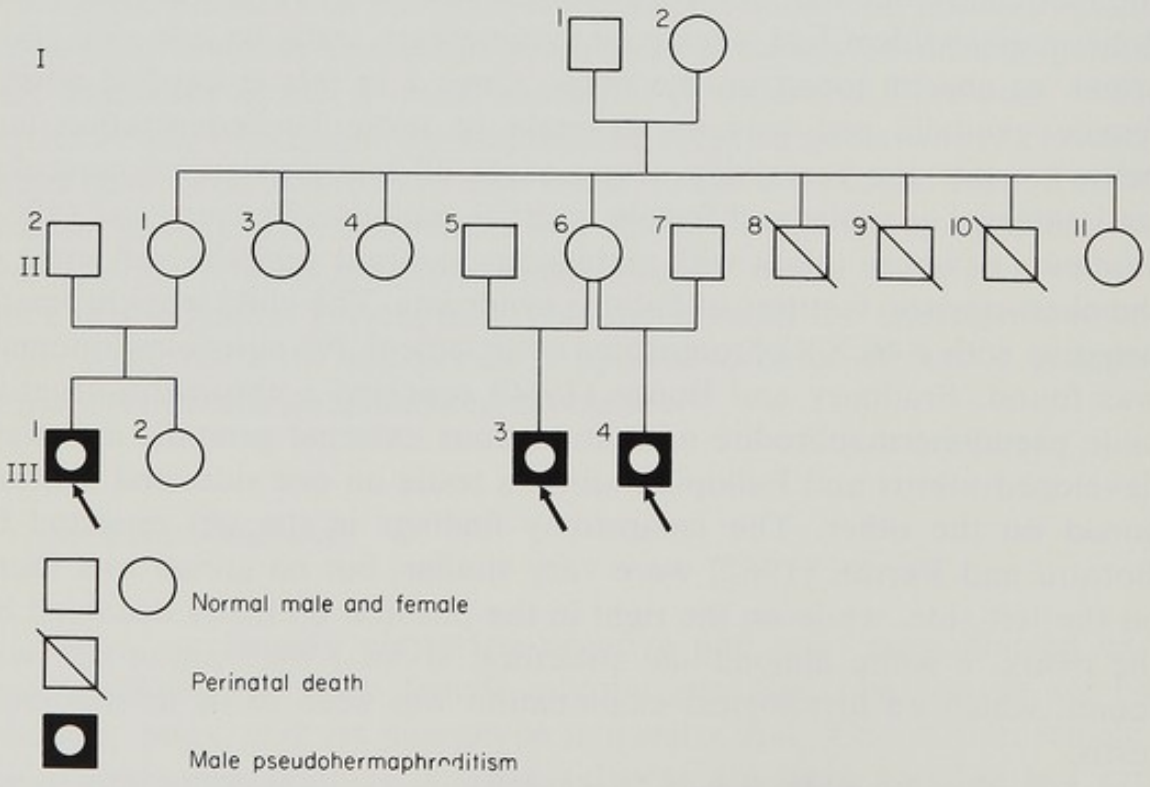


Fig. 3-6. Pedigree of family reported by Boczkowski and Teter (1965) showing familial male pseudohermaphroditism.

TABLE 3–2

Classification of Patients with a 45,X/46,XY Chromosome Complement

Group	No. of patients	Gonadal structure	Clinical phenotype	Table	Comment
I	8	Bilateral streak gonads	Ovarian dysgenesis; pure gonadal dysgenesis.	3-3	
	3	No laparotomy			
II	16	Dysgeneic testis/streak	Male pseudohermaphrodite	3-4	only XY cells in one patient. 45,X/46,XYq- (Case No. 17)
	3	Dysgeneic testis/streak; no laparotomy.	Mixed gonadal dysgenesis		
III	2	Testis/ovary	Ovotesticular intersexes; true hermaphrodites.	3-5	
	1	Rudimentary gonads.			
	1	Ovary/ovotesis			
	1	Ovotestis/ovary/tumor			
IV	4	Dysgeneic testes	Infertile males or male pseudohermaphrodites	3-6	
V	3	Testis/ovary/ovotestis with tumor.	Ovotesticular intersex	3-5	
Total	42				

TABLE 3-3

Case no.	Patient no.	Phenotype	Age at exam (years)	Height (cm)	Laparotomy	Sex chromatin	External genitalia and secondary sexual characteristics
1	111/61	♀	15	125.5	No	-ve	Underdeveloped. No pubic or axillary hair. No breasts.
2	65/62	♀	21	139.5	No	-ve	Underdeveloped. No axillary or pubic hair. No breasts.
3	10/59	♀	26	137.0	Yes	-ve	Underdeveloped. No axillary or pubic hair. No breasts.
4	170/60	♀	30	147.0	Yes	-ve	Underdeveloped. Scant axillary and pubic hair. Slight breasts.
5	200/60	♀	56	–	Yes	-ve	Female development. Axillary and pubic hair female. Limited breast development.
6	30	♀	19	150	No	-ve	Normal female. Scant axillary and pubic hair.
7	28	♀	25	153.7	No	-ve	Limited breast development
8	PRU 67/MC 270439	♀	20	162.6	Yes	-ve	Normal female. Scant pubic and axillary hair. Female distribution. Labia underdeveloped.
9	PRU 2655/VM 171143	♀	21	154.5	Yes	-ve	Normal clitoris. Scant pubic hair. No breast development.
10	PRU 2909/RJ 210749	♀	16½	136.0	Yes	-ve	Normal external genitalia. Pubic hair female scant. No breasts.
11	–	♀	26	172.7	Yes	–ve	Normal female. No breasts. Amenorrhea. Scant pubic and axillary hair.

[a] Here B stands for blood, S for skin, and G for gonad.

dependent on the gonadal structure, the effect of the gonadal hormones on the phenotype, and the timing of their secretion to the relatively short periods when the fetal tissues are sensitive. The phenotype of 45,X/46,XY subjects ranges from ovarian dysgenesis through gonadal dysgenesis with male pseudohermaphroditism to subjects with "mixed gonadal dysgenesis" in whom one gonad is a streak and the other a dysgeneic testis. This distinguishes these subjects from the true ovotesticular intersexes with an ovotestis, or ovary and testis. Subjects with simple ovarian dysgenesis have already been discussed (Chapter 2), and in the present section only the various types of intersex state will be considered.

Clinical Findings in 11 Patients with 45,X/46,XY Gonadal Dysgenesis

Internal genitalia	Tissues studied [a]	Proportion XY	Reference
Not known	B	0.70	Court Brown *et al.*, 1964a
	S	0.03	
Not known	B	0.18	Court Brown *et al.*, 1964a
Uterus and ovaries not palpable.	S	0.03	
Hypoplastic uterus.	B	0.84	Court Brown *et al.*, 1964a
Streak gonads.	S	0.07	
Infantile uterus. Streak	B	0.86	Court Brown *et al.*, 1964a
gonads.	S	0.00	
Infantile uterus. Small left gonad; no right gonad.	B	0.58	Court Brown *et al.*, 1964a
Not known	B	–	Ferguson-Smith *et al.*, 1964
Not known	B	–	Engel and Forbes, 1965
Streak gonads	B	–	Pediatric Research Unit
	S	–	unpublished data
	G	–	
Streak gonads	B	0.53	Pediatric Research Unit
	G		unpublished data
Rudimentary uterus. Right	B	0.63	Pediatric Research Unit
and left fallopian tubes	S	0.21	unpublished data
streak gonads.			Pediatric Research Unit unpublished data
Infantile uterus.	B	0.52	Judge *et al.*, 1962
Right streak gonad. ? Left streak gonad.			

Patients with 45,X/46,XY mixoploidy can be arbitrarily classified into five groups according to their gonadal structure (Table 3-2). Group I consists of 8 girls with bilateral streak gonads and ovarian dysgenesis or, if tall, pure gonadal dysgenesis (Table 3-3) and includes 3 additional girls with this phenotype but in whom the gonadal structure was not known. Group II comprises the largest single group of 16 subjects all of whom have a testis or testicular structure on one side and a typical streak gonad on the other (Table 3-4). Three further subjects who fit into this clinical group were reported with a 45,X/46,XYq– chromosome constitution (Conen *et al.*, 1961; Bigley *et al.*, 1965; Lo and Kobernick, 1965), but in one case the gonadal structure was not known (Table 3-4).

TABLE 3-4

Case No.	Age (years)	Phenotypic sex and sex of rearing	Height (cm)	External genitalia and secondary sexual characteristics
1	22	♀	143	Normal with enlarged clitoris. No breasts. Male pubic and axilliary hair.
2	4 8/12	♀	–	Enlarged clitoris. Separate urethral orifice.
3	14	♀	–	Enlarged clitoris. Amenorrhea. No secondary sexual characteristics. Urethra Normal ♀ opening.
4	14	♀	139.1	Enlarged clitoris. Pubic, axilliary, and facial hair male. Infantile breasts.
5	13	♀	129.5	Hypospadias. Phallus. Rudimentary vaginal canal. Large labial folds. No pubic or axillary hair or breasts.
6	16	♀	–	Enlarged clitoris.
7	25	♂	–	Penis with hypospadias. Scrotum.
8	5	♀	–	Enlarged clitoris with labio scrotal folds. Ambiguous.
9	35	♀		Enlarged clitoris. Normal labia. No breasts. Pubic hair female.
10	17	♀		Phallus. Labio scrotal fusion. No hair. No breast development.
11	–	?	–	Bifid scrotum. Left inguinal hernia. Small phallus. Urethral opening at base.
12	3/12	♀	–	Ambiguous enlarged clitoris. Labial folds. Pea-sized mass in left groin.
13	14	♀	–	Phallus with hypospadias. Labio scrotal folds.
14	1	♂		Phallus, perforate urethra.

Clinical Findings in 19 Patients with "Mixed Gonadal Dysgenesis" and 45,X/46,XY Chromosome Complements

Internal genitalia	Sex chromatin	Tissues studied [a]	Proportion XY cells	Reference
Small uterus. Right and left Fallopian tubes. Left gonad testis (abdominal). Right gonad streak.	-ve	B	0.48	Willemse *et al.*, 1962
Hypospadias. Uterus. Right and left Fallopian tubes. Left gonad streak; right gonad testis (abdominal).	-ve	B	–	Greenblatt *et al.*, 1964
Uterus. Right and left Fallopian tubes. Right gonad testis (abdominal). Left gonad streak gonad.	-ve	B	–	Greenblatt *et al.*, 1964
Small vagina, uterus. Right and left Fallopian tubes. Gonads, testis, and streak.	-ve	B	0.73	H.H. Turner *et al.*, 1963
Uterus. Right and left Fallopian tubes. Right testis. Left streak.	-ve	B	0.81	H.H. Turner *et al.*, 1963
Rudimentary uterus and Fallopian tubes. Right testis. Left streak. Right vas deferens.	-ve	B S	– –	W.P.U. Jackson *et al.*, 1966
Rudimentary uterus and left Fallopian tube. Right Fallopian tube absent. Right testis scrotal. Left streak gonad.		B S	– –	W.P.U. Jackson *et al.*, 1966
Rudimentary uterus and right Fallopian tube No left Fallopian tube. Right streak. Left testis. Left epididymis and vas deferens.	-ve	B	–	Zourlas and Jones, 1965
Uterus. Right Fallopian tube, no left Fallopian tube. Right testis. No left gonad.	-ve	B	–	Zourlas and Jones, 1965 46,XY cells only found
Unicornate uterus. Left Fallopian tube. Hypospadias. Left streak. Right testis.	-ve	B BM	– –	Zourlas and Jones, 1965 46,XY cells only found
Uterus. Right Fallopian tube. Right gonad streak. Left gonad testis (scrotal).	-ve	B	–	Conen and Erkman, 1963a
Uterus. Right and left Fallopian tubes. Right gonad streak. Left gonad testis. Left epididymis.	-ve	BM B S G	0.00 0.20 0.00 0.00	Fraccaro *et al.*, 1966
Uterus. Right gonad streak. Left gonad testis.	-ve	B S	–	Pediatric Research Unit/2850
Uterus. Right and left Fallopian tubes. Right gonad streak, left gonad testis. Left epididymis.	-ve	B S	– –	Pediatric Research Unit/2198

TABLE 3-4 (cont'd)

Case No.	Age (years)	Phenotypic sex and sex of rearing	Height (cm)	External genitalia and secondary sexual characteristics
15	13	♀	–	Phallus, perforate urethra
16	14	♀	147	Enlarged clitoris. Peniforme vulva. Normal secondary sexual characteristics–masculine.
17	13	♀	147.3	Enlarged clitoris. Post-urethral orifice. No breasts. Amenorrhea. Pubic hair female.
18	–	–	?	–
19	3	♀	–	Ambiguous phallic enlarged clitoris. Hypospadias. Thick labia.

[a] Here B stands for blood, S for Skin, BM for Bone Marrow, G for Gonad, and Tu for Tumor.

The sex or rearing of 15 out of 17 of these subjects was female while of the remaining four, two were reared as males and two were of doubtful sex. In most cases the external genitalia were ambiguous while the internal genitalia consisted of a rudimentary or normal uterus and Fallopian tubes. The phallus was usually enlarged and a rudimentary vagina was usually present. The testes were normally dysgeneic and spermatogenesis was absent. Where the phenotype was female, there was usually no breast development and stature was frequently short.

Group III comprises eight ovotesticular intersexes (true hermaphrodites) (Table 3-5); two of these have an ovary on one side and a testis on the other, one an ovary and an ovotestis, while of the remaining five patients, one had rudimentary gonads; three had missing gonads on one side and an ovotestis on the other. Two of these three patients had a seminoma in the testicular part of the ovotestis. The final patient had an ovary on one side and a gonocytoma on the other. The external genitalia consisted of a phallus which in some cases could have been a penis or a clitoris and which was usually abnormal in structure. The internal genitalia usually consisted of a vagina, uterus, and tubes.

There is an interesting group of four subjects with this chromosome constitution (group IV) who have a masculinized or even a male pheno-

Internal genitalia	Sex chromatin	Tissues studied[a]	Proportion XY cells	Reference
Uterus. Right and left Fallopian tubes. Right gonad streak. Left gonad testis.	-ve	B S	– –	Pediatric Research Unit/2325
Infantile uterus. Right and left Fallopian tubes. Right gonad testis, left gonad streak. Right epididymis.	-ve			Lambert and Netter, 1962
Right uterus. Right and left Fallopian tubes. Small left gonad testis. Right gonad streak. Left epididymis.	–ve	B BM	0.60 –	Conen *et al.*, 1961 45,X/46,XYq-
Rudimentary uterus. Right and left Fallopian tubes. Right gonad testis. Left gonad streak.	–ve	B S G Tu	– – – –	Bigley *et al.*, 1965 45,X/46XYq-
No laparotomy	–ve	B	–	Lo and Kobernick, 1965 45,X/46,XYq-

type, relatively normal external male genitalia, and infertile dysgeneic testes (Table 3-6). Two out of these four subjects were married (F. J. W. Lewis *et al.*, 1963a; Ferrier *et al.*, 1963), and one of them had a congenital hypospadias with a perineal orifice and bifid scrotum, although his male sex had apparently never been questioned. His internal genitalia consisted of a uterus and rudimentary right Fallopian tube, and in the position of an ovary a mass of tissue superficially resembling that structure but which lacked any true ovarian tissue. The left gonad of this patient had been removed earlier and histologically defined as a "malignant seminoma of an undescended testis." The second of these males had a normal penis and a right scrotal testis which was originally undescended; an orchidopexy was performed at the age of 5 years; the right gonad was unfortunately not biopsied so that true hermaphroditism based on the presence of ovarian stroma cannot be excluded. The left gonad was small and of testicular structure but with a complete absence of spermatogenesis. These two males should therefore perhaps both be included in group II, but in view of their normal male phenotype, they have been arbitrarily placed in a separate group. Two other subjects (Table 3-6), one with an essentially masculine and the other with a feminine phenotype were reported by De Grouchy *et al.* (1963a) and Mellman *et al.*

TABLE 3-5

Case No.	Age (years)	Phenotypic sex and sex of rearing	Height (cm)	External genitalia and secondary sexual characteristics
1	10	♂	100	Phallus. Urethral meatus at base of Phallus. Bifid scrotum.
2	18	♀	–	Not known
3	14	♀	–	Not known
4	4/12	♀	–	Phallus with external urethral meatus. Vaginal orifice normal. Enlarged labia majora.
5	11	♂	–	Phallus bifid scrotum. Perineal urethra. Vagina.
6	–	♀	–	Enlarged clitorus otherwise normal ♀ Perineal urethra. Vagina.
7	–	♀ (masculinized)		Enlarged clitoris. Perineal urethra. Vagina
8	11	♀	–	Enlarged clitoris. Secondary amenorrhea. Breast atrophy. Excessive hair.

[a] Here B stands for blood, SR for Skin Right, SL for Skin Left, S for skin, and BM for bone marrow, NK for not known.

(1963). The first was a child with a vulviforme hypospadias and histologically normal scrotal testes. Laparotomy did not reveal any female internal genitalia or remnants of the Müllerian ducts. This subject can strictly be classed as a male pseudohermaphrodite. The second subject had a female phenotype with clitoral enlargement and intra-abdominal testes. She had a normal appearing uterus and Fallopian tubes. Neither of the gonads revealed any evidence of ovarian tissue and 45,X/46,XY mixoploidy was found in both gonads as well as skin, bone marrow, and blood. A final group of three patients (group V) (Table 3-5) had an essentially female phenotype. The external genitalia consisted of an enlarged clitoris with a perineal urethra. Internally a vagina, uterus, and bilateral Fallopian tubes were present. On one side there was a rudimentary

Clinical Findings on Eight Presumptive True Hermaphrodites with 45,X/46,XY Chromosome Complements

Internal genitalia	Sex chromatin	Tissues studied [a]	Proportion XY cells	Inter-sex class	Reference
Uterus. Left Fallopian tube. Left ovary, right testis (scrotal).	-ve	B SR SL	0.67 0.46 0.38	Lateral	Court Brown *et al.*, 1964a
Uterus. Right and left Fallopian tubes. Right testis. Left ovotestis.	-ve	NK	NK	Bilateral	Capanna *et al.*, 1964
Rudimentary uterus and right and left Fallopian tubes. Rudimentary gonads.		NK	NK	?	Capanna *et al.*, 1964
Uterus. Right and left Fallopian tubes. Right ovotestis. Left ?	-ve	BM	0.40	?	Hirschhorn *et al.*, 1960a
Uterus. Right and left Fallopian tubes. Right ovary. Left testis. No left epididymis.	-ve	B S	–	Lateral	Pediatric Research Unit (unpublished data) 3026
Uterus. Right and left Fallopian tubes. One gonad absent, other seminoma in ovotestis.	-ve	B	0.79	Unilateral variant	O.J. Miller *et al.*, 1960
Uterus. Right and left Fallopian tubes. One gonad absent. Other seminoma in ovotestis. Large clumps of Leydig cells in gonad.	-ve	B Connective tissue	0.46 0.00	Unilateral variant	O.J. Miller *et al.*, 1960
Uterus. No Fallopian tubes. Right ovary, left rudimentary. Developing gonocytoma.	-ve	B	0.41	Lateral variant	Borghi *et al.*, 1965

gonad and on the other a developing tumor. In two cases this was a seminoma, and in the other it was identified as a gonadoblastoma (O. J. Miller *et al.*, 1960; Borghi *et al.*, 1965).

Finally, Turpin *et al.* (1965) have reported a pair of monozygotic twins, one of whom was 45,X and the other 46,XY. The origin of these was presumably from a single XY zygote with loss of the Y chromosome from one of the blastomeres at the first cleavage division as the two separated to form the twin pair (see Volume I, Chapter 7, Section II). The XY twin was a normal male while his sister had ovarian dysgenesis.

b. Other Mixoploid States in Testicular Intersexes. Several other types of mixoploid testicular intersexes have been re-

TABLE 3-6

Case No.	Age (years)	Phenotypic sex and sex of rearing	Height (cm)	External genitalia and secondary sexual characteristics
1	35	♂	173	Penis normal. No gynecomastia. Scrotum.
2	4	♂	102	Vulviforme hypospadias phallus, bifid scrotum.
3	9	♀	111	Enlarged clitoris. Urogenital sinus.
4	45	♂	–	Penis. Male hair distribution. Hypospadias, perineal orifice, and bifid scrotum.

[a] Here B stands for blood, S for skin, RT for right testis, and LT for left testis.

ported (Table 3-7) and nine subjects are included in this group, five of whom are of male and four of female phenotype. In each case the external genitalia are somewhat ambiguous. In five subjects both gonads are testes which are generally intra-abdominal but may be inguinal or even scrotal. In three patients one gonad was a testis, while the other was an undifferentiated streak in one case, and completely missing in two. In the female reported by Fraccaro *et al.* (1962c) the gonads could not be palpated and laparotomy was not performed. These subjects should therefore perhaps be termed *mixed gonadal dysgenesis with intersexuality*.

C. *Mixed Ovotesticular Intersexes (Chromatin-Positive or -Negative True Hermaphrodites)*[13]

Ovotesticular intersexes can be classified into three groups according to the type of gonad. These are (1) lateral, in which there is a testis on one side and an ovary on the other (Fig. 3-7); (2) unilateral, with an ovotestis on one side and an ovary or testis on the other (Fig. 3-8), and (3) bilateral with an ovotestis on both sides (Fig. 3-9). If we

[13]Since this section was written my attention has been drawn to a paper by Neimann and Fonder (1967) in which data on 250 true hermaphrodites were summarized.

Clinical Findings on Four 45,X/46,XY Males with Dysgeneic Testes

Internal gentalia	Sex chromatin	Tissues studied [a]	Proportion XY cells	Reference
Right testis small. Left testis. Slightly larger, scrotal. No spermatogenesis.	-ve	B	0.53	Ferrier *et al.*, 1963
Right and left scrotal testes. Epididymis right and left. Right and left vasa. No uterus or Fallopian tubes.	-ve	S B	0.00 0.50	De Grouchy *et al.*, 1963a
Uterus and right and left Fallopian tubes. Right and left testes (abdominal).	-ve	B S RT LT Uterus	0.53 0.41 0.30 0.00 0.00 0.23 0.00	Mellman *et al.*, 1963
Small vagina. Small cervix. Rudimentary uterus. Rudimentary right Fallopian tube. Left gonad seminoma. Right streak.	-ve	B	0.30	F.J.W. Lewis *et al.*, 1963a

exclude for the present the very rare 46,XX/46,XY condition because of its different origin, there are 84 ovotesticular intersexes reported, in 71 of which the chromosomes have been studied (Table 3-8).

1. 46,XX True Hermaphrodites

Forty-five of these intersexes have a 46,XX chromosome complement and of these 24 are unilateral or presumptive unilateral, seven are lateral, and 12 are bilateral (Table 3-8). The major clinical findings are given in Table 3-9. The external genitalia in 22 of the 24 unilateral intersexes are ambiguous and consist usually of a phallus or enlarged clitoris; a scrotum is present in eight subjects, absent in one, and enlarged labioscrotal folds are reported in eight cases. Where the phenotype is masculine there is often gynecomastia (Fig. 3-10). A uterus is usually found and may be rudimentary or in some cases unicornate, and at least one Fallopian tube is found in most subjects. The ovotestis is found most frequently in place of the right gonad rather than the left, and the opposite gonad is far more frequently an ovary rather than a testis. Male ducts (Wolffian derivatives) are recorded infrequently; an epididymis is recorded on the same side as the testis or ovotestis in six subjects and vasa deferentia are present in five. The seven lateral ovotesticular intersexes have a testis on one side which is usually intra-abdominal or inguinal, although it may be scro-

TABLE 3–7

Clinical Findings in Some Other Mixoploid Testicular Intersexes

Case No.	Age (years)	Phenotypic sex and sex of rearing	Height (cm)	External genitalia and secondary sexual characteristics	Internal genitalia	Sex chromatin	Tissues studied [a]	Chromosome complement	Reference
1.	13/12	♀	–	1.5 cm phallus with large labia. No palpable gonads.	Uterus. Right and left Fallopian tubes. Intra-abdominal testes with infantile seminiferous tubules.	-ve	B	45,X/47,XXY	Miles *et al.*, 1962
2.	–	♀	–	Phallus underdeveloped. Perineal hypospadias. Bifid scrotum with two small gonads.	Uterus. Right and left Fallopian tubes.	-ve	B S G	45,X/46,XY/47,XYY	Fraccaro *et al.*, 1966
3.	–	♀	–	Phallus with bifid scrotum. Urinogenital sinus at base of phallus. Vagina.	Uterus. Right and left Fallopian tubes. Right and left testes.	-ve (S) +ve (B)	B S G	45,X/46,XX 45,X(S & G) 45,X/46,XX(B)	Conen and Erkman, 1963a
4.	–	–	–	Ambiguous hypospadias. Bifid scrotum.	No laparotomy. Right testis scrotal.	+ve	B	46,XX/46,XXp–	Conen and Erkman, 1963a
5.	25	♀	162	Enlarged penile clitoris; primary amenorrhea. Excess hair. Labia majora.	No uterus or Fallopian tubes. Right and left testes in labia. Normal testicular tissue.	-ve	BM	45,X/46,XY/47,XYY	Milcu *et al.*, 1964b
6.	18	♀	165.1	Large phallus. Primary amenorrhea. No breasts. Excess hair. Labio scrotal folds and extensive fusion;	No uterus. Right and left Fallopian tubes present plus vasa deferentia. Right gonad, intra-abdominal testis, left undifferentiated.	-ve	B S (arm) S (clit)	45,X/46,XY 45,X/46,XX 45,X/46,XX/46,XY	Schuster and Motulsky, 1962
7.	61	♀	149.9	Enlarged clitoris. Scant pubic and axilliary hair. Primary amenorrhea. Small breasts.	No palpable uterus. State of gonads not known. ? testes.	-ve	B S (3)	45,X/46,XYp–/48,XXXYp–	Fraccaro *et al.*, 1962d
8.	2/52	♂	–	Penis, bifid abnormal scrotum.	Right inguinal hernia with uterus plus Fallopian tube. Left hernia with testis No vas.	-ve +ve	B S	45,X/48,XXXY	Warkany *et al.*,1962a
9.		♂	–	Short curved phallus. Hypospadias. Bifid scrotum.	Uterus. Blind Fallopian tubes, no left gonad. Right gonad testis (abdominal).	-ve	B	45,X/48,XYYY	D. Cox and Berry, 1967

[a] Here B stands for blood, S for skin, G for gonad, and BM for bone marrow.



FIG. 3-7. Diagram to show internal genitalia in a lateral true hermaphrodite. The patient had broad hips, female pubic hair, and gynecomastia. The external genitalia consisted of a glans with a dimple, a small prepuce, small right scrotum with normal testis, epididymis, and vas. External urethral orifice opens in the midline of the perineum. Left gonad ovary (urogenital types III and IV). (From Overzier, 1963c.)

tal in a few subjects. Details are only available for three of these seven subjects and these are summarized in Table 3-9. The 12 bilateral intersexes (Table 3-9) have ambiguous external genitalia, usually a small or rudimentary uterus, frequently bilateral Fallopian tubes, and occasional bilateral Wolffian derivatives (epididymes).

Positive sex chromatin was recorded for only 34 subjects. The chromosomes are 46,XX in all 45 subjects. In 22 patients, however, only one

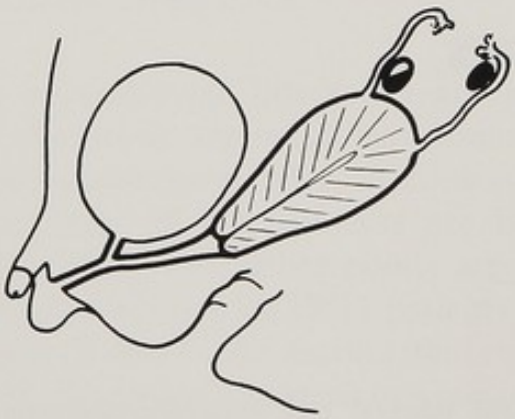


FIG. 3-8. Diagram to show internal genitalia in a unilateral true hermaphrodite. Right ovotestis, left ovary (urogenital types II and III). (From Overzier, 1963c.)

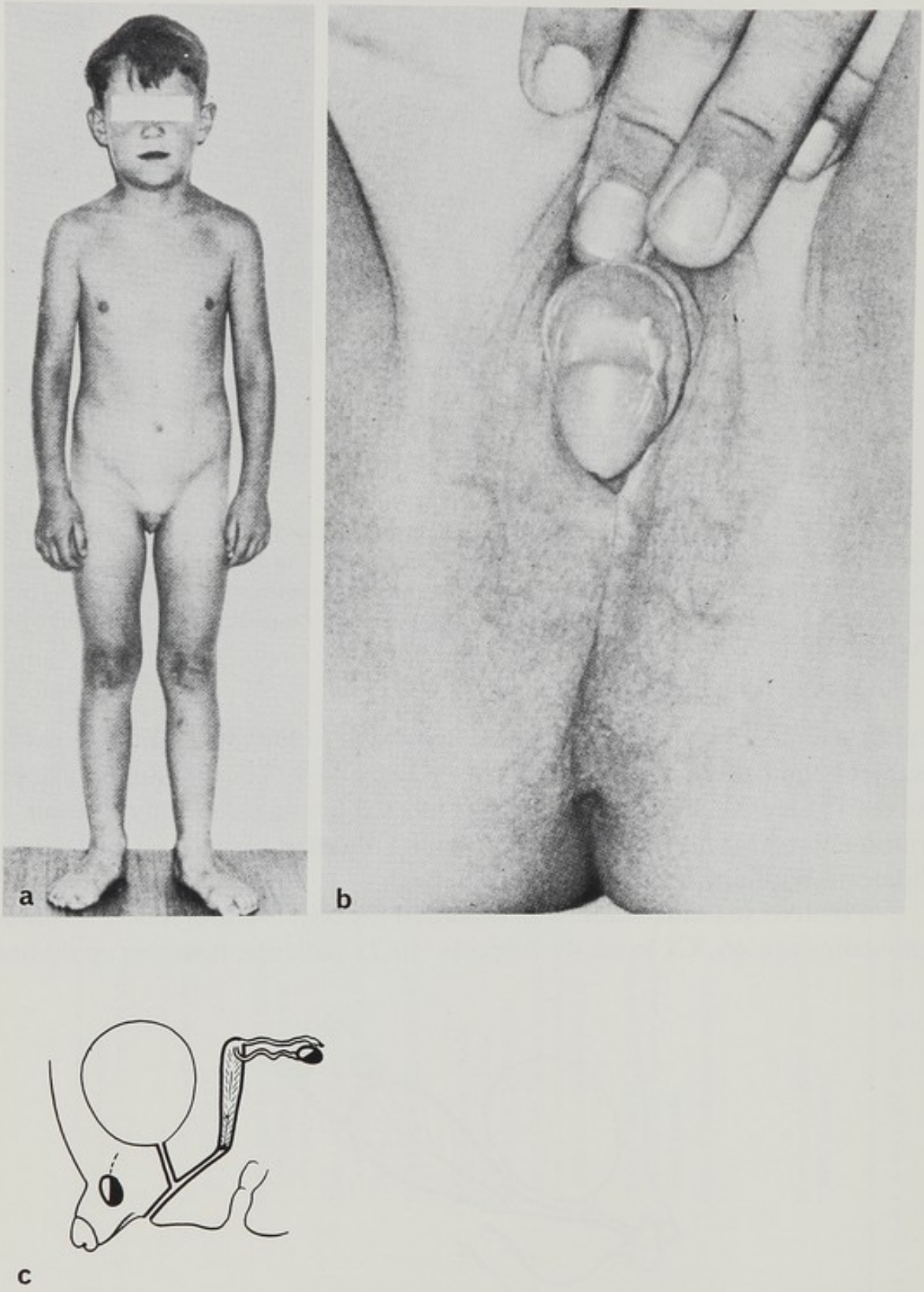


FIG. 3-9. Five-year-old bilateral true hermaphrodite with normal male habitus. Chromatin negative. Urogenital opening at base of phallus (type IV). (From Overzier, 1963c.)

TABLE 3–8

Classification of 84 Ovotesticular Intersexes

Chromosome constitution	Classification			Total
	Lateral	Unilateral	Bilateral	
XX	7 (0.156)	26 (0.578)	12	45
XY	9 (0.642)	4 (0.285)	1 ?	14
Mixoploid (exc. XO/XY XX/XY)	5	5	2	12
Total	21	35	15	71
Chromatin +ve	2	5 (2?)	1	8
Chromatin –ve	4	–	1	5
Total	27	40	17	84

tissue has been studied and it is therefore not possible to exclude mixoploidy in these. It is clear, however, that at least a proportion of ovotesticular intersexes have a normal female chromosome complement. The finding of a testis or testicular tissue indicates an error of gonadal determination, the nature of which will be discussed below.

2. 46,XY True Hermaphrodites

Fourteen XY ovotesticular intersexes are reported (Table 3-8), and it is now clear that these are much less common than those with a 46,XX chromosome complement. Also, in contrast to the XX true hermaphrodites, the majority of XY subjects are lateral hermaphrodites (9/14, 64.2%) (Table 3-8). Two other points are interesting: first, that when the phenotypic sex is recorded (9/11 patients) it is male in nine and female in two subjects (Table 3-10); second, that there seems to be a definite preference for the formation of a testis or a gonad containing testicular material on the right in both XX and XY subjects (Tables 3-9 and 3-10). Once again, in these subjects little attempt has been made to exclude mixoploidy and in only two of these patients was more than one

TABLE 3-9

Case No.	Age (years)	Phenotype	External genitalia and breast development	Uterus[b,f]	Fallopian tubes[a,b,f]		Gonads[a,c]	
					R	L	R	L
1 (KC)	1	♀	Phallus. Labio scrotal folds. Vagina.	+	+	+	O	OT
2 (CB)	33	♂	Phallus. Scrotum. ♂–type urethra.	–	–	–	OT	T
3 (LW)	4/12	?♀	Phallus. Labio scrotal folds. Hypospadias. Urethra.	+	+	–	O	OT
4 (JM)	3	?♀	Enlarged clitoris. Labio scrotal folds. ♀urethra.	+	+	+	OT	O
5	17	♀	Phallus. Labio scrotal folds, perineal hypospadias. Urethra.	+ unicornate	–	+	OT	O
6	2/52	♀	Enlarged clitoris. Labio scrotal folds. Perineal urethra.	+	+	?	OT	O
7	30	♀	Enlarged clitoris. ♀urethra.	+	+	+	OT	O
8	5/365	♀	Phallus, Labio scrotal folds. Perineal hypospadias. Vagina.	+ unicornate	+	–	O	OT
9	16	♂	Phallus. Scrotum. Perineal Hypospadias. Right and left gynecomastia.	–	–	–	OT	O
10 (1)	2 9/12	♀	Phallus. Labio scrotal folds. Urogenital sinus.	+	+	+	T	OT
11 (4)	?	?	Phallus. No scrotum. Perineal hypospadias.	–	–	–	OT	O
12	5	♀	Enlarged clitoris.	..	..	..	OT	O
13(66/62)	43	♂	Phallus. Scrotum. Perineal urethra.	No laparotomy			OT	..
14	24	♂	Phallus. Scrotum. Perineal urethra. Right and left gynecomastia.	–	+	–	T	OT
15	40	♂	Phallus. Scrotum. Perineal urethra. Right and left gynecomastia.	ru[f]	ru	ru	OT	–
16	15	⚥	Phallus. Scrotum. Perineal hypospadias. Right and left gynecomastia. Vagina.	+	+	+	OT	O
17	12	♀	Phallus. Scrotum. Perineal urethra. Right and left gynecomastia.	+	+	+	O	OT
18	15	⚥	Phallus. Scrotum. Perineal hypospadias. Vagina. Right and left gynecomastia.	–	–	+	OT	O

Clinical Features of Forty-two 46,XX Ovotesticular Intersexes

Epididymis [a,b]		Vasa deferentia [a,b]		Sex chromatin	Tissues studied [d]	Type [e]	Reference
R	L	R	L				
–	–	–	–	+	B	U	Jones *et al.*, 1965
–	+	–	–	+	B	U	Jones *et al.*, 1965
–	+	–	–	+	B OT	U	Jones *et al.*, 1965
..	..	..	..	+	B G	U	Jones *et al.*, 1965
+	–	+	–	+	B	U	Merrill and Ramsey, 1963
+?	–?	..	..	+	B	U	Solomon and Green, 1963
–	–	–	–	+	B	U	Friedberg and Rosenberg, 1965
–	+	–	+	+	BS OT	U	Root *et al.*, 1964a
+	–	–	–	+	S	U	Clayton *et al.*, 1958
..	..	..	..	+	B	U	Massimo and Vianello, 1965
..	..	..	..	+	?	U	Peña and Rivas, 1964
..	..	..	..	+	?	U	Sakatoku *et al.*, 1964
..	..	..	..	+	B S	Pu	Court Brown *et al.*, 1964a
–	–	–	–	+	B S	U	Leiba and Lunenfeld, 1964
–	–	–	–	+	B S	Pu	Dewhurst *et al.*, 1963
–	–	–	–	+	B BM	U	Marshall, 1954
–	+	–	+	+	B	U	Di Lorenzo *et al.*, 1964
–	–	+	–	+	BM	U	Ferguson-Smith *et al.*, 1960c

TABLE 3-9 (cont'd)

Case No.	Age (years)	Phenotype	External genitalia[a] and breast development	Uterus[a]	Fallopian tubes[a,b]		Gonads[a,c]	
					R	L	L	R
19	17	♀	Phallus. Scrotum. Hypospadias.	+	+	+	O	OT
20	14	⚥	Phallus. Labio scrotal folds. Right and left gynecomastia.	+	+	+	OT	O
21	25	⚥	Phallus. Labio scrotal folds. ♀urethra.	ru	..	..	OT	–
22	..	..	..	..	..	..	..	..
23	..	..	..	..	..	..	..	..
24	21	♂	Short phallus with marked chordee. Left scrotum with testis. Right scrotum empty. Perineal urethra. Rudimentary vagina. Right and left gynecomastia.	ru	+	–	OT	T
25	38	♂	Phallus scrotum. Hypospadias. Urethra.	–	–	–	T	O
26	21	⚥	Phallus scrotum ♂urethra. Abs. vagina. Right and left gynecomastia.	+	+	–	O	T
27	..	..	..	..	..	..	T	O
28	..	..	..	..	..	..	T	O
29	5	..	..	ru	–	+	T	O
30	..	⚥	Phallus. Scrotum. Urethra. Hypospadias. Right and left gynecomastia.	+	–	+	T	O
31	66	⚥	Phallus. Scrotum. Perineal urethra.	ru	+	+	OT	OT
32	12½	♂	Phallus. Scrotum. ♂urethra. Right and left gynecomastia.	ru	+	–	OT	OT
33 (PH)	8½	♀	Enlarged clitoris. ♀urethra.	+	+	+	OT	OT
34	15	♂	Phallus. Scrotum. ♂urethra.	..	+	+	OT	OT
35	80	♀	Phallus. Scrotum. ♂urethra. Right and left gynecomastia	+	+	+	OT	OT
36	7	♂	Phallus. Scrotum. Hypospadias.	–	+	+	OT	OT
37	..	..	..	..	..	..	OT	OT
38	..	..	..	..	..	..	OT	OT
39	16	..	Phallus.	..	..	..	OT	OT

Epididymis[a,b]		Vasa deferentia[a,b]		Sex chromatin	Tissues studied[d]	Type	Reference
R	L	R	L				
..	..	..	..	..	..	U	Overzier, 1963c
–	–	+	–	+	BM	U	De Assis *et al.*, 1960
+	..	..	..	+	BM	Pu	Makino and Sasaki, 1960 Sasaki and Makino, 1960
..	..	..	..	..	B	Both described as unilateral.	Klempman and Wilton, 1963
..	..	..	..	..	B	Very little data.	
–	+	..	..	+	B	U	K. Fraser *et al.*, 1966
..	..	..	..	+	B	L	Jones *et al.*, 1965
–	+	–	+	+	S T O	L	Bregman *et al.*, 1963
..	..	..	..	+	B	L	Klempman and Wilton, 1963
..	..	..	..	+	B	L	Klempman and Wilton, 1963
..	..	..	..	+	BM	L	Civantos, 1961
..	..	..	..	+	BM	L	Gordon *et al.*, 1960
–	–	–	–	+	BM S	Bil	Armstrong, 1955 Court Brown *et al.*, 1964a
+	+	..	..	+	BS	Bil	Hungerford *et al.*, 1959, 1965
..	..	..	..	+	B OT BM	Bil	Jones *et al.*, 1965
..	..	..	..	+	S OT	Bil	Rosenberg *et al.*, 1963
..	..	..	..	+	?	Bil	Roberts and Khajavi, 1964
+	+	..	..	+	B BM S	Bil	Clayton *et al.*, 1958
..	..	..	..	..	..	Bil	Klempman and Wilton, 1963
..	..	..	..	..	..	Bil	Klempman and Wilton, 1963
..	..	..	..	..	B	Bil	Capanna *et al.*, 1964

TABLE 3-9 (cont'd)

Case No.	Age (years)	Phenotype	External genitalia and breast development	Uterus[a]	Fallopian tubes[a,b,f]		Gonads[a,c]	
					R	L	R	L
40	15	♀	Phallus. Scrotum. Hypospadias. Vagina. Right and left gynecomastia.	ru	+	+	OT	OT
41	13	♀	Phallus. Scrotum. Hypospadias. Vagina.	ru	+	+	OT	OT
42	45	♂	Female virilized. Rudimentary vagina.	–	+	+	OT	OT

[a] Here R stands for right and L for left.
[b] Here "+" indicates present, "–" absent, and .. not recorded.
[c] Here O indicates ovary; T, testis, and OT, ovotestis.
[d] Here B stands for blood, S, skin; BM, bone marrow; G, gonad; T, testis; O, ovary, and OT, ovotestis.
[e] Here U stands for unilateral; L, lateral; Bil, bilateral, and Pu, presumptive unilateral.
[f] ru stands for rudimentary.
[g] stands for gonocytoma.

tissue examined. The external genitalia were generally hypospadiac, and a scrotum or labioscrotal folds were usually present. The phenotype is usually male although there would seem to be no more increase in the frequency of development of the Wolffian ducts than in the XX subjects and the recorded presence of an epididymis or vas deferens is rare (two subjects).

3. The 46,XX/46,XY Chromosome Constitution

Nine subjects have been reported who are 46,XX/46,XY mixoploids and are also true hermaphrodites (Table 3-11). Apart from these subjects, there are several other reports of XX/XY mixoploidy; Forteza *et al.* (1963a) reported a chromatin-negative girl with gonadal dysgenesis with these two cell lines, while Bain and Scott (1965) have described a subject with the same chromosome findings who has a feminine phenotype and mixed gonadal dysgenesis with a fibrous streak on the one side and a dysgerminoma on the other. Finally, a single subject with a male phenotype and no signs of intersexuality has been reported (Beattie *et al.*, 1964; Zuelzer *et al.*, 1964). Two twin pairs who are blood group chimeras with XX and XY cells (Woodruff and Lennox, 1959; Woodruff *et al.*, 1962; Uchida *et al.*, 1964b; Chown *et al.*, 1963) will not be considered.

a. XX/XY, Ovotesticular Intersexes. The clinical details of these nine subjects are summarized in Table 3-11. The first child to

Epididymis[a,b]		Vasa deferentia[a,b]		Sex chromatin	Tissues studied[d]	Type[e]	Reference
R	L	R	L				
..	..	..	..	+	B BM	Bil	McGovern and Marshall, 1962 German *et al.*, 1962
..	..	–	+	..	B	Bil	McGovern and Marshall, 1962 German *et al.*, 1962a
..	..	–	+	..	B	Bil	Clavero Nunez *et al.*, 1966

be reported with this chromosome complement (Waxman *et al.*, 1962a) had an enlarged clitoris—2.5 cm long—with a terminal meatal dimple and a grooved ventral surface. The urethral opening was in a small vaginal vault. At 2 years of age it was noted that the right iris was brown and the left blue-gray. A buccal smear was positive. At laparotomy a normal uterus and Fallopian tubes were seen. The left gonad was a normal ovary while the right proved to be an ovotestis. Chromosome analysis revealed 46,XX/46,XY mixoploidy. Detailed analysis of the distribution of the two cell types revealed gross intra-tissue differences (Table 3-12) with the proportion of XY cells varying from 0.00 in the ovary to 0.86 in the testicular part of the ovotestis. Blood group analysis (Giblett *et al.*, 1963) revealed two distinct red cell populations, one reacting with anti-*M,S,C,D,E,c,e*, while the other reacted with anti-*M,N,s,C,D,c,e*. Antibodies were present in about equal numbers. The two blood group populations are MS^u/MS, *CDe/cDE*, while the other is MS^u/Ns, *CDe/cde*. From the pedigree (Fig. 3-11), Gartler *et al.* (1962) concluded that the father (*MS/Ns*, *cDE/cde*) contributed both his genes at the *MNS* RH loci to the child, while the maternal contribution of both Rh and *MNS* are the same in both populations (see also Table 3-11). The heterochromia iridis was also interpreted in terms of a double paternal contribution. These findings suggested that two genetically different sperm fertilized two similar female pronuclei and that the two fusion nuclei contributed equally to the growth and development of the zygote. The origin of the two female pronuclei is not clear (see Volume

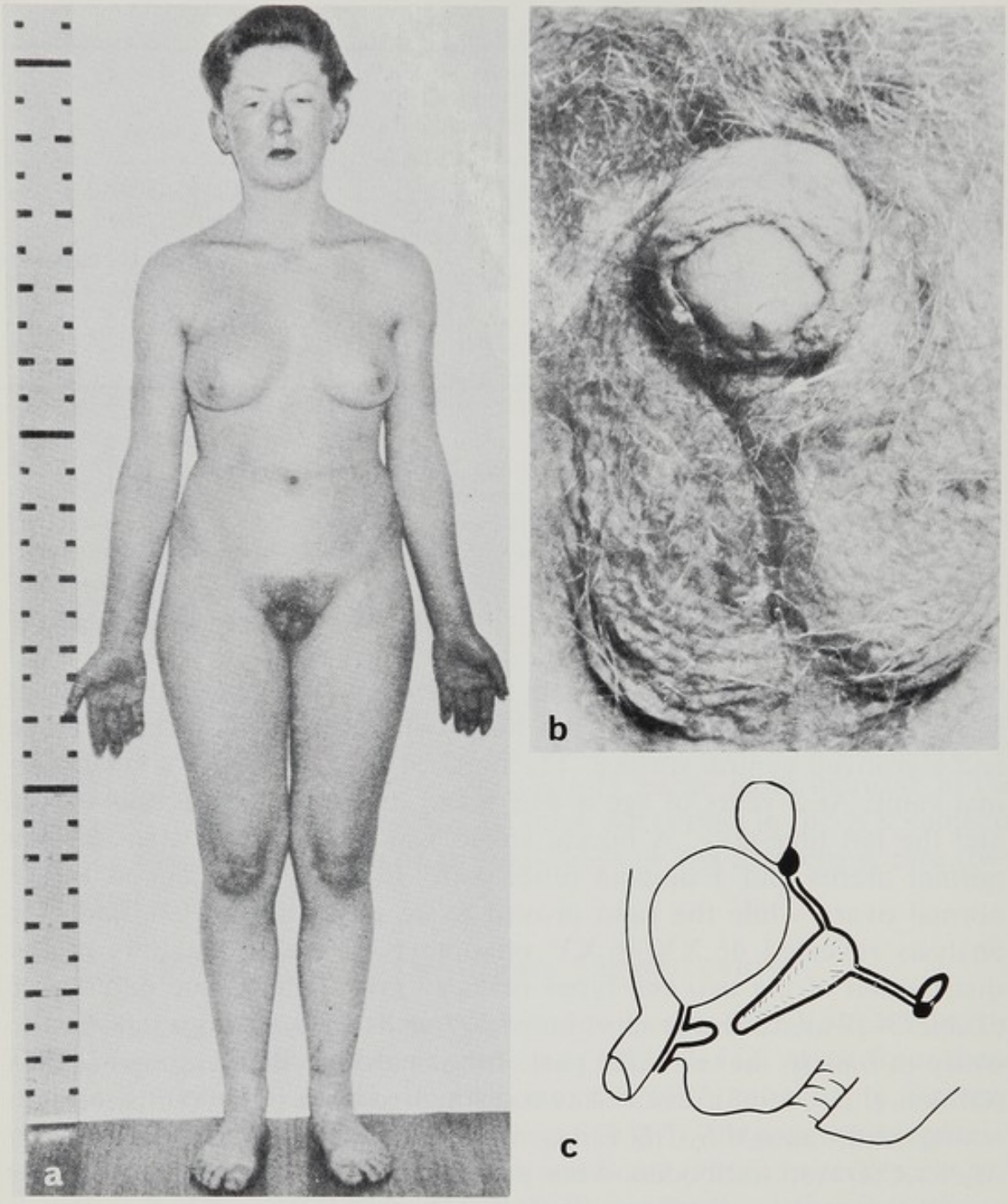


FIG. 3-10. (a) Phenotype of true hermaphrodite with gynecomastia. (b) Male-type external genitalia; urethial opening indicated by arrow at base of phallus. (c) Diagram of internal genitalia; blind vagina. Uterus, ovary, and ovotestis (urogenital types IV and V). (From Overzier, 1963c.)

I, Fig. 7-21, but a possible explanation is the failure of completion of the second maturation division so that the second polar body is not extruded. This would give a binucleate ovum containing two genetically similar female pronuclei. Each of these would then be fertilized by a different spermatozoon and included at first cleavage in separate blastomeres.

The subject reported by De Grouchy *et al.* (1964a) and Josso *et al.* (1965) was very similar. He was a phenotypic 20-year-old male with ambiguous external genitalia, a left ovary, and a right ovotestis. He was also a blood group mosaic and carried both the 2-1 and 2-2 haptoglobin phenotypes (see Table 3-11). It seems most likely that in this case the zygote also resulted from double fertilization. In this patient the proportion of XX and XY cells are very similar in both blood and skin.

There are six further examples of true hermaphrodites with this type of mixoploidy (Table 3-11). Full details, however, are only available for two (Segni and Grossi-Bianchi, 1965; Brøgger and Aagenaes, 1964, 1965); and it is suggested that these two subjects differ in their mode of origin. The child described by Segni and Grossi-Bianchi (1965) is a lateral hermaphrodite with ambiguous external genitalia and a testis on one side and an ovary on the other. She was chromatin positive, and blood cultures showed about 52% XX and 48% XY cells. There is no direct evidence from blood groups of double fertilization, but this was considered to be the most likely explanation. A second lateral hermaphrodite (Brøgger and Aagenaes, 1964, 1965) with ambiguous external genitalia had chromatin-negative oral smears; the blood smears were chromatin positive with 7-8% drumsticks. Chromosome analysis showed a normal female chromosome complement in bone marrow, skin, blood, and one testicular biopsy; a further testicular biopsy from the same gonad, however, showed 36% of cells to be male. The fact that this subject is chromatin negative may be the result of cellular distribution, or the mosaicism could have resulted from a mitotic error in an XY zygote after X inactivation so that both X chromosomes remained isopycnotic. A 2-year-old patient reported by Massimo and Vianello (1965) had ambiguous external genitalia, a right testis, and a left ovary containing some normal follicles, as well as streak tissue. Approximately 50% of the cells in blood culture were XX and 50% XY. This case is again interpreted as the result of double fertilization although no evidence is given to support this.

b. 46,XX/46XY, Subjects with Gonadal Dysgenesis. Bain and Scott (1965) reported a tall girl (67 cm) with mixed gonadal dysgenesis; the clinical data are included in Table 3-11. There was no evidence of intersexuality, and the external genitalia were normal. The uterus was small and the right gonad was represented by a fibrous streak while the left gonad consisted largely of a solid tumor about 5 in. in diameter. Histologically this proved to be a disgerminoma with no evidence of normal ovarian tissue. Two blood cultures showed both 46,XX and 46,XY cell lines, the XY cells forming about 78% of the total. Di-

TABLE 3–10

Case No.	Age (years)	Phenotype	External genitalia	Uterus	Fallopian tubes	
					R	L
1	16	♂	Enlarged clitoris. Labio scrotal folds.	+	–	+
2	27	..	Phallus. Absent scrotum. Perineal urethra. Vagina.	..	..	..
3	44	♂	Penis. Scrotum.	+	..	+
4 (1)	12	♂	Hypospadias. Vagina.	+	..	..
5 (2)	13	♂	Hypospadias. Vagina.	ru	..	..
6 (4)	6	♂	Hypospadias.	..	..	..
7	5	♂	Perineal hypospadias. Labio scrotal folds. Vagina.	+	+	+
8	1 5/12	♀	Enlarged clitoris. No scrotum. ♀urethra. Vagina.	+	+	+
9	16	♂	Phallus. Female urethra. Vagina.	..	+	+
10	12½	♂	Phallus. Scrotum. Hypospadias.	+	+	+
11	12	♂(?)	Hypospadias. Vagina	ru	..	..
12	..	♀	No data	No data		
13	18	..	..	–	+	+

[a] See footnotes to Table 3–9 for explanations of abbreviations.

rect evidence of double fertilization was lacking; there was, however, no evidence of the presence of an unlike-sexed twin and since the present subject was chromatin positive it seemed unlikely that she originated from an XY zygote by a postfertilization error.

Forteza *et al.* (1963a) reported a chromatin-negative girl with gonadal dysgenesis, an infantile and rudimentary uterus and tubes, and streak gonads. About 50% of the lymphocytes were 46,XX and 50% 46,XY, so that the most likely mechanism would be successive mitotic nondisjunctions in an XY zygote. This might account for the chromatin-negative condition in an XX/XY subject.

Finally, in this group there are two males, a normal phenotypic male who was reported by Beattie *et al.* (1964) and Zuelzer *et al.* (1964); he did not show any evidence of intersexuality and had normal testes. The patient was of Negro-Amerindian-Caucasoid ancestry and showed distinctive pigmentation irregularities over the skin with multiple discrete dark areas. Two separate blood cultures showed 7.3% XY and 4%

Clinical Features of Thirteen 46,XY Ovotesticular Intersexes[a]

Gonads		Epididymis		Vasa deferentia		Sex chromatin	Tissues studied	Type	Reference
R	L	R	L	R	L				
T	O	..	..	+	–	–	B S T	L	Shearman *et al.*, 1964
T	O	..	..	..	..	–	..	L	Manchanda *et al.*, 1964
T	O	..	..	..	..	..	..	L	Aisters-Bauer and Kleinhenz, 1963
T	O	..	..	..	..	–	B	L	Tonomura and Honda, 1962
T	O	..	..	..	..	–	B	L	Tonomura and Honda, 1962
T	O	..	..	..	..	–	B	L	Tonomura and Honda, 1962
O	T	..	..	..	+	–	B S	L	Pediatric Research Unit/2804
T	O	..	..	..	..	–	S	L	Eliachar *et al.*, 1962
OT	O	–	..	..	..	–	BM	U	Domenici and Romeo, 1962
OT	O	..	..	..	..	–	B	U	Lonsdale *et al.*, 1963
OT	O	..	..	..	..	–	B	U	Tonomura and Honda, 1962
T	OT	..	..	..	..	–	?	U	Lozzio *et al.*, 1966
Dystrophic									
OT	?OT	..	..	..	..	–	BM	Bil?	Sandberg *et al.*, 1960a

XX cells, respectively. Fibroblast cultures showed no XX cells when derived from light skin and 8 to 13% when derived from dark skin. Evidence for double fertilization came from blood groups and haptoglobin types. Two discrete cell populations can be distinguished in a number of systems (see Table 3-11), and in each case the major component was about 10 times as common as the minor one. The most likely explanation is again the separate fertilization of two female nuclei, which the authors suggest might be the female pronucleus in the ovum and a polar body nucleus. Myhre *et al.* (1965) reported a male with hypospadias whose blood culture showed 53 XX and 47 XY cells. Chimerism was confirmed by the finding of two separate populations of erythrocytes on blood typing. The explanation for this case was considered to be dispermy of a similar type to case 1, referred to above.

c. Origin of the XX/XY State. 46,XX/46,XY mixoploidy can result from nine distinct mechanisms (Ford, 1969, and Volume I,

TABLE 3-11

Case No.[b]	Age (years)	Phenotype	External genitalia and somatic characteristics	Uterus	Fallopian tubes		Gonads		Epididymis		Vasa deferentia	
					R	L	R	L	R	L	R	L
1	2	♀	Enlarged clitoris. Urogenital sinus. Vagina. One eye hazel, one brown.	+	+	+	OT	O	..	..	..	..
2	18	♂	Normal. ♂ Scrotum. Testes of normal size. Slight gynecomastia. Patch skin (Negro-Ameridian Caucasoid ancestry).		–	–	T	T	+	+	+	+
3	20	♂/♀	Phallus. Labio scrotal folds perineal Hypospadias. Vagina. Right and left gynecomastia.	+ ru	+	+	OT	O	+	–	–	–
4	3	–	Extreme hypospadias.	..	..	..	..	..	..	..	..	..
5	12	♂	Penis. Scrotum. Hypospadias.	–	–	–	T	T	+	+	+	+
6	4	♀	Phallus. Urethra-?-type Vagina.	+	+	+	T	O	..	..	..	..
7	2	♀	Phallus. Hypospadias. Urethra Vagina.	+ ru	+	+	T	O	..	..	..	..
8	18	♀	Phallus. Urogenital sinus.	+	+	+	Gon	OT	..	..	..	..

Clinical Findings and Origin of Some 46,XX/46,XY Mixoploids[a]

Tissues	XX (%)	XY (%)	Clinical classification	Evidence for dispermy blood groups	Reference
B	6	94	Unilateral ovotesticular intersex	50% MS^u/MS *CDe/cDE*	Waxman *et al.*, 1962a
S	23	77		50% MS^u/Ns *CDe/cde*	Waxman *et al.*, 1962b
OT	14	86			
O	100	0		Father *MS/Ns cDE/cde*	Gartler *et al.*, 1962
toris	36	64		Mother MS^u/Ns *CDe/cDE*	Giblett *et al.*, 1963 (see also Table 3-12)
B	6	94	Normal male	90% $A_1O\ Jk^bJk^b$ Hb AS *Se se*	Beattie *et al.*, 1964
				10% $B\ Jk^aJk^b$ Hb A *se se*	Zuelzer *et al.*, 1964
				Father $A_1B\ Jk^aJk^b$ *Hb* A *Se se*	
				Mother *BO* Jk^aJk^b *Hb AS se se*	
B	62	38	Unilateral ovotesticular intersex	Hp 2-2 + Hp 2-1	De Grouchy *et al.*, 1964a
S	Mixoploid			Father Hp 2-1	Josso *et al.*, 1965
				Mother Hp 2-2	
B	60	40	Ovotesticular intersex ? type	60% $A_1O\ Lu^aLu^bFy^aFy^a$ Hp 1-1 + Hp 2-1 PGM mixture	J.R. Miller *et al.*, quoted by Bain and Scott, 1965 and Race and Sanger, 1968
				40% OO $Lu^bLu^bFy^aFy^b$ Hp 1-1 + Hp 2-1 PGM mixture	
				Father *OO* $Lu^aLu^bFy^aFy^a$ Hp 1-1 PGM2-1	
				Mother $A_1O\ Lu^bLu^bFy^aFy^b$ Hp 2-1 PGM2-1	
B	53	47	Male with hypospadias	85% *OO* Jk^bJk^b	Myhre *et al.*, 1965
				15% *BO* Jk^aJk^b	
				Father *BO* Jk^aJk^b	
				Mother $A_2O\ Jk^aJk^b$	
B SK BM T	All show mixoploidy		Lateral ovotesticular intersex	No blood group data	Brøgger and Aagenaes 1964, 1965
B	–	–	Lateral ovotesticular intersex	No blood group data	Segni and Grossi-Bianchi, 1965
B S OT	–	–	Presumptive Unilateral ovotesticular intersex	No blood group data	Overzier, 1964

TABLE 3-11 (cont'd)

Case No.[b]	Age (years)	Phenotype	External genitalia and somatic characteristics	Uterus	Fallopian tubes R	Fallopian tubes L	Gonads R	Gonads L	Epididymis R	Epididymis L	Vasa deferentia R	Vasa deferentia L
9	24	♀	Normal ♀. Pubic hair ±. Moderate breast development Primary amenorrhea.	+ ru	+	+	Streak Dysgenetic	O	–	–	–	–
10	..	..	Small hypospadic penis. Small scrotum. Partial chordee. No vagina.	+ ru	+	+	OT	OT	–	–	–	–
11	2	♂♀	Phallus. Medium-sized hypospadias. Urethra Vagina ..	+ ru	+	+	T	O	..	..	..	..
12	15	♂		..	..	..	OT	OT	..	..	..	..

[a] See footnotes to Table 3-9 for explanation to abbreviations.

[b] Cases 1 and 5. Two sperm fertilizing two identical egg nuclei or one egg nucleus and the nucleus of the second polar body (Fig. 3–12).. Cases 2,4, and 12. Two sperm fertilizing two nonidentical egg nuclei perhaps the ovum nucleus and nucleus of first polar body (Fig. 3–13). Case 3. Evidence based on Hp mixture; blood groups do not demonstrate mosaicism despite the fact that the father was heterozygous in six systems. Cases 6,7, and 8. No blood group data available. Cases 9 and 10. Blood group did not give evidence of dispermy and two further examples of this situation were reported by Race and Sanger (1968) as well as an additional normal female with two populations of 46,XX cells; i.e., both sperm carried an X chromosome and fertilized two identical X egg nuclei.

Table 7-4), the most important of which are: (1) the transfer of hemopoietic tissue between opposite sexed twins in the intrauterine stage of development, (2) dispermic fertilization, and (3) a series of mitotic errors in an XY zygote. The presumptive origin of 12 subjects, is summarized in Table 3-11, together with the evidence for the existence of two genetic components where this is present. The majority of these subjects are presumed to have arisen by double fertilization.

There are two possible types of double fertilization, the first resulting from a failure of cytokinesis at the first meiotic division so that the first polar body is not extruded and is subsequently fertilized by a different spermatozoon to that which fertilized the female pronucleus; the two diploid fusion nuclei are then included in different blastomeres at the first cleavage division and contribute equally or nearly equally to the formation of the zygote (Fig. 3-12). A modification of this mechanism was postulated by Zuelzer *et al.* (1964) to account for the discrepancy

Tissues	XX (%)	XY (%)	Clinical classification	Evidence for dispermy blood groups	Reference
B	–	–	Mixed gonadal dysgenesis	None	Bain and Scott, 1965
B	60	40	Bilateral ovotesticular intersex	None	Manuel *et al.*, 1965
S	100	..			
B	..	..	Lateral mixed ovotesticular intersex	No blood group data	Massimo and Vianello, 1965
B	5	95	Bilateral mixed ovotesticular intersex	97% *OO*, AcP BB,PGM1-1	Ferguson Smith *et al.*, 1966, quoted by Race and Sanger, 1968
S	73	27		3% A_2O, AcP AC,PGM2-1	
				Father A_2O, AcP AC,PGM1-1	
				Mother *OO*, AcP AB,PGM2-1	

TABLE 3–12

Distribution of 46,XX and 46,XY Cells in Different Tissues in a True Hermaphrodite [a]

Tissue	XX	XY	Total	Proportion XY	Chromatin +ve nuclei (%)
Skin (right abdomen)	3	10	13	0.77	13
Skin (left abdomen)	8	1	9	0.11	36
Ovary (left)	10	0	10	0.00	50
Ovotestis (right)					
Testicular area	2	12	14	0.86	35
Ovarian area	9	2	11	0.18	15
Clitoris	4	7	11	0.64	29

[a] From Waxman *et al.* (1962a,b).

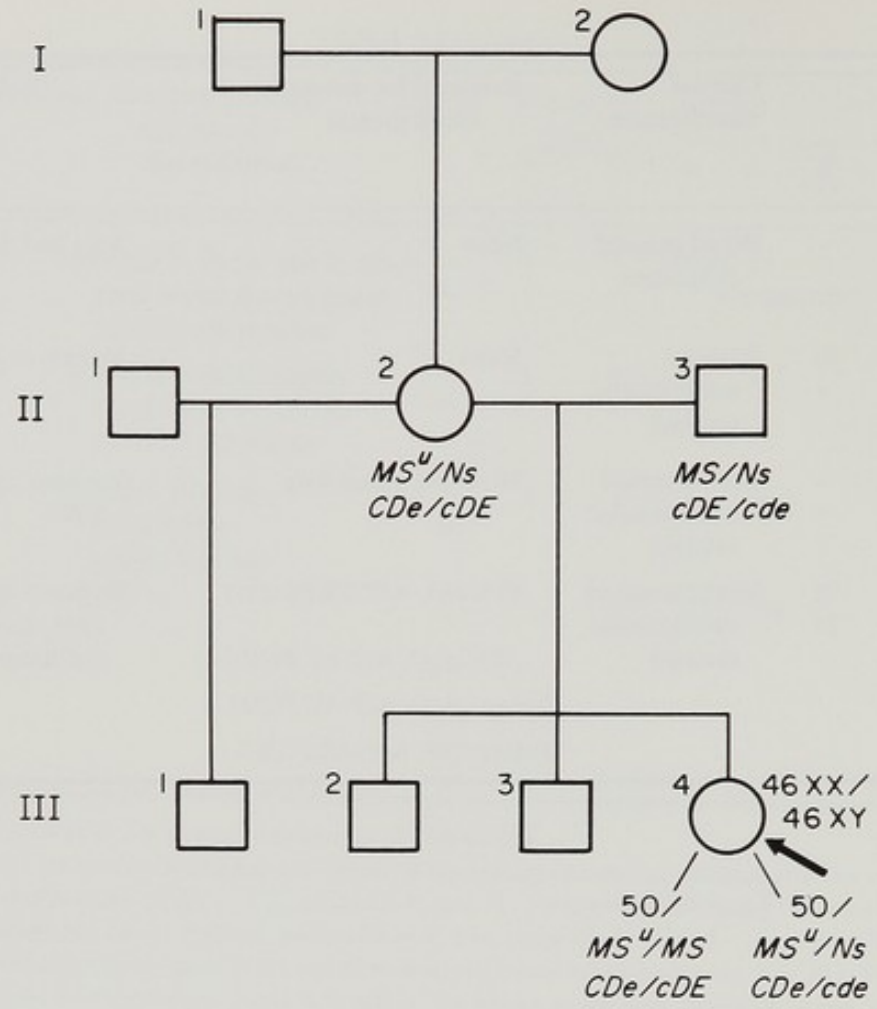


FIG. 3-11. Pedigree of 46,XX/46,XY mixoploid showing the distribution of the blood groups, which indicate a double paternal contribution to the 46,XX/46,XY zygote. (Modified from Giblet *et al.*, 1963.)

observed between the proportions of the two genotypes. They suggested that the polar body extrusion is partial but that before it is completed the haploid polar body nucleus is fertilized as well as the female pronucleus and that the polar body fusion nucleus divides more slowly and so contributes a lower proportion of cells to the zygote (Fig. 3-13).

The second type of double fertilization would result from the fertilization of two separate ova and their subsequent fusion (Fig. 3-14). It is well known that fusion of fertilized ova can be performed experimentally in mice (Tarkowski, 1965; Mintz, 1965; Mystkowska and Tarkowski, 1968), and there is presumably no reason why it should not occur spontaneously. If sufficient genetic markers were available it should be possible to differentiate between these mechanisms in suitably informative families. In the first type there would be a single maternal contribution to the genotype while the paternal contribution would be double. In the second type both maternal and paternal contributions should be doubled

since initially there would be two separate ova present. A mitotic origin is suggested in at least one case and perhaps two where the subject is chromatin negative. It is presumed that these arose by successive mitotic nondisjunction from an XY zygote (Fig. 3-15) at some division after the first so that one cell line remains XY and the other becomes XX, either via the XO state after the loss of the Y chromosome or as a result of nondisjunction of both the X and Y at the same division.

The two twin pairs referred to are considered to have arisen as the result of an exchange of hemopoietic cells during fetal life.

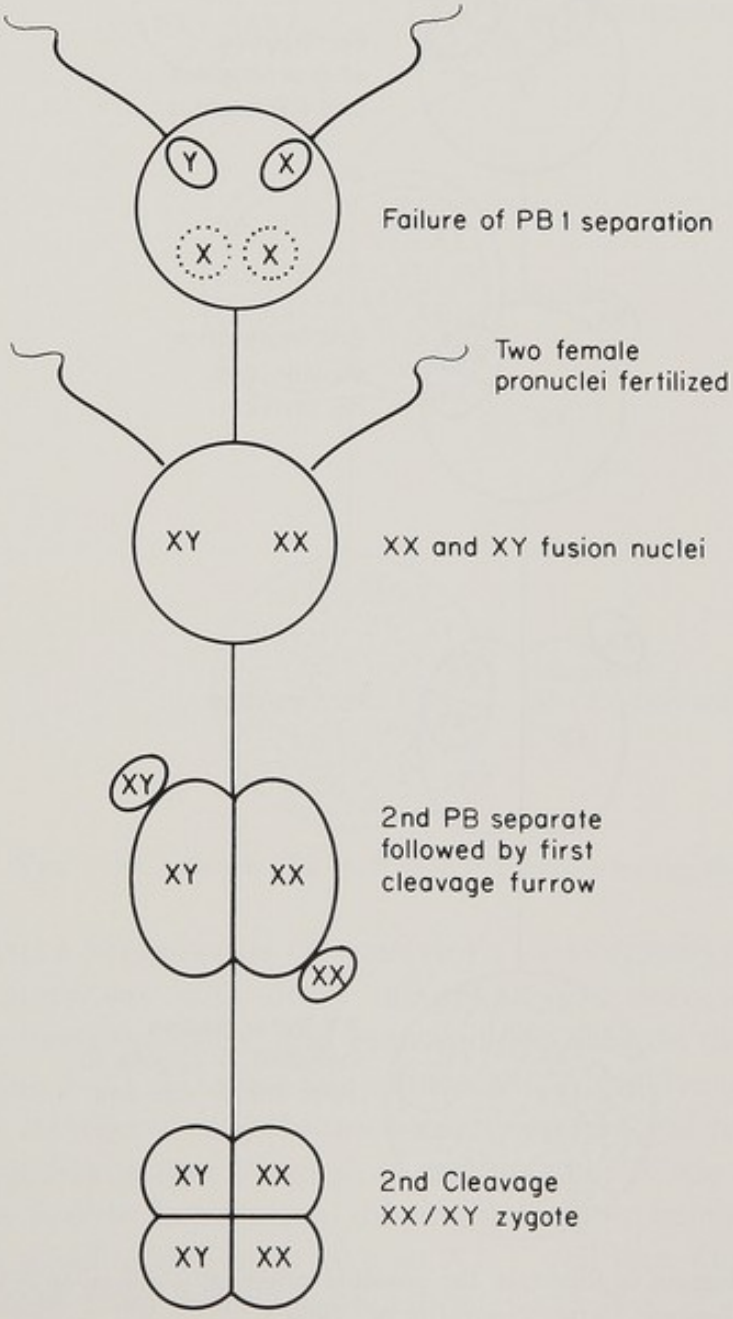


FIG. 3-12. Diagram to illustrate the origin of a 46,XX/46,XY zygote by dispermy.

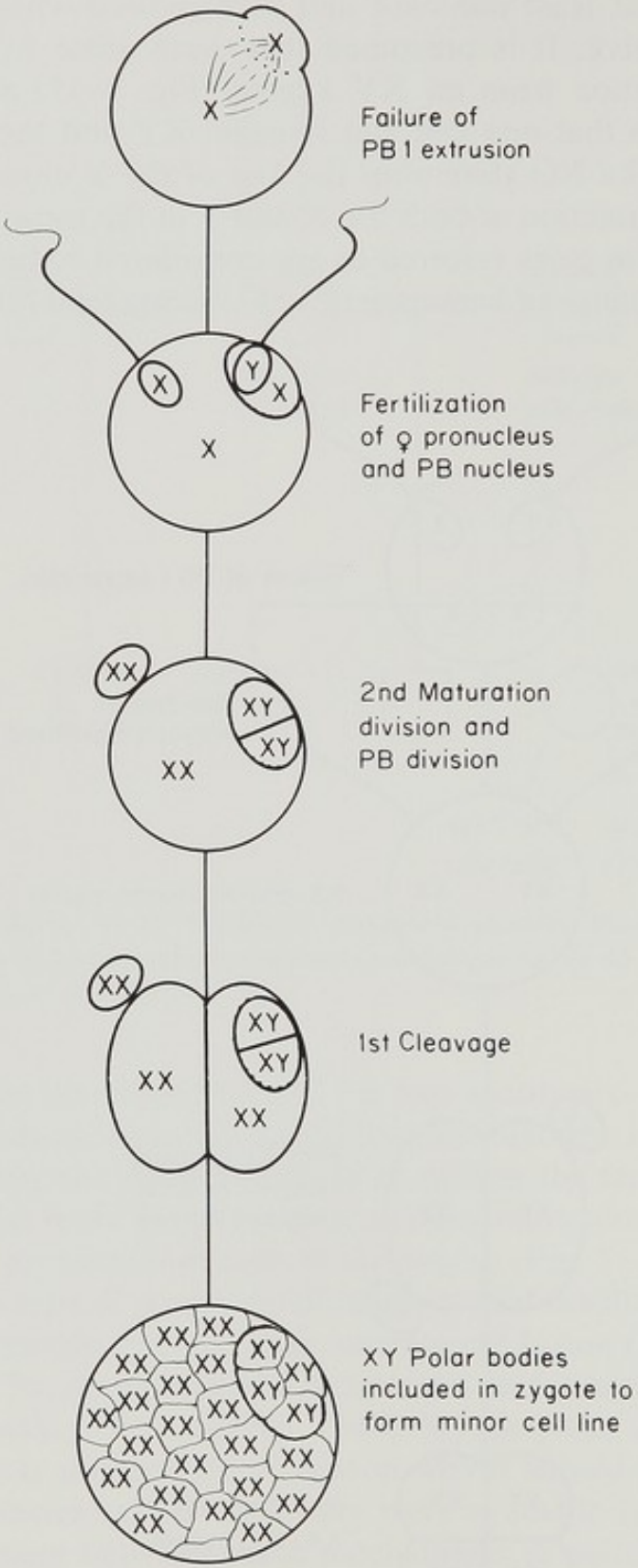


FIG. 3-13. Diagram to illustrate the possible origin of a minor 46,XY cell line in a 46,XX zygote by dispermy. (After Zuelzer *et al.*, 1964.)

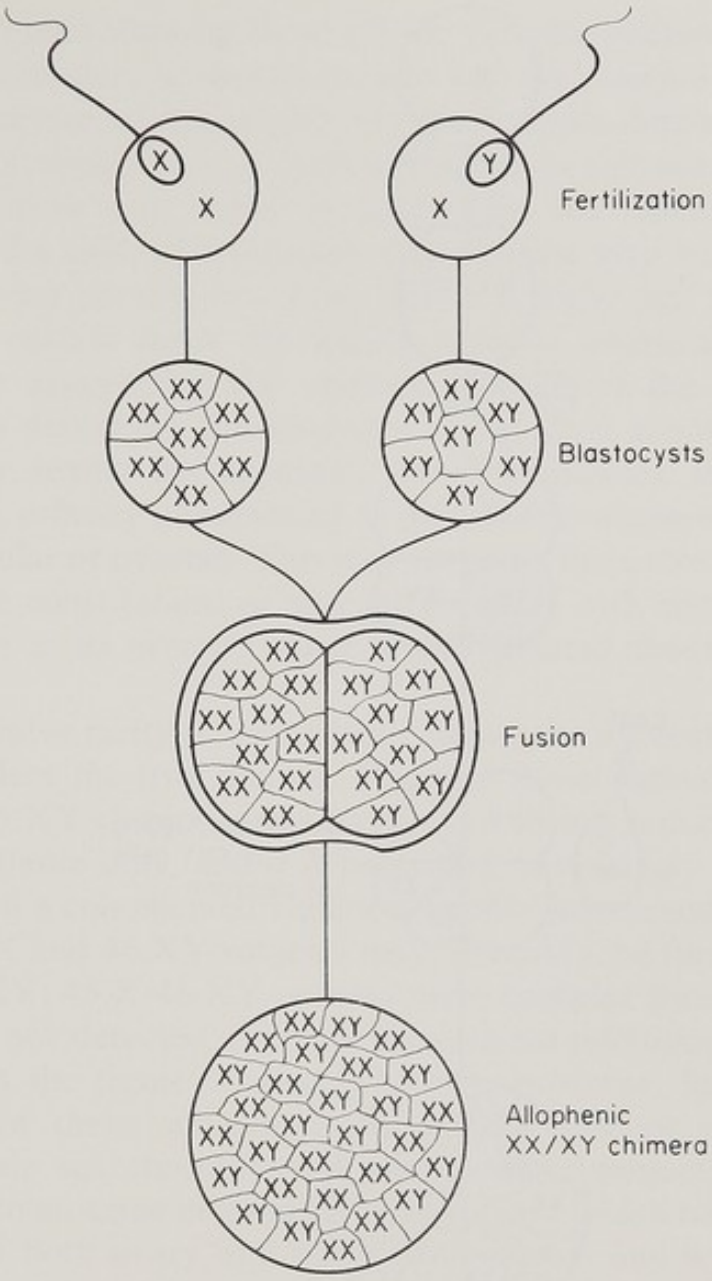


FIG. 3-14. Origin of a 46,XX/46,XY zygote by egg fusion.

d. OTHER MIXOPLOID OVOTESTICULAR INTERSEXES. Ten ovotesticular intersexes with other mixoploid sex chromosome complements have been recorded, and the available data on these subjects are given in Table 3-13. Five are lateral intersexes, and five unilateral and bilateral. The mixoploid sex chromosome complements have presumably arisen by nondisjunction although in one instance (Case No. 10) there is evidence for double fertilization, the original zygote being 46,XX/46,XY, followed by nondisjunction to give an XXY cell line. One subject could have originated from double fertilization (Case No. 3) who has 46,XX/46,XY/47,XXY.

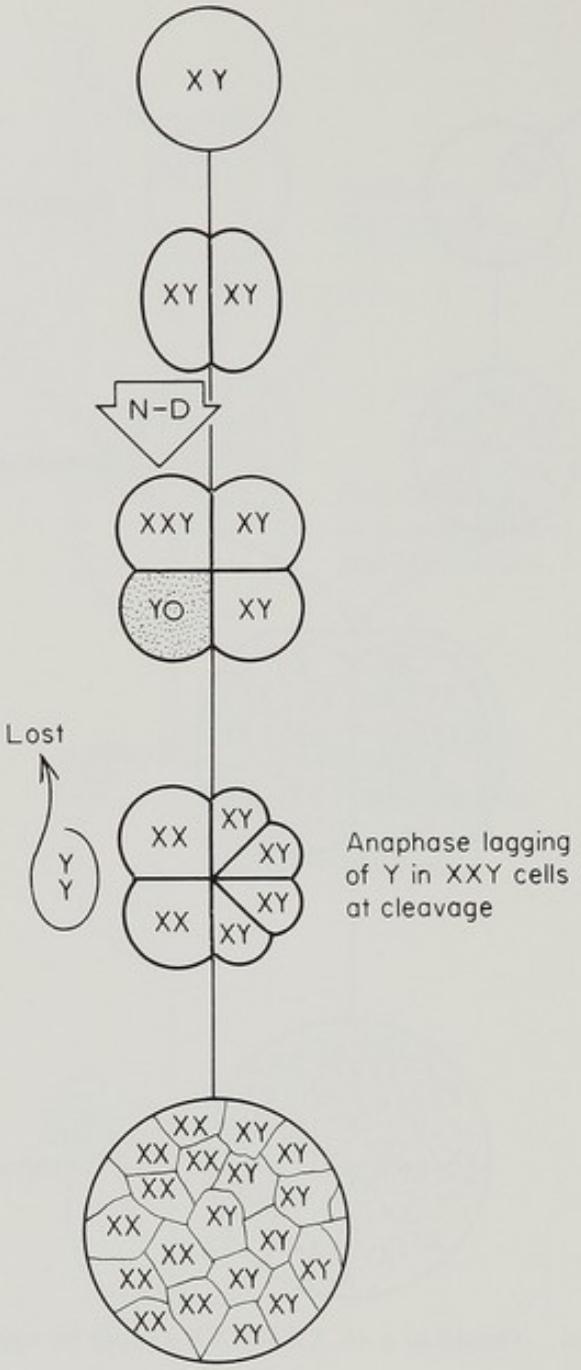


FIG. 3-15. Possible mode of origin of a 46,XX/46,XY zygote by nondisjunction in an XY zygote. The intermediate YO cell line would be lethal.

Examination of Table 3-13 reveals that the mixoploid group do not have any distinctive features when compared to the 46,XX or 46,XY groups.

IV. The Significance of the Variable Chromosome Complement in Human Intersexes

The significance to be attached to the variable sex chromosome complements which are found in human intersexes must be considered

in relation to the following facts: (1) the variable phenotype both in relation to the secondary sexual characters and the external genitalia; (2) the variable structure of the gonad; (3) the various different chromosome complements, which include both normal male and normal female complements. These can result in essentially the same phenotype and conversely the same chromosome complement may be associated with widely differing phenotypes. From this it is clear that the chromosome state alone cannot cause the widely variable intersexual states which exist. If we accept that the primary function of the sex determining factors is to determine the structure of the fetal gonads which in turn control later sexual development, then the intersex states can be explained by a primary abnormality of gonadal development which may be either testicular or ovarian. This may (in some instances of abnormal sex chromosome constitution) or may not (in cases with normal sex chromosomes) have as its primary cause a chromosome abnormality (see also Chapter 4).

The relative rarity of mixoploidy among the ovotesticular intersexes may not reflect the true picture. Many of these patients with apparent 46,XX or 46,XY chromosomes have had a chromosome analysis carried out on one tissue only, and it is becoming increasingly clear that this is inadequate in a complicated situation such as intersexuality. Thus, some of the 46,XX and 46,XY subjects may, in reality, be further examples of 46,XX/46,XY; 45,X/46,XY or even more complex forms of mixoploidy which were not detected, perhaps because the additional cell line(s) did not occur in the tissue studied. There is, however, little doubt that a proportion of these subjects have normal male or more commonly normal female sex chromosomes, and in these subjects there had presumably been an error in gonadal development which has resulted in the formation of both ovary and testis or ovotestis, and which in turn has resulted in the observed ambiguity of the external genitalia. Examination of the tables in the present chapter gives no indication of any correlation between the external or internal genitalia, the gonads, and the chromosome complement. Two facts, however, do emerge. First, there is generally a correlation between the presence of an ovary and the development of the Müllerian ducts, the Fallopian tube, and uterus on the same side; conversely, where the gonad is a testis the Fallopian tube on that side is often absent and the uterus rudimentary, while the Wolffian ducts are present although these are recorded only rarely. An ovotestis is usually accompanied by a Fallopian tube. Second, there does seem to be a correlation between the type of ovotesticular intersex and the chromosome complement, which is demonstrated by the fact that about 58% of XX true hermaphrodites are unilateral with an ovotestis and an ovary or testis while only 29% XY subjects have an ovotestis. On the other hand,

TABLE 3-13

Case No.	Age (years)	Phenotype	External genitalia	Uterus	Fallopian tubes		Gonads		Epididymis		Vasa deferentia	
					R	L	R	L	R	L	R	L
1	4	♂	Phallus. Scrotum. Perineal hypospadias.	–	–	–	O	T	..	..	..	..
2	16	♀	Enlarged clitoris. Vagina. Right and left gynecomastia.	–	–	–	OT	OT	..	..	..	..
3	9	..	Phallus. Labio scrotal folds. Perineal urethra.	..	..	..	T	O	..	..	..	..
4	1	♂	Phallus. Scrotum. Hypospadias. Urethra. Vagina.	+ (u)[b]	–	+	T	O	+	–	+	–
5	3/52	♂	Phallus. Hypospadias. No scrotum. No vagina.	+	+	+	T	OT	..	..	..	..
6	10	♂	Phallus. Scrotum. Hypospadias.	ru	+	–	O	OT	..	..	..	..
7	1 2/12	♀	Phallus. Scrotum. Urethra.	+ (u)[b]	+	–	O	T	–	–	–	+
8	9 1/2	♂	Phallus. Scrotum. Hypospadias. Urethra. Neck webbing. (♂ TS)	–	+	+	OT	OT	–	–	+	–
9	2 10/12	♀	Phallus. Labio scrotal folds. Perineal urogenital sinus.	+	+	–	O	OT	–	+	..	..
10	14	⚥	Phallus. Scrotum. ♀ urethra. Vagina.	+	–	+	T	O	+	–	+	–

[a] See Footnotes to Table 3–9 for explanations of abbreviations.
[b] Here (u) stands for unicornate.

64% XY subjects are lateral intersexes with a testis and an ovary compared to only 16% of XX subjects. This difference, even with the relatively small number involved, is highly significant although its precise meaning is not clear. Perhaps in mammals where the "neutral sex" is female there is a far greater tendency for subjects with 46,XX chromosomes to form an ovotestis or ovary rather than a testis. Finally, in both XX and XY unilateral subjects, the gonad opposite the ovotestis is most commonly an ovary and only rarely a testis. This seems to suggest that a Y chromosome is necessary for the maintenance of the medullary sex cords.

Clinical Features of Ten Ovotesticular Intersexes with Various Mixoploid Chromosome Complements[a]

Tissues studied	Type	Sex chromatin	Sex chromosome complement	Reference
S	L	+	46,XX/47,XXY	Turpin *et al.*, 1962b
BM	Bil	+	46,XX/47,XXY	Clavero *et al.*, 1965 Moncada *et al.*, 1964
B	L	..	46,XX/46,XY/47,XXY No evidence of dispermy.	Ribas-Mundó and Prats, 1965 Race and Sanger, 1968
STO	L	+	46,XX/48,XXYY	Blank *et al.*, 1964
BST	U	+	46,XX/47,XXY/49,XXYYY	Fraccaro *et al.*, 1962c
BS	U	+	45,X/46,XX/47,XXYqi	Klevit *et al.*, 1963
BS	L	+	45,X/46,XX, fra+	Dewhurst *et al.*, 1965
..	Bil	+	46,XX/47,XXY	Pediatric Research Unit/2854
..	U	+	46,XY/46,XX/47,XXY	Pediatric Research Unit/958
BM	L	+	46,XX/47,XXX	Goodwin *et al.*, 1954 Money *et al.*, 1955 Ferguson-Smith *et al.*, 1960c Case 1 in Overzier, 1963c

There is no clear-cut phenotype even among the XX/XY subjects, three of which are lateral and three unilateral ovotesticular intersexes, while the remaining subjects cannot be defined as true hermaphrodites.

The clearest correlation between phenotype and karyotype is found in subjects with 45,X/46,XY chromosomes who can vary from females with ovarian dysgenesis or Turner's syndrome to infertile males (Table 3-2). The most characteristic phenotype is a variety of male pseudohermaphroditism which has been variously termed *mixed gonadal dysgenesis* or *asymmetrical gonadal differentiation*. These subjects have ambiguous external genitalia, usually a testis on one side and a streak

gonad on the other. The testes are dysgeneic and usually intra-abdominal. Other subjects with this chromosome complement may be mixed ovotesticular intersexes, subjects with a gonad on one side and a gonocytoma on the other, or infertile males.

The simplest explanation for this variable phenotype is perhaps one of timing and distribution of the two cell types, both in relation to the tissues in which 45,X and 46,XY cells are found and also to the proportion of the different cell types in different tissues. Thus, if XY inductor cells compose the indifferent gonad then the medulla will be stimulated and a testis formed; on the other hand, if the inductor cells are 45,X, then an ovary will be produced in which the germ cells will undergo total atresia by puberty leaving the typical streak gonad which is associated with ovarian dysgenesis. Therefore, we have a situation in which the phenotypic expression can be explained by a variation in the proportion of the two cell types. A high proportion of 45,X cells in the correct tissues and at the correct time will give ovarian dysgenesis; a high proportion of 46,XY cells should result in testicular development of both gonads and a male phenotype; and intermediate proportions should give a variable phenotype ranging from mixed gonadal dysgenesis to true hermaphroditism.

V. Testicular Feminization

Testicular feminization is included in this chapter although it is basically not an intersexual state nor is there any detectable cytogenetic anomaly. The condition is a genetically determined state of phenotypic sex reversal. It has been classed by several authors, notably Hauser (1963b), as a syndrome of male pseudohermaphroditism. Usually, however, despite the presence of testes the external genitalia are normal and female and only rarely do they become masculinized, in which case the term *male pseudohermaphrodite* would be correct.

The syndrome was first described and named *testicular feminization* (Fig. 3-16) by Morris (1953) who defined the syndrome as follows: (1) female habitus with a eunuchoid tendency, (2) normal or enlarged breast development with poorly developed nipples, (3) absent or scant pubic and axillary hair, (4) normal female external genitalia with a normal clitoris and a blind vagina (Fig. 3-17), (5) absent or rudimentary internal genitalia, and (6) testes which are usually intra-abdominal or inguinal but may lie in any position along the normal course of testicular descent, and which produce normal amounts of androgens and slightly less or normal amounts of estrogens.

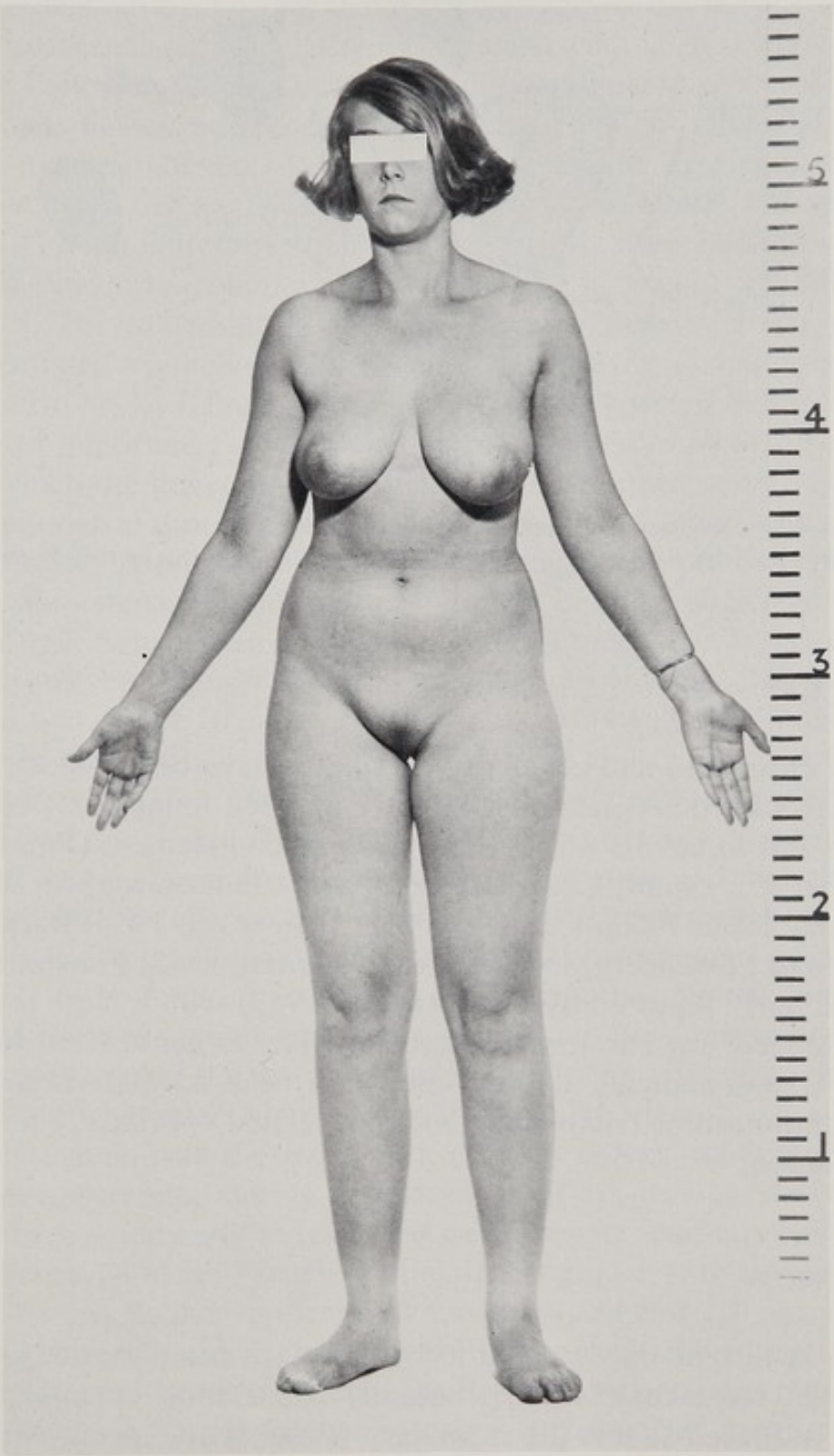


FIG. 3-16. Clinical photograph of a "girl" with testicular feminization (age 21 years) and XY sex chromosomes. (Reproduced by permission of Dr. P. M. F. Bishop and Professor P. E. Polani.)

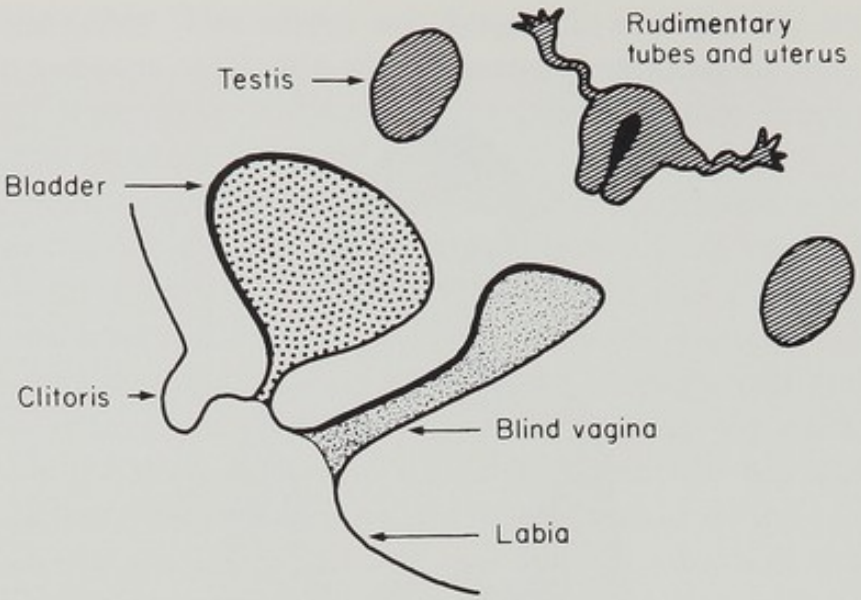


FIG. 3-17. Diagrammatic representation of internal genitalia in testicular feminization. (Reproduced by permission of Dr. P. M. F. Bishop and the editor, *British Medical Journal*.)

A. *Sex Chromatin and Chromosomes*

Sex chromatin and chromosome studies have been reported for 53 "females" with this condition who have all been found to be chromatin negative and to have a 46,XY chromosome complement (Polani, 1962; Makino *et al.*, 1962b; Court Brown *et al.*, 1964a; Gropp *et al.*, 1963; Flor *et al.*, 1962; Philip and Sele, 1965; Iliya *et al.*, 1965; Barno, 1962; Kendall and Lowenberg, 1962; Gans and Rubin, 1962; Pimstone, 1962).

The "girl" reported by Gropp *et al.* (1963) with a Yq+ is the only subject to have any chromosome anomaly. Her father also carried a similar Yq+; this anomaly is now known to be a normal variant of the human chromosome complement and not related specifically to the clinical condition.

B. *Phenotype*

The syndrome may present in two forms, a complete and an incomplete type; the incomplete type usually has clitoral enlargement or a phallus. In these patients the secondary sexual characters are unpredictable. They may resemble the complete form, they may be essentially male, they may be intermediate with sexual hair and breast development, or they may have no hair or breast development. More correctly the incomplete form is a type of male pseudohermaphroditism, particu-

larly if the external genitalia are ambiguous. In the complete form the affected males have a normal female phenotype with a normal-sized clitoris and external genitalia, usually a vagina ending in a blind sac, no uterus or Fallopian tubes. There is usually complete absence of pubic or axillary hair. Testes are present and are situated either intra-abdominally or in the inguinal canals, where they often herniate. Testicular development resembles that seen in undescended testicles. There is no spermatogenesis. The seminiferous tubules are narrow, often lacking a lumen, their diameter corresponding to that of tubules in fetal or infantile testes (Fig. 3-18). It is stated that they are mainly composed of a syncytium of undifferentiated epithelial cells which can be easily distinguished from typical Sertoli cells (Hauser, 1963b), and it is suggested that this observation is of importance since it enables an estimate to be made as to the time at which the developmental disturbance occurred and also because a distinctive endocrine function has been assigned to the Sertoli cells in the adult testis. A number of authors have suggested, on the other hand, that the seminiferous tubules consist almost entirely of Sertoli cells (J. Morris, 1953; Schaumkell and Stange, 1956; Prader, 1957; Netter *et al.*, 1958). However, Hauser (1963b) was only able to see Sertoli cells clearly in two out of 10 cases. Goldberg and Maxwell (1948) also found that the majority of cells were undifferentiated and that only a few Sertoli cells were present. On the other hand, Leydig cells are common and are very well developed (Hauser, 1963b). J. Morris and Mahesh (1963) suggested that the seminiferous tubules are immature and that clumps or nodules of Sertoli cells are found. These authors confirm the absence of germ cells. Leydig cells may be absent entirely from some parts of the gonad only to be found in extensive clumps in other regions. Spermatogonia and other stages of spermatogenesis have only rarely been seen, suggesting again that the testes are infantile and the seminiferous tubules embryonic in character. Hauser (1963b) took the view that the absence of spermatogonia was the result of a primary defect rather than a secondary disappearance during development. If so, it suggested that the genetic block acted early in testicular development, perhaps before even the primordial germ cells reach the indifferent gonad. If this were so then it would be yet further evidence of the somatic nature of sex decision (see also Chapter 4). A feature of this syndrome is the frequency with which the testes become malignant. For this reason, castration after puberty followed by subsequent estrogen replacement therapy is often indicated. J. Morris and Mahesh (1963) reported that in 50 cases of 30 years of age or older, there were 11 malignant neoplasms, chiefly germinomas, 15 tubular adenomas, and 10 cysts. This incidence of 22% of malignant tumors is obviously high in this small and selected series.

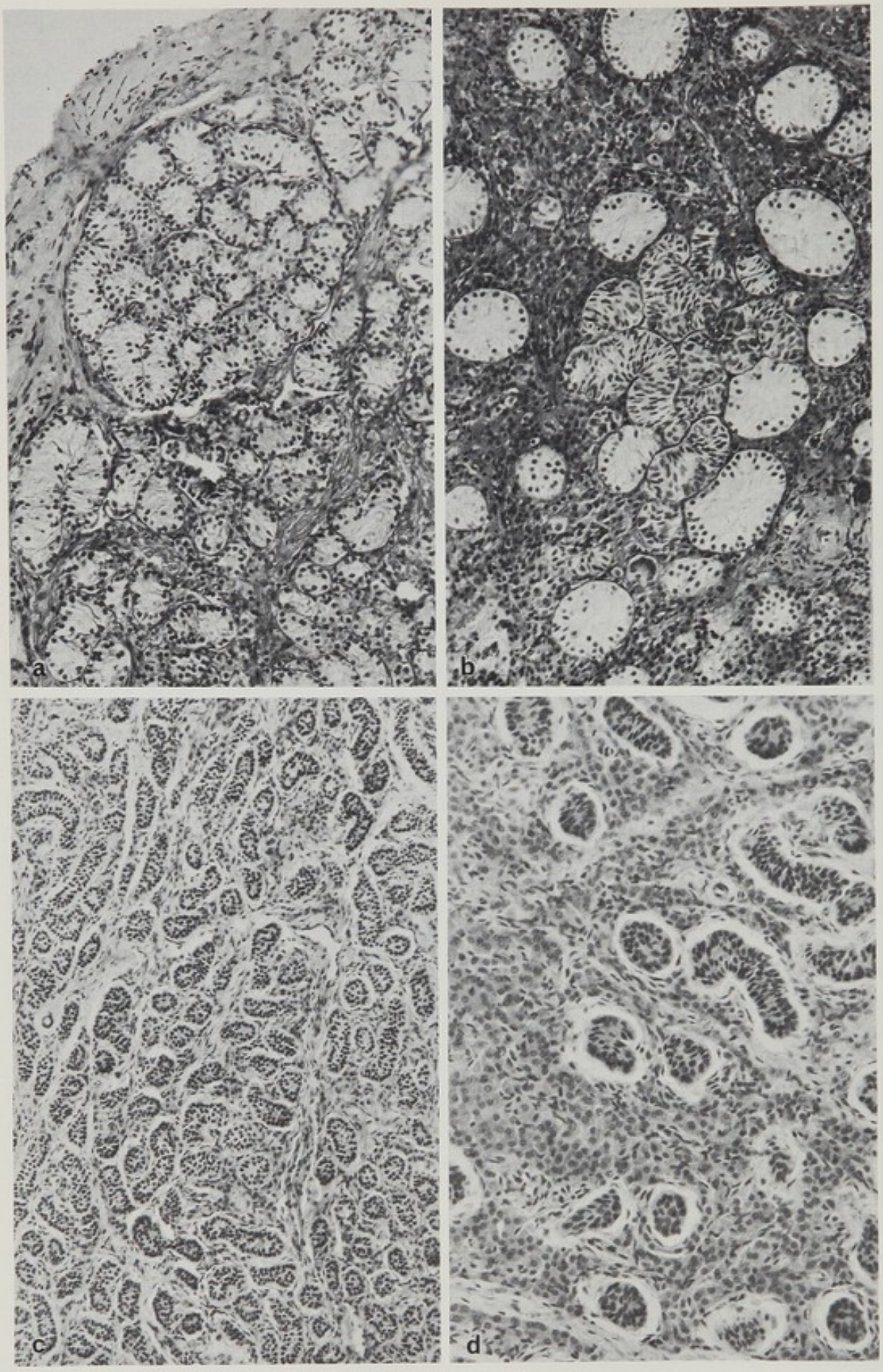


FIG. 3-18. Testicular histology in testicular feminization showing tubular histology in two cases (a, b and c, d). (Reproduced by permission of Professor P. E. Polani.)

Hauser (1963b) does not consider the risk to be as great as has been suggested. In 128 cases he found only 10 carcinomas of which six were seminomas, an incidence of under 10%. A high incidence of neoplasm would seem to be a feature of intra-abdominal testes and not specifically of testicular feminization.

C. *Endocrine Findings*[14]

The endocrine findings are conflicting, but it appears that estrogen levels are average or slightly reduced compared to normal females, although higher than the level in normal males. It is now established that the estrogens are produced by the testes. Evidence for this is based on a number of observations: the first is that estrogens disappear or are greatly reduced after castration and require replacing if normal female development is to continue, the second is that direct estimation of estrogen levels in the testes can be made. Cavallero and Zanardi (1953) and Netter *et al.* (1958) reported an increase in 17-ketosteroid levels above the normal values even for men. This, however, is unconfirmed, and the majority of authors report normal male levels, while others have found levels equivalent to normal females (Hauser, 1963b). Androgens and particularly testosterone are produced in normal or slightly less than normal male amounts.

D. *Genetics and Inheritance of Testicular Feminization*

It has long been recognized that this condition is genetically determined and frequently occurs in families and sibships often with several affected male or presumptively male siblings. Taillard and Prader (1957) considered the following facts to be significant:

1. The condition is always transmitted by normal females, some of whom may show signs of secondary amenorrhea or early menarche (Puck *et al.*, 1960; Zampa, 1961, quoted by Polani, 1962), and affects only their "sex-reversed" sons, who, although of female phenotype, are of male gonadal and chromosomal sex.
2. These authors found a sex ratio in 178 children of 98:80 made up of 30 boys, 80 girls, and 68 affected boys with testicular feminization.

A study of any series of patients with testicular feminization immediately reveals an excess of sibships with several affected subjects. For

[14]Very recently it has been shown that the target tissues in testicular feminization are incapable of metabolizing testosterone to dihydrotestosterone and this may provide support to the target organ hypothesis to account for this condition (Wilson).

instance, 11 out of the 20 cases reported by Court Brown *et al.* (1964a) are accounted for by five sibships. Of the remaining nine cases, two had no sibs, four did not have complete histories, in two, the other female sibs were dead, while in one only was there evidence that both female sibs menstruated normally. A typical pedigree showing transmission of testicular feminization is shown in Fig. 3-19.

These observations suggest that the condition is either transmitted as a sex-linked recessive or as a sex-limited autosomal dominant gene. Under normal circumstances these two types of inheritance can readily be distinguished in suitable matings. In sex-linked recessive inheritance, the condition is always transmitted by heterozygous females to half their sons, who are affected, and half their daughters, who are themselves heterozygous and can thus transmit the condition (Fig. 3-20). These affected sons transmit to half their daughters, who become heterozygotes, but to no sons. In sex-limited dominant inheritance (Fig. 3-20) affected males transmit to half their daughters, who are heterozygous carriers, and to half their sons, who are affected. In other words, the condition is dominant in affected males and recessive in females who transmit it. In testicular feminization it is not possible to make this distinction since all the affected males are sterile and cannot therefore transmit the condition. (See Addendum.)

It might be possible to distinguish between the two types of inheritance by means of linkage studies. There is, however, little evidence that the testicular feminization locus is closely linked to any of the sex-linked conditions, which may suggest that sex-limited autosomal dominance is the more likely explanation. Prader (1957) estimated the frequency of this condition to be about 1 in 20,000 (0.05/1000). Hauser (1963b) considered the frequency to be about 10 times that figure, or about 0.5/1000, while Netter *et al.* (1958) believed that about 15-20% of all forms of intersex are accounted for by testicular feminization. It is clearly not easy to arrive at a true figure because of the inconspicuous nature of the condition so that any series is likely to be highly selective,

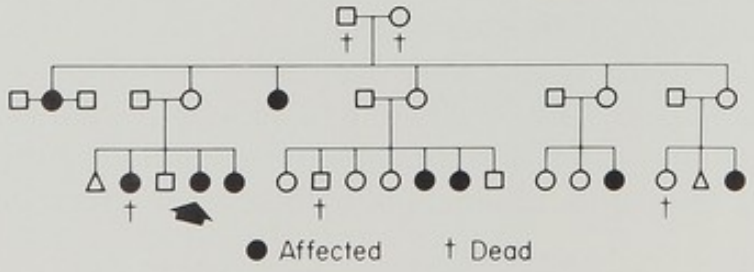


FIG. 3-19. Pedigree to show transmission of testicular feminization. The condition is transmitted by carrier females to affected "males" who are phenotypic females. (Reproduced by permission of Professor P. E. Polani and Dr. P. M. F. Bishop.)

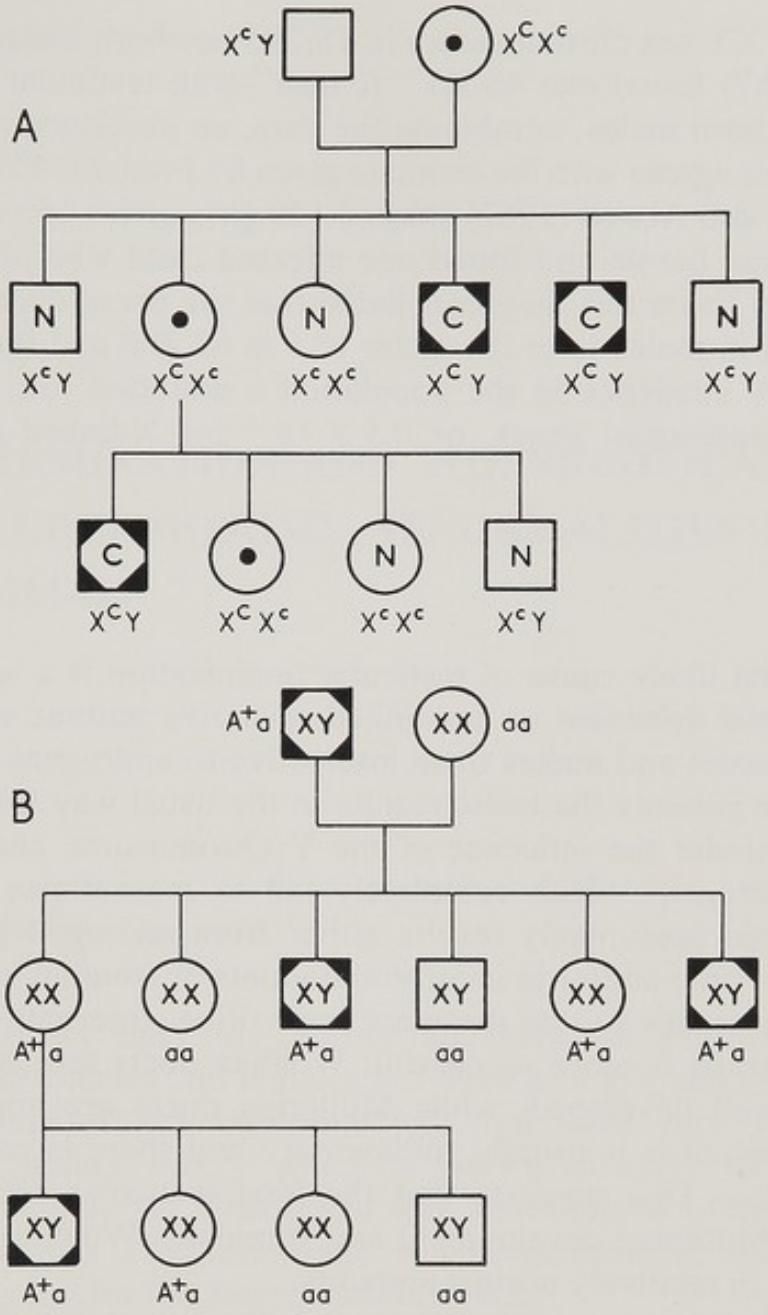


FIG. 3-20. Pedigree to illustrate the difference between (A) X-linked recessive inheritance and (B) sex-limited autosomal dominant inheritance. In (A) half the sons of carrier females are affected and half normal, and half the daughters are carriers. In (B) only males are affected when they carry the dominant allele while females are unaffected.

as, for instance, girls who are referred with inguinal hernias. One of the best estimates may be obtained from sex chromatin surveys of the newborn. This, however, may be complicated by the phenomenon of sex chromatin suppression (D. W. Smith *et al.*, 1962a; Taylor 1963). However, K. L. Moore (1959), Bergemann (1961), Wiesli (1962), Marden *et al.* (1964), and Maclean *et al.* (1964) found no chromatin-negative "fe-

males" with XY sex chromosomes in 18,295 newborn males. Taylor and Moores (1967) found one 46,XY "female" with testicular feminization in 4934 newborn males; combining the data, an incidence of 1/23,229 is obtained. This agrees with the estimate given by Prader (1957).

Jagiello and Atwell (1962) studied 120 girls under 15 years operated on for inguinal hernia and found one affected child who also had an affected sister. From this they concluded that the prevalence of testicular feminization in males is of the order of 1 in 62,400 and that in order to maintain this incidence in the population a mutation rate of about 0.4×10^{-5} for autosomal genes, or 0.5×10^{-5} for X-linked genes, would be required.

E. *Cause*

The most likely cause of testicular feminization is a single sex-limited autosomal dominant or sex-linked recessive mutant which acts on the target tissues and makes them insensitive to androgens. It is thought that in these patients the testis results in the usual way from medullary stimulation under the influence of the Y chromosome and that it then secretes androgens which completely fail to masculinize the external genitalia. This presumably results either from androgen production at the incorrect time and/or in incorrect amounts or from an enzyme defect in the target tissues so that these are insensitive. Internally the local action of the testis is more successful; Wolffian ducts are usually present and fairly well developed, while Müllerian ducts are absent; when a uterus is present it is usually rudimentary and there is usually a blind ending vagina. This suggests that the fetal testicular secretion which suppresses Müllerian development and stimulates Wolffian development is produced in relatively normal amounts.

Estrogen response is also abnormal; the breasts are large, but the nipples, areolae and glandular tissue are poorly developed. The vulva also shows a lack of response to estrogens, which, although secreted in normal amounts for women, do not in some cases appear able to suppress the production of pituitary gonadotrophin. These "women" generally lack sexual hair and the reason for this is not clear; it may result, once again, from a target organ failure of response to hormonal stimulation.

This then is a condition in which the primary defect is genetic and which appears to act by preventing target tissues from responding to normal hormonal stimuli so that a sterile but female phenotype results in a chromosomally normal male.

Chapter 4

SEX DETERMINATION AND THE SIGNIFICANCE OF THE SEX CHROMOSOME ABNORMALITIES IN MAN AND MAMMALS

I. Introduction

The discovery early this century that there was a chromosome difference between males and females provided a simple and basic solution to the problem of sex determination, and until very recently the X-autosome balance theory which is known to apply to the control of sex determination in *Drosophila* was also thought to apply to man. In *Drosophila* the Y chromosome is heterochromatic and necessary for fertility but not for the determination of sex.

There have been a number of recent reviews on the chromosome basis of sex determination in plants and animals (White, 1954; Swanson, 1957; Westergaard, 1958; Stern, 1960, 1963; Beatty, 1964; Mittwoch, 1967, 1969; Ohno, 1967; Hamerton, 1968b; K. R. Lewis and John, 1968). Henking (1891) observed a differentially staining chromosome in grasshoppers which segregated during male meiosis without dividing. He called this the *X factor* because he was not sure of its significance. McClung (1902) observed an accessory chromosome in the males of some insect species and suggested that this might be the sex determinant. Stevens (1905a,b) and E. B. Wilson (1905 a,b) observed two unequal chromosomes in male *Hemiptera*, which segregated during spermatogenesis so that half the sperm had one chromosome and half the other. These chromosomes were called the *heterochromosomes* or sex chromosomes.

In females no such heterogamety existed and all the ova had like sex chromosomes. The chromosome which was morphologically similar in males and females was called the *X* chromosome and the chromosome occurring only in males was called the Y. In those groups of animals, notably the birds, reptiles, and some insects, where the male is homogametic and the female heterogametic, the sex chromosomes are termed *ZZ* male and *ZW* females (Beatty, 1964) in order to distinguish them from the more common male heterogametic system.

The early theories of sex determination were based on work with *Drosophila* which Stevens (1908) showed to have XX and XY sex chromosomes. In man, it is now firmly established that the male has one X and the Y chromosome, and the female two X chromosomes, so that the sex chromosome mechanism is XX females and XY males, as in most other mammals.

II. Theories of Sex Determination

In many groups, despite a well-defined chromosome basis for sex determination, and provided that the right experimental conditions are applied at the right stage of embryogenesis, it is extremely easy to demonstrate the bipotentiality of the sex of a zygote irrespective of its sex chromosomes (see Beatty, 1964, for review). Jost (1953, 1961) has shown that early castration of male rabbit fetuses led to their subsequent development as females. In mammals where the correct hormonal environment is the major factor in sex differentiation, administration of hormones causes virilization or apparent sex reversal in the homogametic sex but not so easily in the heterogametic state (Beatty, 1964). Thus in mammals the "neutral sex" is female and an embryo deprived of male hormonal influences at the critical period of embryogenesis will always develop as a female. An example of this situation in man is that of so-called pure gonadal dysgenesis in which there is complete absence of gonads and hence lack of gonadal hormonal influences. The sex chromosomes can be either XX or XY, but the phenotype is always female. A particularly specialized situation is found in the freemartin condition in cattle. This condition occurs in bovine twins are of dissimilar sex if the two fetal circulations have anastomosed. The female fetus becomes masculinized and intersexual, while the male fetus remains normal. The classic explanation of this condition was that the female becomes masculinized as a result of exposure to fetal androgens produced by the developing testes of the male twin. The failure to reproduce this condition by injection of

testosterone into cows carrying female fetuses suggested that the androgen involved was not testosterone, which produces masculinization of the external genitalia but does not affect the fetal ovaries or uterus. Recently, Short *et al.* (1969) have suggested that the condition results from an induction of testicular development in the female and that masculinization results from the androgens produced by the developing testes in the female. In the goat (*Capra hirca*) a pleiotropic autosomal dominant gene causes intersexuality in homozygous genetic females. These three exceptions throw considerable light on the mechanisms of sex determination in mammals and will be discussed in some detail.

It is clear, however, that up to a certain point in development the mammalian gonad is indifferent and can develop either into a testis or an ovary, depending on the influence of the genotype. Beyond this point sex differentiation depends on an interaction between genotype and environment. In the present chapter therefore we shall consider the two aspects of sexual development: sex determination, by which is meant the decision whether the bipotential embryonic gonad develops into a testis or an ovary, and sex differentiation or the development of the phenotype, which may be male, female, or intersexual depending on an interaction between the type of gonad, the hormonal environment, and the genotype.

First, however, various theories of sex determination will be discussed; these have been summarized by Beatty (1957) as follows:

X/A ratio: Sex is determined by the ratio between the number of X chromosomes and the number of haploid autosomal sets.

X/Y ratio: Sex is determined by the ratio between the number of X chromosomes and the number of Y chromosomes.

A-X difference: Sex is determined by the difference between the number of autosome sets and the number of X chromosomes.

Total X: Sex is determined by the total number of X chromosomes present as in hymenopteran insects.

III. Autosome/X Chromosome Ratio Hypothesis

A. *Drosophila*

Bridges (1922, 1932) put forward the X/A ratio theory of sex determination to account for findings in *Drosophila*. On this hypothesis femaleness and maleness are a reflection of the balance between the

number of X chromosomes and the number of haploid sets of autosomes with the former influencing development in the female direction and the latter in the male direction. The system is so balanced that a ratio of one X chromosome to one set of autosomes gives femaleness, while one X to two sets of autosomes gives maleness (Table 4-1). The Y chromosome has, as we shall see, no influence on sex determination, but it is essential for fertility. The normal male fly has a chromosome constitution of 2A + XY (throughout this discussion A is equal to one haploid set of autosomes) which results in an X/A ratio of 0.5. Normal females, on the other hand, are 2A + XX giving an X/A ratio of unity. Thus flies with an X/A ratio of 0.5 or below are males or of a male type. Flies with an X/A ratio of unity or above are females and between 0.5 and unity are intersexes. This applies to all flies which have been studied; thus, a 3X + 3A fly is a triploid female, an XXY + 2A is a female, and an XO + 2A is a sterile male (Table 4-1). The important point to note here is that it is the ratio between the *number of X chromosomes and the number of haploid sets of autosomes* which determines whether a fly is going to develop into a male, a female, or an intersex. Therefore a tri-

TABLE 4–1

Sexual Phenotype and Chromosome Complement in D. melanogoster [a]

Sexual phenotype		X chromosome	Sets of autosomes (A)	Sex index (ratio X/A)
Superfemale		3	2	1.5
Normal female				
	Tetraploid	4	4	1.0
	Triploid	3	3	1.0
	Diploid	2	2	1.0
	Haploid [b]	1	1	1.0
Intersex		2	3	0.67
Normal male		1	2	0.50
Supermale		1	3	0.33

[a] From Sinnott *et al.* (1958).

[b] A whole individual of this type has not been obtained, but patches of tissue with one X and one of each autosome have been found in diploid flies. These patches show female characteristics.

TABLE 4–2

Sex and Probable Chromosome Constitution in Amblystomid Euploids Classified by Number of Sets of Autosomes and Number of W Chromosomes [a]

No. of sets of autosomes	Number of W chromosomes			
	O	1	2	3
1	1A + Z (♂)			
2	2A + ZZ (♂)	2A + ZW (♀)	2A + WW (♀)	
3	3A + ZZZ (♂)	3A + ZZW (♀)	3A + ZWW (♀)	3A + WWW (♀)
4	4A + ZZZZ (♂)	4A + ZZZW (♀)	4A + ZZWW (♀)	
5	5A + ZZZZZ (♂)		5A + ZZZWW (♀)	

[a] From Beatty (1964).

ploid or tetraploid fly with three or four sets of autosomes and the same number of X chromosomes will develop as a female; a diploid fly with 3X chromosomes is a "superfemale"; and a triploid fly with 2X chromosomes is an intersex. An XO diploid fly is a sterile male because it lacks a Y chromosome.

B. *Vertebrates Other Than Mammals*

The situation in the vertebrates is confusing and has been discussed in detail by Beatty (1964). In fish visible sex chromosomes cannot usually be seen, and the heterogametic sex can be either male or female (XX:XY; ZW:ZZ). Studies on triploids were inconclusive as to whether the balance was between femaleness on the X or W chromosomes and maleness on the autosomes or on the Y or Z chromosomes. In amphibia the situation seems to be variable. In *Amblystoma* genetic studies have shown that the female is the heterogametic sex and the male homogametic, and that the number of haploid autosome sets has no effect on sex determination, which is entirely controlled by a balance between the number of Z and W chromosomes (Table 4-2). In other groups, for instance, in the European newts of the genus *Triturus*, the male is probably the heterogametic sex and the female homogametic, and the number of autosomal sets does appear to affect sex determination. Kezer (1969) has demonstrated an XX/XY sex chromosome mechanism, similar to that found in mammals, in three South American genera of plethodontid salamanders.

There is very little data on sex determination in the Reptilia, largely because this order does not lend itself to breeding experiments. Recently, however, ZW:ZZ sex chromosomes have been seen in some snakes, indicating female heterogamety. The female is also the heterogametic sex in those species of birds where the sex chromosomes are known. These observations show that in vertebrates sex determination must have evolved many times and may vary from an XY:XX to a ZW:ZZ system within the same group as well as between an X/A or X/Y balance system.

IV. X/Y Ratio Hypothesis

A. *Melandrium*

In the plant *Melandrium album* sex is determined by a balance between female determiners situated on the X chromosome and male determiners on the Y (Warmke, 1946; Westergaard, 1958), and examination of Table 4-3 shows that the number of autosomal sets has little effect on the sexual phenotype in euploid individuals; there is, however, some slight effect in aneuploids (Westergaard, 1958). The sex chromosomes in this species (Fig. 4-1) are divided into five regions, of which region IV is the only homologous region, and crossing over between the X and Y is confined to this region. Regions I, II, and III constitute differential portions of the Y and region V the differential portion of the X. The following functions have been assigned to these different regions: region I has a female suppressor action and region II a male promoting action, while the third region of the Y has a secondary sex function. Region V of the X chromosome is the major region for female determination. In this species, therefore, the Y chromosome has a positive male influence which is exerted both negatively as female suppression and positively by male promotion.

B. *Mammals*

1. The Sex Chromosomes

Until very recently sex determination in mammals was thought to be controlled by the X/A ratio, and the Y chromosome was considered to be relatively inert, although Beatty (1957) commented, "It may be noted that these conclusions provisional though they are, do not give first place to the *Drosophila* type of sex determination."

TABLE 4–3

Sexual Phenotype and Chromosome Constitution in Melandrium

Ploidy	No. of autosome sets	No. of sex chromosomes		Sexual phenotype
		X	Y	
2 +	2	2	–	♀
		3	–	
		1	1	♂
		2	2	
		1	2	
3 +	3	2	–	♀
		3	–	
		2	1	♂
		1	1	
4 +	4	2	–	♀
		3	–	
		4	–	
		5	–	
		1	1	♂
		2	1	
		3	1	
		3	2	
		4	1	
		4	2	

Generally speaking, in mammals the female is homogametic (XX) and the male heterogametic (XY or more rarely XO); one species (*Ellobius lutescens*) is known in which no cytological sex difference can be observed (White, 1957; Matthey, 1958, 1964). There are a few species with more complicated multiple sex chromosome mechanisms. Koller, in his classic studies on the sex chromosomes of various species (Koller and Darlington, 1934; Koller, 1937), considered the X and Y chromosomes to consist of two segments: a pairing or homologous seg-

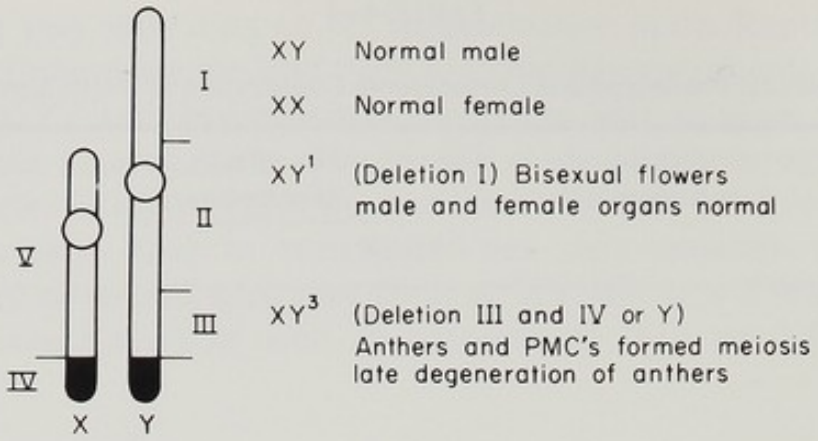


FIG. 4-1. Diagram of the sex chromosomes of *Melandrium*. The function of each segment is well known (see text). (After Westergaard, 1958).

ment and a nonpairing or differential segment. The sex determining factors were restricted to the differential segments between which there was no crossing over, while crossing over was believed to occur in the pairing segments thus allowing for both equational and reductional first meiotic divisions and partial sex linkage of genes carried in this region (Fig. 4-2). However, it has been questioned recently whether true

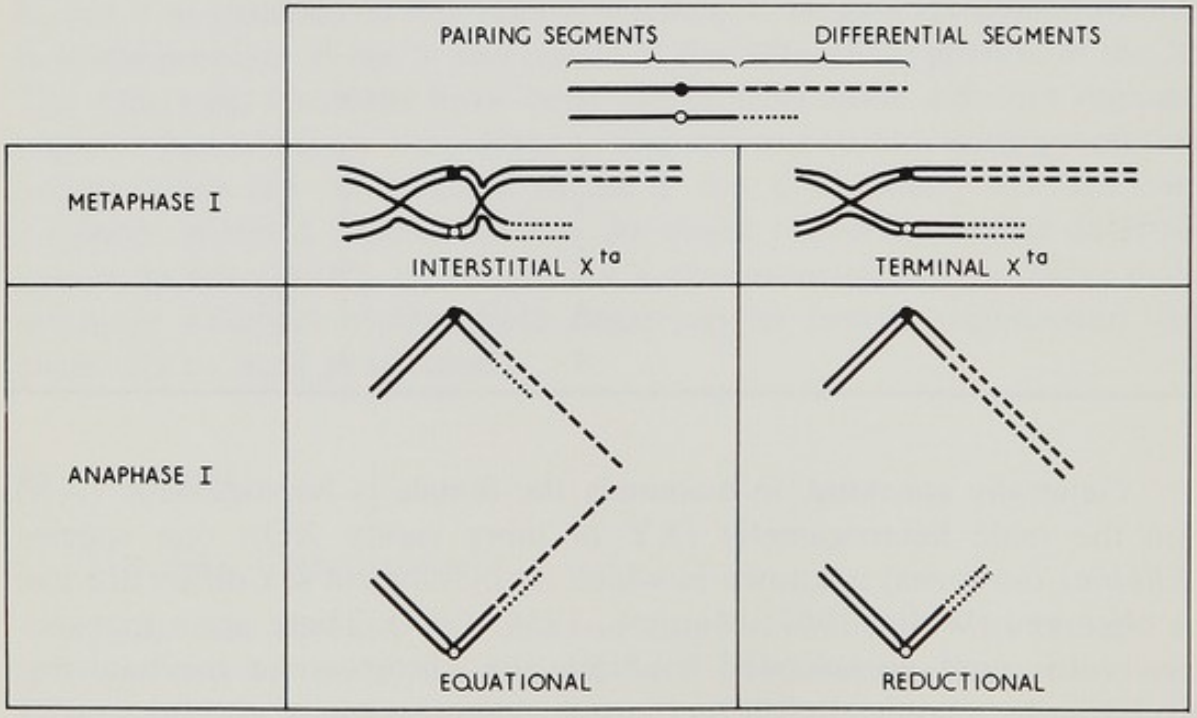


FIG. 4-2. Diagram to illustrate the hypothesis of pairing and differential segments in the mammalian X and Y chromosomes, and the effects of equational and reductional first division. (Redrawn from White, 1954, after Koller, 1937). (X^{ta}, Chiasmata.)

crossing over or chiasma formation occurs between any part of the X and Y in mammals, and this question is still not entirely settled (see Volume I, Chapter 5, Section II, C). Recent electron microscope studies have, however, shown clear parasynaptic pairing between parts of the X and Y in the sex vesicle at pachytene (see Volume I, Fig. 5-4), and other authors have shown interstitial chiasmata between the X and Y in various species. The final answer to this question must, however, be genetic and must demonstrate partial sex linkage.

2. Sex Determination (See Addendum)

Most of the recent evidence for the X/Y ratio hypothesis as applied to mammals has come from studies on the abnormal sex chromosome complements in man and the mouse, and it is now clear in at least these two species that the Y chromosome is strongly male determining and that the basis of sex determination is an interaction between the X and Y chromosomes. The little evidence available from mammalian polyploids suggests that the autosomes play a very small part in determining the sex of an individual (Beatty, 1957). This contrasts with the situation in *Drosophila* where the Y chromosome is required for the production of functional spermatozoa. The strength of this "Y effect" in man is illustrated by the observation that 47,XXY, 48,XXXY, and even 49,XXXXY subjects are male (see Chapter 1). We have to consider therefore how the Y chromosome acts to cause testis formation and what is the function of the two X chromosomes in females. Are both necessary for the formation of an ovary?

Much of the information needed can be obtained from a study of various types of abnormalities such as the XO condition in man and the mouse, XO as the normal female chromosome complement of *Microtus oregoni*, the XX males and XY females in man, the sterile XX male pseudohermaphrodites in the domestic goat (*Capra hirca*), and a variety of intersexual conditions in man. There are also a whole series of aneuploid sex chromosome complements in man which indicate the very strong male determining function of the Y chromosome. In its presence a testis is formed; in its absence the result is usually an ovary (Fig. 4-3).

a. XO in the Mammalian Female. In man, 45,X females are almost invariably sterile girls with ovarian dysgenesis, short stature, and often other somatic anomalies. The gonads are streaks and lack germ cells. However, 45,X fetuses have relatively normal gonads containing germ cells in similar numbers to 46,XX gonads up to the third month of gestation. After this time the germ cells begin to degenerate and the ovarian stromal tissue increases in the 45,X relative to 46,XX ovaries.

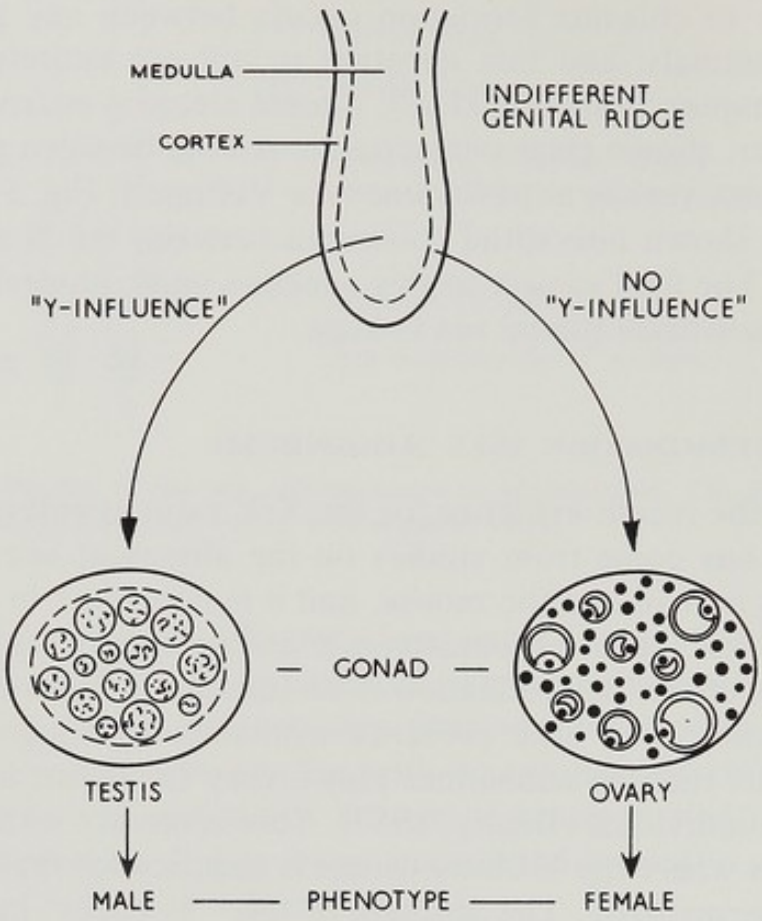


FIG. 4-3. Developmental pathways available to the indifferent gonad.

Germ cells are, however, still present at birth (see Fig. 2-3) and up to six months *postpartum*, although in considerably lower numbers than in normal ovaries; they have completely disappeared by puberty. Ohno (quoted by Singh and Carr, 1966) has suggested that this complete atresia results from a deficiency of follicle cells and failure of organization of the primordial follicles; however, the finding of follicles soon after birth does not support this. These observations do, however, make it clear that the loss of one X chromosome does not prevent the formation and migration of the primordial germ cells into the germinal ridge; nor does it prevent the organization of the germinal ridge into an ovary. The loss of one X does, however, prevent the later development of a normal ovary. In the mouse, 39,X females are fertile although a reduced litter size may indicate fewer germ cells or resorption of 39,X or Y fetuses. T. Morris (1968), in an extensive study of breeding data of 39,X compared to 40,XX female mice, concluded that the reduced litter size could be accounted for by complete pre-implantation loss of 39,Y zygotes and both pre- and postimplantation loss of a proportion of the 39,X zygotes. He also considered that there was probably an abnormally low

segregation of nullo-X gametes from 39,X females. In *Microtus oregoni* 17,X females are fertile as a result of predirected nondisjunction so that only Y-bearing or nullisomic sperm are produced by the testes, while in the female nondisjunction results in the formation of an XX ovary (Fig. 4-4). It seems clear, therefore, that although a single X is sufficient to determine the developmental pathway taken by the indifferent gonad, as well as for the formation of primordial germ cells, both X chromosomes are needed to maintain normal ovarian development.

b. AUTOSOMAL MODIFIERS. In mammals, certain autosomal genes can affect both the developmental pathway taken by the indifferent gonad and the formation of the germ cells. In the mouse the *W*(*W* W^vW^j) series of alleles cause sterility in both sexes and affect the

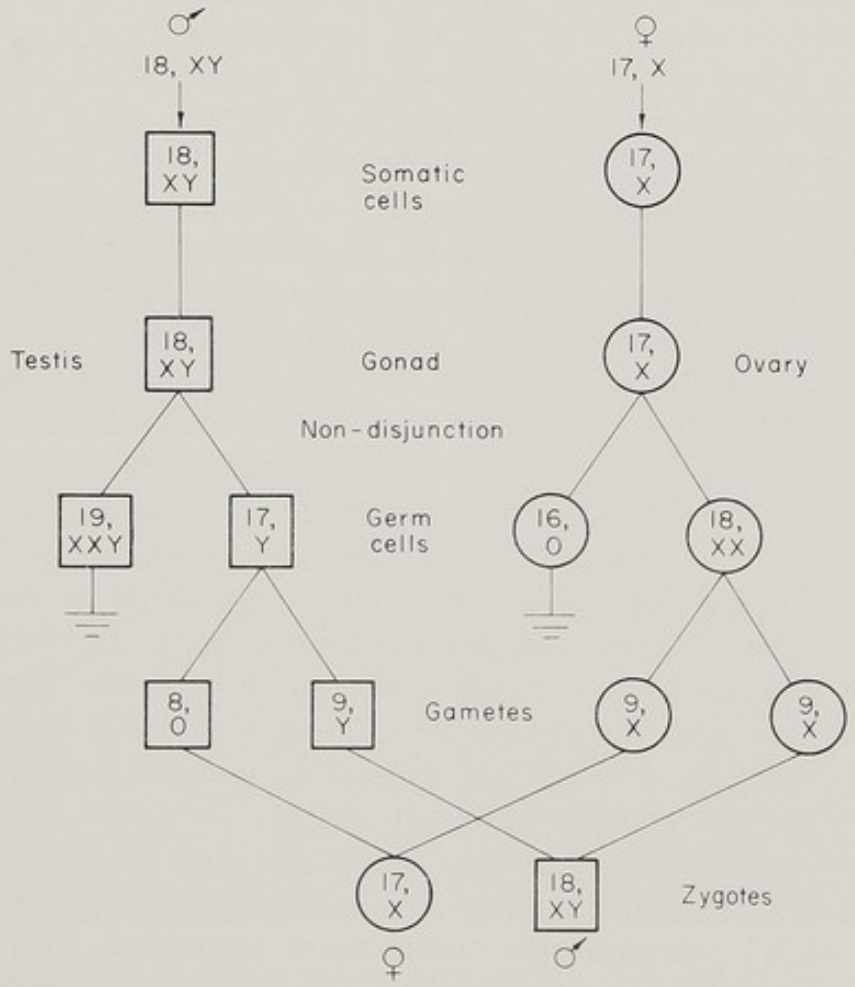


FIG. 4-4. The course of oogenesis and spermatogenesis in *Microtus oregoni*. In the male nondisjunction in a primordial germ cell gives rise to 17,Y germ cells giving 8,O and 9,Y sperm. In the female nondisjunction gives an 18,XX ovary and a single class (9,X) of ova.

number of germ cells but not the type of gonad (Mintz, 1957). In W^jW^j and WW mice very few germ cells ever reach the gonadal ridge, but despite this a testis is formed in the male and an ovary in the female. This is good evidence that the primary act of sex decision is at the somatic and not the gonial level.

In the goat (*Capra hirca*) the autosomal dominant gene controlling horn growth (polled *P*) also has a large number of pleiotropic effects in the homozygous state (*PP*). Homozygous (*PP*) genetic females are sterile polled male pseudohermaphrodites with testes which lack germ cells at birth but otherwise function normally and secrete normal levels of testosterone (Hamerton *et al.*, 1969). The same gene which may cause sterility in some homozygous males as a result of epididymal occlusion also affects litter size and sex ratio.

In homozygous (*PP*) intersex goat fetuses germ cells have been observed in relatively normal numbers in the testis at about 63 days gestation (Hamerton *et al.*, 1970). By 126 days germ cells are still present, but a greater proportion are in the process of degeneration, and by birth all the germ cells have disappeared (Fig. 4-5). This is conclusive evidence of the somatic nature of sex determination, for in this species we are dealing with a gene, which in genetic females causes testicular development despite the presence of an XX sex chromosome complement and XX germ cells. These are formed, migrate to the germinal ridge, but despite this genotype are unable to prevent the formation of a testis; nor are they able to survive beyond birth in a testicular environment.

In man, it has been suggested that 46,XX males are either mixoploids (46,XX/47,XXY), in which the XXY cell line has not been detected, or were originally 47,XXY zygotes, in which the Y chromosome was lost after sex decision. Alternatively, the translocation of the "Y borne male determining" genes onto the X chromosome might have occurred. Neither of these suggestions seems really convincing and a similar, but rare, autosomal modifier leading to testicular development and hence a masculine phenotype seems more reasonable. Such a modifier, with variable penetrance and expressivity, could also account for 46,XX male pseudo- and true hermaphrodites.

The other conditions of interest in man are pure gonadal dysgenesis with XX or XY sex chromosomes, and testicular feminization, in which there is a 46,XY chromosome complement associated with a female phenotype and testicular development. The condition is probably, but not certainly, caused by the action of a sex-limited autosomal dominant gene which makes the target organs insensitive to the action of testosterone.

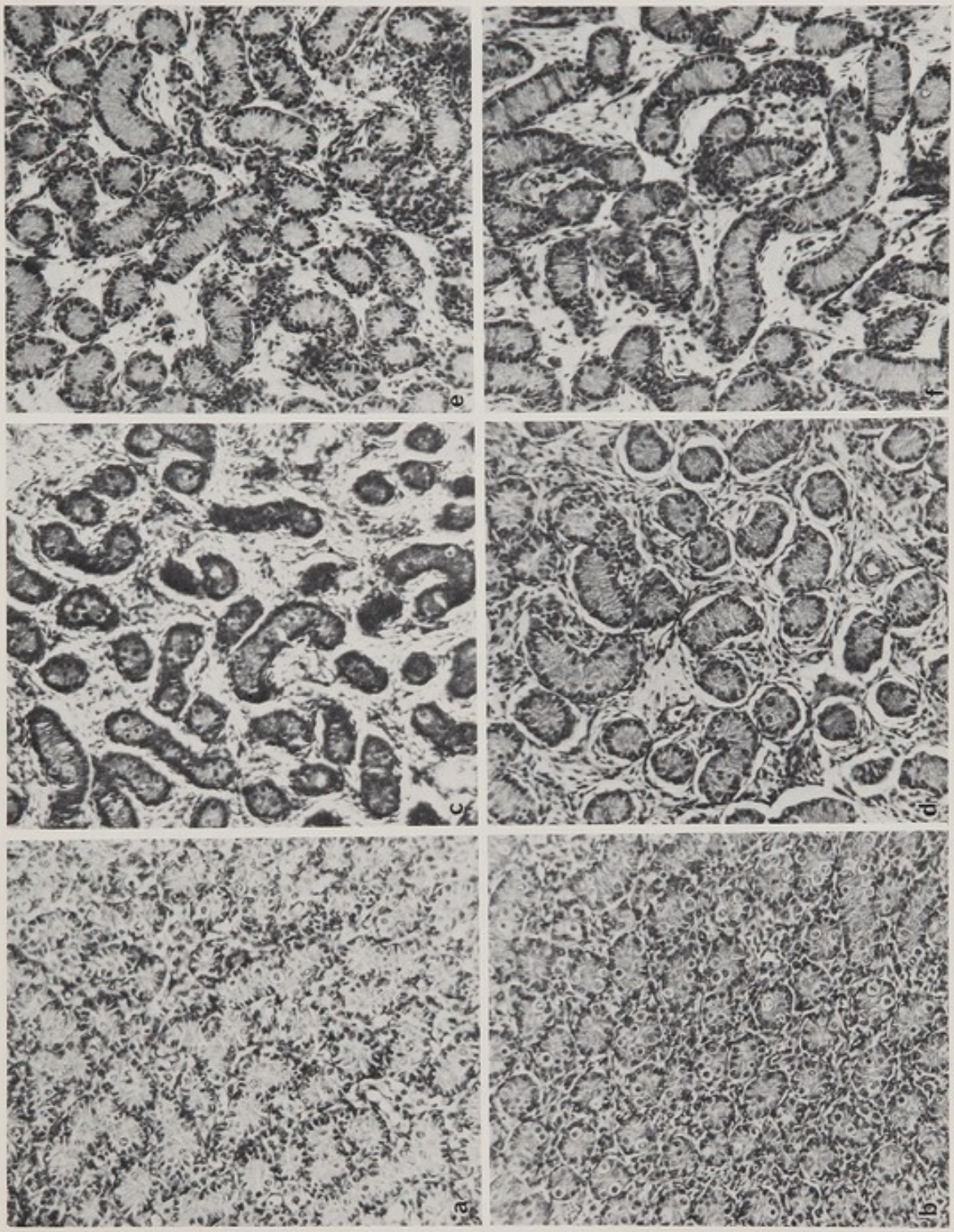


FIG. 4-5. Histology of fetal and newborn intersex (XX) and normal testes (XY) in the goat: (a) 63 days intersex, (b) 63 days normal ♂, (c) 126 days intersex, (d) normal male co-twin to (c), (e) newborn intersex, and (f) normal male co-twin to (d). Note presence of germ cells in both normal and intersex animals up to 126 days gestation and absence in intersex after birth. (Reproduced from Hamerton *et al.*, 1969.)

c. ACTION OF THE Y. Usually, the presence of a Y chromosome results in the development of a testis, and hence a male phenotype, while in its absence an ovary is formed and a female phenotype develops. However, the presence of additional X chromosomes as well as the Y leads to abnormal male development, resulting not from an effect on testis determination which is mediated by the Y chromosome but from an effect of additional X heterochromatin on the regulation of testicular development. An excess number of Y chromosomes with only one X does not seem to affect sex determination or fertility. Finally, subjects with a Yqi have a female phenotype which suggests that the male determining or regulating factors are on the short arm of the Y which is deleted.

d. MECHANISM OF SEX DETERMINATION IN MAMMALS. The data which are outlined here show clearly that (1) the act of sex decision simply depends on whether the indifferent gonad develops into a testis or an ovary, (2) this act is mediated through the somatic elements of the genital ridge and not the gonia, (3) normally a Y chromosome is necessary for the development of a testis but under the influence of certain autosomal modifier genes a testis can be formed in the presence of two X chromosomes and no Y chromosome, and (4) only one X is necessary for the determination of an ovary although the second X is necessary for its normal development. Finally, it is necessary to remind the reader that only one X chromosome is euchromatic, while in diploids the remaining X chromosomes and the Y chromosome become heterochromatic at an early stage of development (Volume I, Chapter 6).

Bearing all these facts in mind the following hypothesis is suggested:

1. The act of sex decision is the stimulation of the primary sex cords of the medulla of the indifferent gonad to develop into a testis. In the female the medulla regresses allowing the secondary sex cords of the cortex to develop into an ovary (Fig. 4-6).

2. In the female one X chromosome only is necessary for cortical development which must therefore carry both the gene for cortical stimulation and its operator (Fig. 4-7).

3. In the male the Y chromosome or some part of the Y acts as a "controlling center" for the gene controlling the stimulation of the medulla or its operator and these genes are situated elsewhere in the complement than on the Y itself. In the presence of a Y chromosome, or perhaps the short arm of the Y, these become activated and stimulate the medulla; stimulation of the medulla inhibits development of the cortex (Fig. 4-8).

4. Autosomal modifers such as *P* in the goat, and perhaps genes

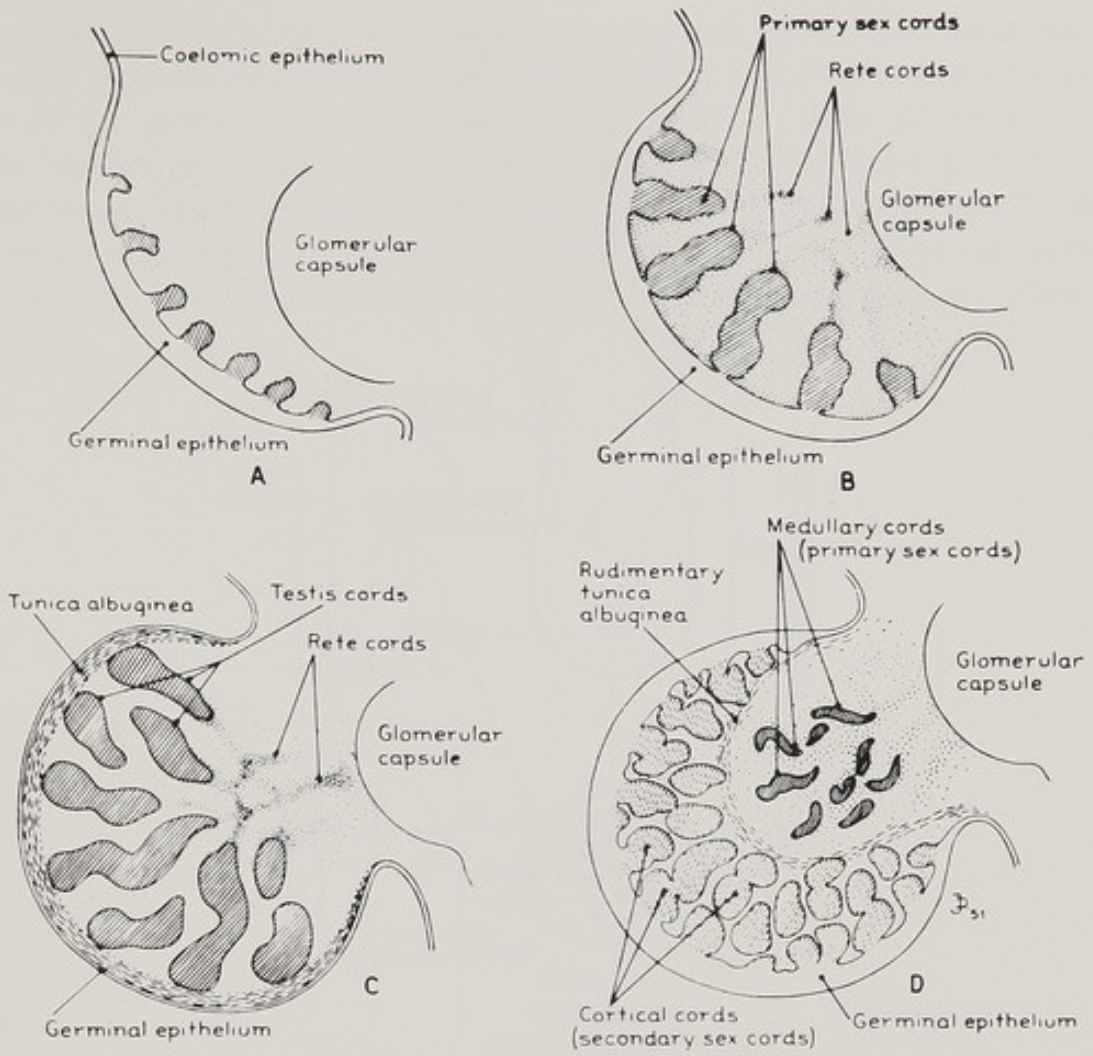


FIG. 4-6. Diagram to illustrate the main features of gonad differentiation in amniote embryos with reference to the origin of cortical and medullary components. (A) Origin of primary sex cords from the germinal epithelium. (B) Indifferent gonad. The well-developed primary sex cords represent the male or medullary component, whereas the germinal epithelium potentially represents the cortical component. (C) Differentiation of a testis consists in the further development of the primary sex cords, the reduction of the germinal epithelium, and the development of a *Tunica albuginea*. (D) Differentiation of an ovary consists of the reduction of the primary sex cords to the medullary sex cords of the ovary; the secondary sex cords of the cortex develop from the germinal epithelium. (Reproduced by permission of Dr. R. K. Burns of Williams and Wilkins Co. From Sex and Internal Secretions, Third Edition, 1961.)

in the pig and in other species including man, act in a similar way to the Y controlling center by activating the gene controlling medullary stimulation (Fig. 4-9).

5. The most likely site both for the gene for medullary stimulation as well as that for cortical stimulation is on the X chromosome. This was originally suggested by Polani (1962) and more recently by McFeely *et al.* (1967). It should be remembered that the heteromorphic XY pair seen in modern mammals evolved from a homomorphic pair presumably

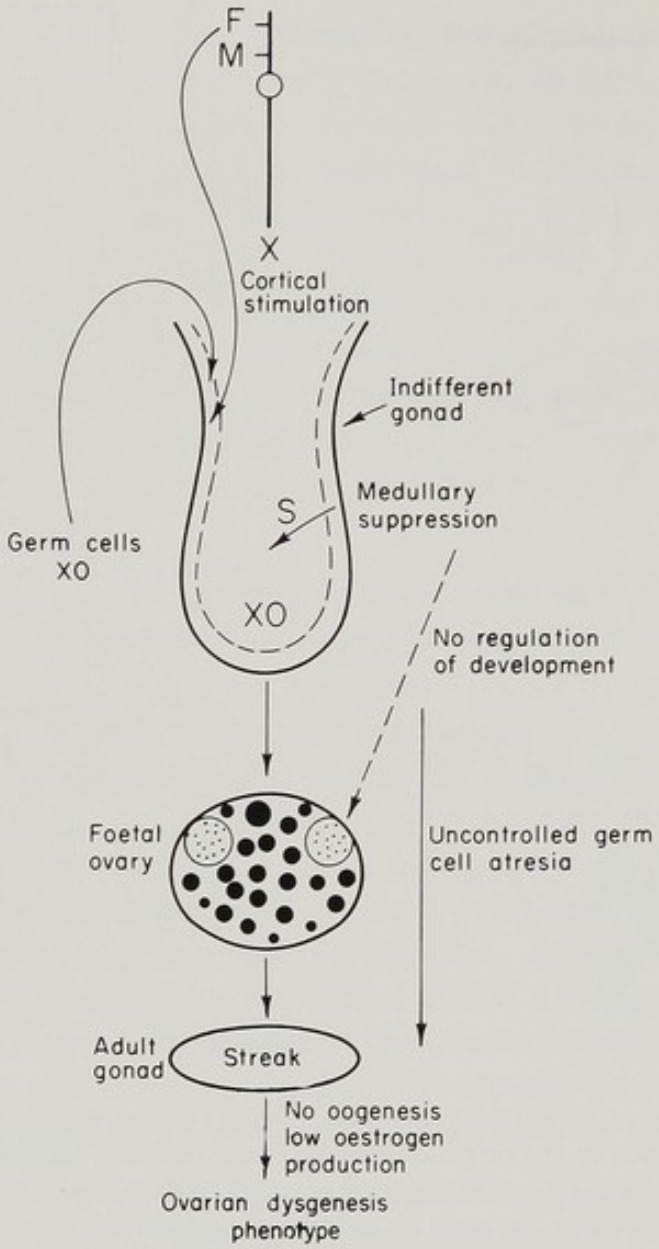


FIG. 4-7. Schematic diagram to illustrate a possible mode of action of the single X chromosome in XO females leading to degeneration of the medulla and stimulation of the cortex to form an ovary. The second X is necessary for maintenance of ovarian development. In its absence the germ cells regress and the streak gonad of the adult 45,X female is formed. (Hamerton, 1968a).

carrying homologous genetic material and furthermore that the two genes are likely to be situated in fairly close proximity, particularly if the activity of one leads to the suppression of the other.

6. As we have seen, only one X chromosome is necessary for ovarian formation and the formation and migration of germ cells, and it is suggested that the second heterochromatic X acts as a regulator of ovarian development and in particular regulates the rate of germ cell

atresia (Fig. 4-10). In normal ovaries germ cell atresia is a continuous process throughout gestation and postnatal life and only a small proportion of the gonia remain to form ova. In the 45,X state atresia is complete so that no germ cells survive to puberty. The second X may also regulate estrogen production by the ovary, and abnormalities in this pathway may result in reduced amounts of estrogen and hence sexual infantilism. The abnormalities in somatic development seen so often in

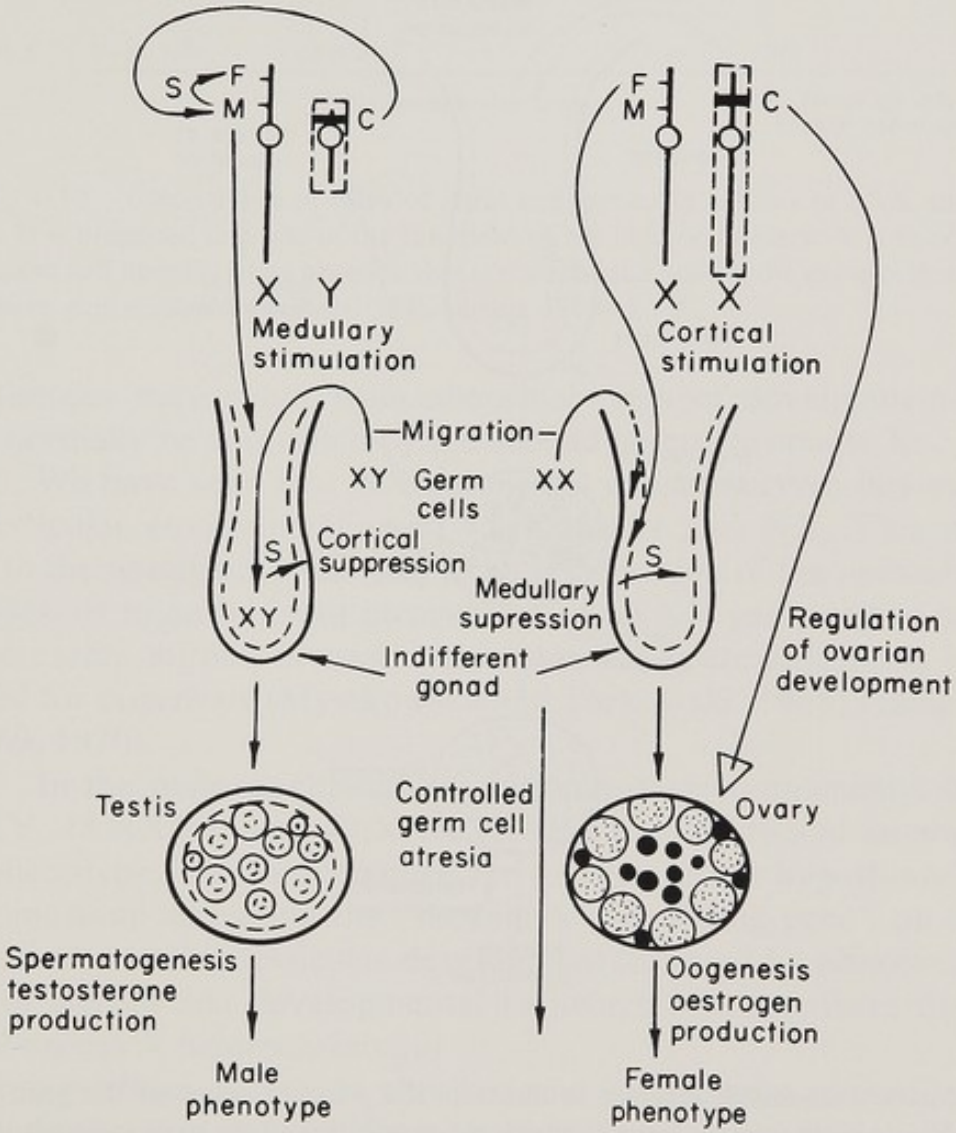


FIG. 4-8. Schematic diagram to show the possible course of sex determination in mammals. It is assumed that one X chromosome carries both the "male and female determining" gene loci. In the presence of a Y chromosome this becomes activated causing the production of a male inductor which stimulates the primary sex cords to form a testis. In its absence the medullary cords regress and the secondary sex cords develop to form an ovary. An inductor substance may be required here or ovarian development may occur in the absence of a male inductor. (Hamerton, 1968a).

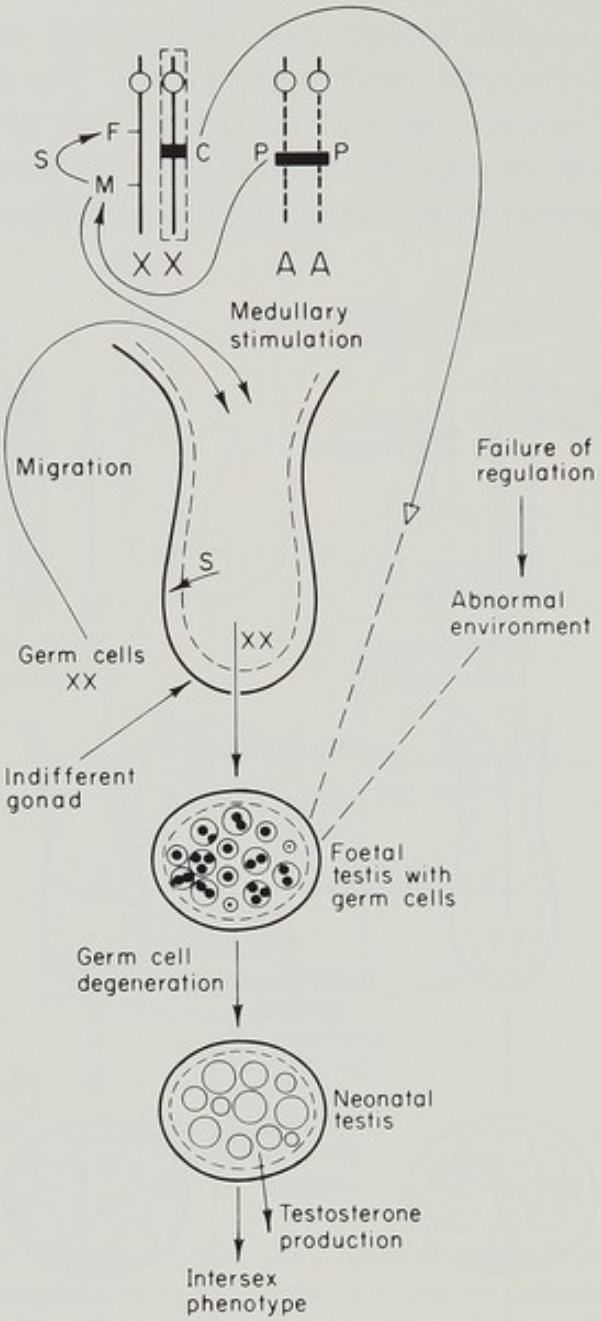


FIG. 4-9. Schematic diagram to illustrate the possible action of the gene *P* in the goat. This acts on the "male locus" causing the production of the male inductor substance which stimulates the medulla to form a testis. The timing of the switching on of the male locus could be the cause of the variable phenotype. An early switch leads to complete testicular development and a fairly fully masculinized phenotype; an intermediate switch may lead to testicular development, but fetal androgen production may occur after the period of maximal sensitivity so that the phenotype is only partly masculinized; a late switch may lead to only partial testicular formation so that an ovotestis is formed and the phenotype is only slightly masculinized. (Hamerton, 1968a, 1969.)

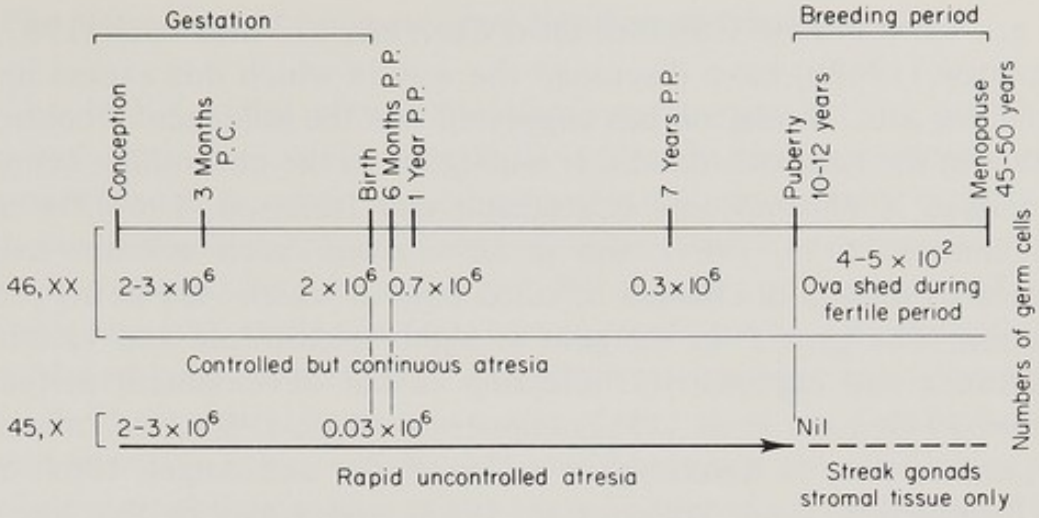


FIG. 4-10. Comparison of rates of germ cell atresia in ovaries in 45,X and 46,XX females. It is proposed that one of the functions of the heterochromatic X is to control the rate of germ cell atresia. In its absence this is unregulated and all the germ cells of a 45,X female have degenerated by puberty. (Hamerton, 1969b.)

45,X females may result from abnormal rates of development which would normally be controlled by the second heterochromatic X.

7. We have seen that XX germ cells cannot survive beyond birth in a testicular environment even when this is also XX. This may be owing to the wrong environment, to an acceleration of the normal atretic processes, or to an inherent incapability of an XX germ cell to perform the successive mitotic divisions necessary for spermatogenesis but not required for oogenesis (Mystkowska and Tarkowski, 1968; Hamerton *et al.*, 1969, 1970).

8. In the male, aneuploid sex chromosome complements such as 47,XXY, 48,XXXY, and 49,XXXXY lead to sterility and an abnormal male phenotype. This is accounted for on the present hypothesis by the Y chromosome activating the "medullary stimulating gene" on the euchromatic X causing testicular development followed by abnormal regulation of steroid and developmental pathways resulting from the presence of excess X heterochromatin.

Abnormalities of the sex chromosome complement in man lead not only to abnormal sexual development but also to abnormalities of stature and psychosocial development (see Chapters 1 and 2; also, Hamerton, 1968b), and it is suggested that these abnormalities result from imbalance in the amount of sex-chromosome-derived heterochromatin since it is the amount of heterochromatin which varies in all the sex chromosome aneuploids while the amount of euchromatin remains constant (see above and Volume I, Chapter 6).

e. CONCEPT OF CONTROLLING CENTERS. Mittwoch (1967) and Hamerton (1968b) have discussed the way in which this excess heterochromatin acts. Hamerton has suggested that the influence of controlling centers in the heterochromatin is analogous to the controlling centers in the mouse X chromosome (Cattanach and Isaacson, 1967), in maize (McClintock, 1956, 1965), and in *Drosophila*. Such systems may be affected by dosage or changes of state, both of which vary in the present situation. The gene *P* in the goat is highly pleiotropic and variable in penetrance and expressivity, affecting sexual development in females (Eaton, 1945; Laor *et al.*, 1962; Hamerton *et al.*, 1969), sex ratio, litter size, and fertility in homozygous males (Soller and Angel, 1964; Soller and Kempenich, 1964; Soller *et al.*, 1963); and it may be that like the *t* alleles in the mouse it should be considered as a short chromosome region rather than as a single gene (Hamerton *et al.*, 1969). If so, this region may also be heterochromatic and act as a controlling center, especially in its effects on sex determination and fertility.

If these controlling centers exist and as suggested are situated in heterochromatin, they might function by nucleotide sequestration (Commoner, 1964), although there is no direct evidence for this. They could thus control mRNA synthesis either by blocking polynucleotides required for a particular mRNA or by blocking the action of mRNA polymerase or amino acyl RNA synthetase, an enzyme essential for protein synthesis. Alternatively, expressing this in more conventional terms, the controlling centers could become decondensed at specific times and in specific cells, thus exposing the DNA template to mRNA polymerase so that appropriate mRNA's could be produced. A close control over pulse length and the amount of messenger produced might equally well exercise the type of control required.

V. The Intersexual States, Sex Reversal and Sex Determination

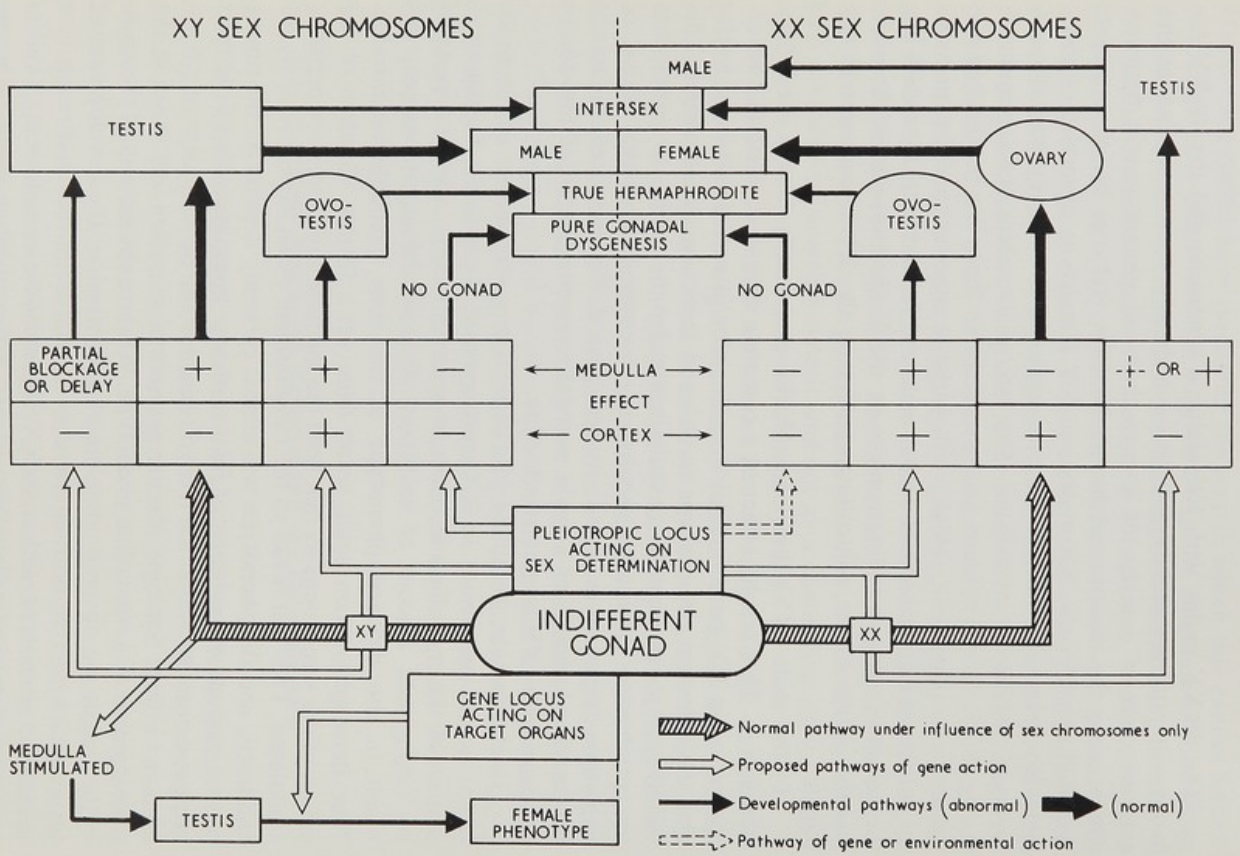
The intersexual states can be separated into two main groups according to their cytogenetic characteristics; these are (1) the nonmixoploids and (2) the mixoploids. The nonmixoploid groups clearly have no obvious cytogenetic basis for their intersexuality or sex reversal, and these will now be considered in the light of the theory of sex determination put forward above. The mixoploid groups, especially the 46,XX/46,XY and the 45,X/46,XY subjects, have already been discussed in some detail (Chapter 3) and will not be considered further here.

A. *The Nonmixoploid Intersexes and Sex-Reversed Subjects*

The 46,XX males with Klinefelter's syndrome and the 46,XY females with pure gonadal dysgenesis have already been considered as the extreme ends of a series of abnormal sexual phenotypes in between which come the male pseudohermaphrodites and true hermaphrodites. We shall consider the XX males and XY females as examples of complete sex reversal, while the true hermaphrodites are only partially sex reversed and hence intersexual. The interrelationships are summarized in Fig. 4-11. In this scheme it is assumed that there is a sex-limited autosomal recessive gene, which, with variable penetrance and expressivity, affects sex determination in the male and female fetus by modifying the action of the controlling centers on the Y chromosome in the male and the action of the controlling centers on the X chromosome in the female.

In the male (XY) this locus blocks or partially blocks medullary stimulation. This results either in a complete failure of testicular development as in XY pure gonadal dysgenesis or in partial failure of testicular development, or perhaps in delayed testicular development. This would lead to incomplete masculinization by the testes, or perhaps to the production of fetal masculinizing hormones after the period of maximum target tissue sensitivity had passed. The result of this would be the development of a male pseudohermaphrodite or, if the cortex develops, of an XY true hermaphrodite.

In the female, complete blockage of any stimulation of the indifferent gonad will result in XX pure gonadal dysgenesis. Partial stimulation of the medulla will result in testis formation, which, depending on timing and amount of secretion of masculinizing hormones, will result in the virilized phenotype of the male pseudohermaphrodite. True hermaphroditism could result from yet a further variation of the action of the same locus so that both the medulla and cortex are partially stimulated. This will result in the development of an ovotestis or ovary and testis, and the phenotype will almost certainly depend on the timing of and amount of secretion of fetal testicular hormones. Too little fetal hormone or its secretion too late will result in the development of a feminine or virilized feminine phenotype; normal secretion will result in the development of a masculine phenotype. At the extreme end of the scale in the female we observe complete masculinization: the development of testes which secrete normal amounts of fetal hormones and result in a masculine phenotype with a 46,XX chromosome complement. This interaction of testicular development and XX controlling mechanisms results in a phenotype which closely resembles Klinefelter's syndrome. It


XY SEX CHROMOSOMES
XX SEX CHROMOSOMES
MALE
TESTIS
TESTIS
INTERSEX
MALE
FEMALE
OVARY
OVO-TESTIS
TRUE HERMAPHRODITE
PURE GONADAL DYSGENESIS
OVO-TESTIS
NO GONAD
NO GONAD
PARTIAL BLOCKAGE OR DELAY
MEDULLA
EFFECT
CORTEX
OR
PLEIOTROPIC LOCUS ACTING ON SEX DETERMINATION
XY
INDIFFERENT GONAD
XX
GENE LOCUS ACTING ON TARGET ORGANS
MEDULLA STIMULATED
TESTIS
FEMALE PHENOTYPE
Normal pathway under influence of sex chromosomes only
Proposed pathways of gene action
Developmental pathways (abnormal) (normal)
Pathway of gene or environmental action

may be assumed that here the testes are sterile and lack germ cells, not because no germ cells are produced but because XX germ cells are unable to survive in a testicular environment (Mystkowska and Tarskowki, 1968; Hamerton *et al.*, 1969, 1970).

Finally, at the other end of the scale, the male with testicular feminization and a female phenotype probably results from an entirely different gene effect. In this condition the XY genotype mediates testicular development which has a relatively normal hormonal spectrum; however, it would seem that the genetic effect is at the level of the target organs which are completely insensitive to testosterone and that their estrogen sensitivity is not normal; the result is a sterile female phenotype with testes and fairly normal, if infantile, female external genitalia.

Table 4-4 summarizes the causes of intersexuality in various species, and there is evidence for a genetic cause in the goat, the pig, and in man, largely obtainable from breeding studies. In man the finding of families containing several "females" affected with pure gonadal dysgenesis and pseudohermaphroditism (see Chapters 2 and 3) argues that perhaps, as suggested above, the same locus is involved. These ideas obviously require considerably more data before they are proven but would seem to fit the available facts.

VI. The Germ Cells

It is now clear (see above) that the mammalian germ cell does not play a significant part in the development of the gonads but rather is completely passive in its action. Studies on the *W* series of alleles in the mouse (Mintz, 1957) have shown that both testis and ovary can develop in the almost complete absence of germ cells. Hamerton *et al.* (1969, 1970) have shown the development of testes in the goat in the presence of XX germ cells, which however are not able to survive in a testicular environment after birth.

FIG. 4-11. A schematic diagram to show how a pleiotropic mutant gene of variable penetrance and expressivity acting at the level of the indifferent gonad could result in the whole range of intersexual states from the XX male on the one hand to the XY female with pure gonadal dysgenesis on the other. The mutant is presumed to act by altering the production of male and female inductor substances so that the development of the gonad may be completely blocked (pure gonadal dysgenesis XX or XY) or completely reversed (XX males). The syndrome of feminizing testes is believed to be caused by a different mutant which causes the target organs to be insensitive to testosterone so that as a result a female phenotype develops (see text).

TABLE 4–4

Cause and Type of Intersexuality in Some Mammals

Species	Cause	Evidence	Type
Goat	Genetic	Breeding	XX Male pseudohermaphrodite. XX True hermaphrodites – rare. ? Sex reversal.
	Chimerism	Cytology	Rare male pseudohermaphrodite of female type – freemartin.
Sheep	Chimerism	Cytology and blood groups	Male pseudohermaphrodite. Masculine or feminine type – freemartin.
Cow	Chimerism	Cytology and blood groups	Freemartin – females rarely masculine.
Horse	Chromosomal	Cytology	Male pseudohermaphroditism.
Man	Genetic	Breeding	XY and XX gonadal dysgenesis and pseudo and true hermaphrodites. XY and XX sex reversal.
	Chromosomal	Cytology	Various mixoploid intersexes.

The reason for this is not clear; Fig. 4-12 summarizes the difference between the behavior of an XX and an XY germ cell in the gonad. The XX germ cell undergoes relatively few mitotic divisions before entering prophase of meiosis I in which stage it remains until just prior to ovulation (see Volume I, Chapter 5, Section III, A) when it completes the remainder of the first maturation division. The XY germ cell, on the other hand, has a long proliferative period, during which it completes numerous mitoses, and it does not enter meiosis until around the time of sexual maturity. It seems possible, therefore, that the Y chromosome not only serves as a regulator of sex determination but also controls the development of the male germ cells, both prior to and during spermatogenesis and spermiogenesis, and that in the absence of the Y chromosome the germ cells are only able to complete the number of mitoses required for development in the ovary so that if placed in a testicular environment they degenerate at this stage (Fig. 4-13). Alternatively, the failure of an XX germ cell to survive in a medulla may rest with the hormonal or cellular environment rather than the genome; only further studies can give the answer to this question and also give some information on the fate of an XY germ cell in an XX gonad.

VII. Conclusions

It is clear from the data outlined in this chapter that in man and the mouse sex determination is controlled by the Y chromosome which exerts a positive male determining action on the indifferent gonad. This results in stimulation of the primary sex cords in the medulla to develop into a testis. In the absence of a Y chromosome the medulla regresses and the secondary sex cords in the cortex develop into an ovary, only one X being necessary for this to occur. It is suggested here that a controlling center or centers situated on the heterochromatic Y chromosome activates the gene controlling stimulation of the medullary sex cords, which is probably situated on the X chromosome. This "medullary gene" can also be stimulated by autosomal activators such as the "*P* chromosome region" in the goat leading to the development of testes in a genetic female. The second heterochromatic X chromosome also carries controlling centers which may regulate such processes as germ cell atresia in the ovary, estrogen production, and certain other developmental pathways.

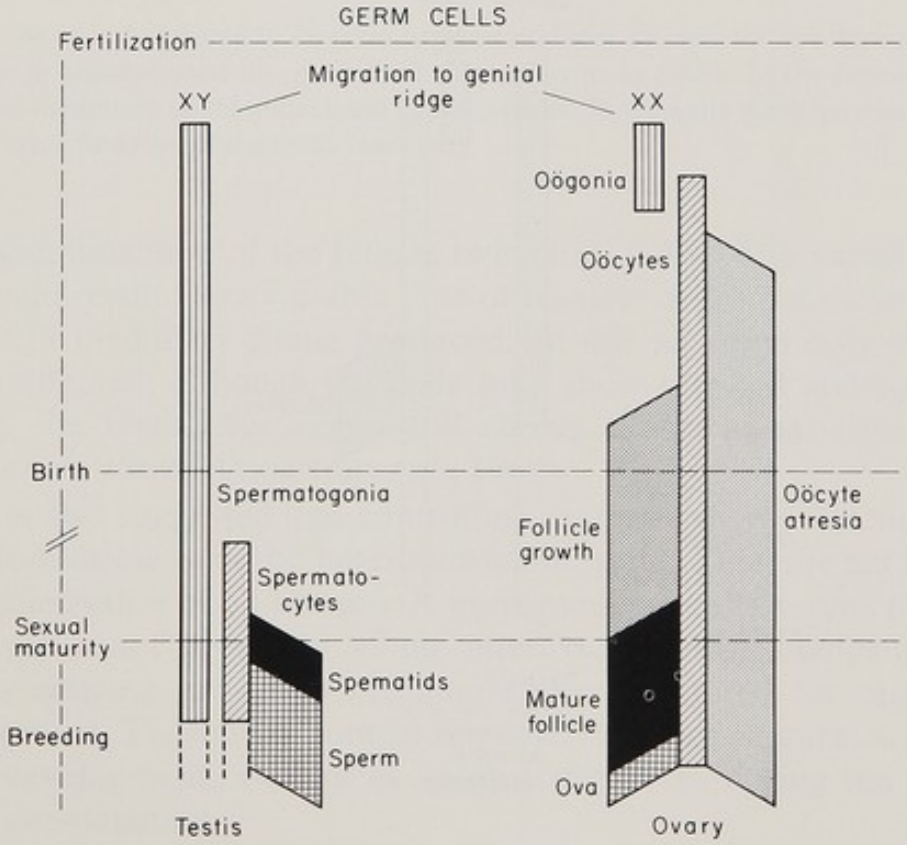


FIG. 4-12. A schematic diagram to show the different "programming" of XY and XX germ cells (see text).

These ideas support the concept of the female sex as the neutral sex in mammals, which develops in the absence of a Y chromosome, or of a male gonad if this is removed early enough. The function of the Y or an autosomal modifier such as *P* is clearly to control medullary stimulation which in turn secretes at least two fetal hormones irrespective of the genotype of the tissue; one of these is an androgen which causes masculinization of the external genitalia and the other a fetal testicular hormone which inhibits Müllerian development. We thus have a situation where the genotype of a particular cell has no effect on the type of secretion produced but only on whether that cell will develop or not, and once developed the particular secretions follow as a matter of course. If this is so, it would account for the freemartin condition in cattle in which it would be necessary to postulate transfer of inductor cells or substances from the male co-twin to the female, resulting in stimulation of the medulla and the formation of a testis. The medulla, once stimulated, then proceeds to produce male-type hormones leading to Müllerian inhibition

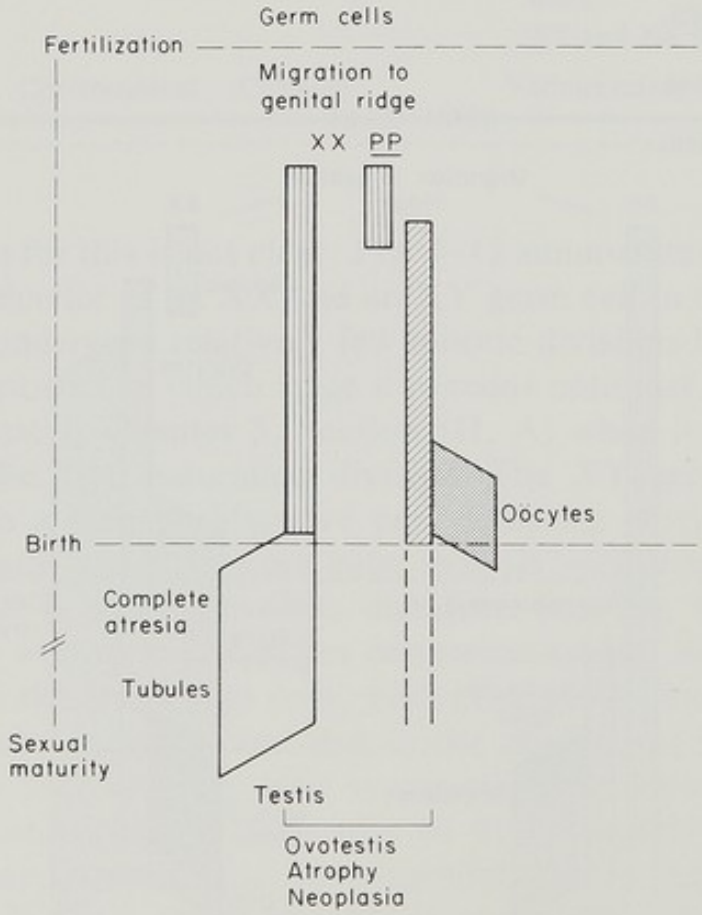


FIG. 4-13. A schematic diagram to show the fate of germ cells in the intersexual state in the goat. Complete atresia in the testes and possibly some survival to birth in the ovarian part of an ovotestis.

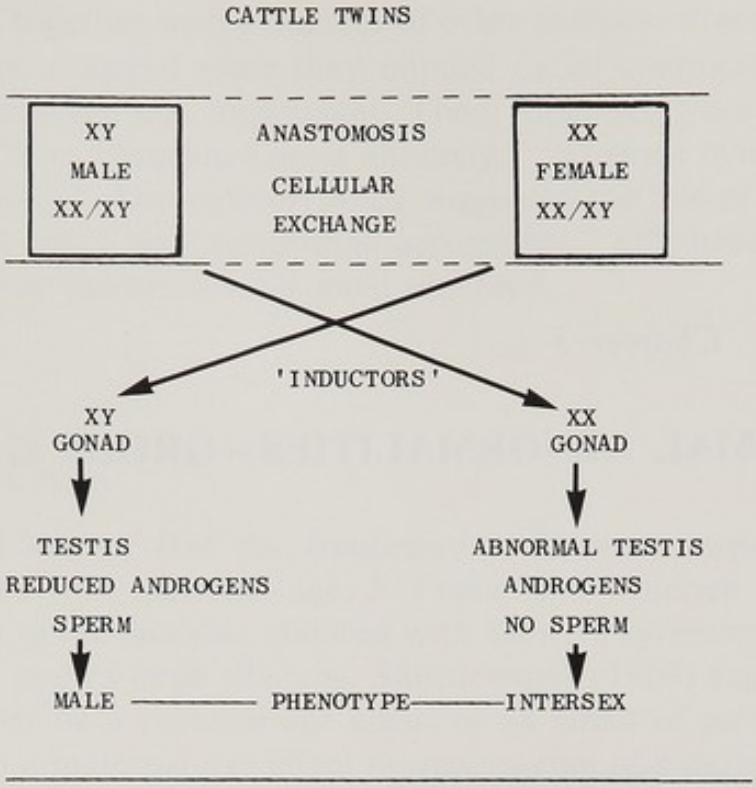


FIG. 4-14. A schematic diagram to show transfer of inductor substances across the placentae in anastomosed dizygotic unlike-sexed twins in cattle. In the female the inductors cause medullary development and hence a testis. In the male there may be an effect on the endocrine function of the testis (see text).

and masculinization of the female twin (Fig. 4-14). The variable phenotype could result from variable time of transfer or from a variation in the amount of medullary tissue produced. In this situation only the female twin is affected; although the male may show reduced androgen secretion by the testis, this organ still shows a normal exocrine function (Short *et al.*, 1969; Hamerton *et al.*, 1969).

It is also suggested that controlling centers are only functional when the chromosome is in the heterochromatic state. Thus the act of heterochromatinization of all but one X in mammalian cells serves not only to inactivate major gene loci in the interest of dosage compensation but also to activate certain controlling centers required for regulation of development. These may control sex determination, stature, and psychosocial development, as well as various processes during the course of sexual development.

Chapter 5

AUTOSOMAL ABNORMALITIES—GROUP G

I. 21-Trisomy—Down's Syndrome

A. *Introduction*

Down's syndrome or, as it was originally termed, *mongoloid idiocy* or *mongolism* was first reported in 1866 by Langdon Down, who described a syndrome of mental deficiency and abnormal mongoloid-like facies. Waardenburg (1932) and Penrose (1939) both suggested that this condition might be caused by a chromosome abnormality, and Penrose concluded that "mongolism and some other malformations may have their origins in chromosome abnormalities." This hypothesis was not tested until 1952 when Mittwoch studied meiosis in a male mongol and found 24 bodies in the spermatocytes. She concluded from this observation that the chromosomes were normal and that the human diploid number was 48. Finally, Lejeune (1959) and Lejeune *et al.* (1959) were able to demonstrate an identical chromosome abnormality in nine affected children. More recently, both the clinical and major cytogenetic features have been extensively reviewed (Hamerton *et al.*, 1965; Giannelli *et al.*, 1965; Polani *et al.*, 1965; Penrose and Smith, 1966).

B. *Nomenclature*

The terms *mongol* and *mongolian idiot* have been used to refer to these patients since the original description by Langdon Down (1866).

In 1961 Allen, together with a number of other authors, urged that these terms should be dropped since they implied racial connotations which were both misleading and unpleasant. They suggested various alternatives such as "The Langdon-Down anomaly," "Down's syndrome," or "Down's anomaly." Alternatively, they suggested the use of a more descriptive name such as "congenital acromicria." Of these, the term *Down's syndrome* has become the most accepted.

C. *Etiology*

1. Maternal Age

It is well known that the frequency of Down's syndrome (DS) births increases with maternal age. J. Fraser and Mitchell (1876) first drew attention to the fact that children with Down's syndrome tended to be born at the end of large sibships. Shuttleworth (1909) suggested that this could either be a parental age effect or an effect of parity. Jenkins (1933) favored a maternal age effect as against that of paternal age or of parity and produced evidence to show a greatly increased incidence of Down's syndrome births at maternal ages of over 40 years. Penrose (1933, 1934a,b, 1939, 1954) was able to show conclusively that the increased incidence of Down's syndrome births is related to the age of the mother and not to any other single factor such as paternal age or parity. The significance of this relationship is not at present clear but may represent a decrease in meiotic efficiency with increasing age of the oocyte. German (1968) proposed that the relationship of Down's syndrome to increasing maternal age might be explained by delayed fertilization among older women consequent to spasmodic or decreased frequency of coitus. This hypothesis has been examined in relation to duration of marriage by Penrose and Berg (1968) who concluded that the duration of marriage at the birth of a sample of 988 mongols was significantly longer than for the controls, but that this effect was entirely related to increasing maternal age and that when maternal age was kept low the difference disappeared. Cannings and Cannings (1968) have examined the decline in frequency of coitus with increasing age of the mother and have shown that if this is related to an increase in frequency of DS the upper limit of this increase should come at about 35 years. Finally, Matsunaga and Maruyama (1969) have demonstrated that the frequency of marital coitus fits a Poisson distribution for each age group and have concluded that German's hypothesis cannot account for the empirical data unless some other factors are related to age apart from prolongation of coital intervals. The relationship of maternal age to

increasing frequencies of nondisjunction therefore still remains a mystery which may be open to an experimental approach.

Penrose (1961, 1964) and Penrose and Smith (1966) showed that the bimodal (bitangential) maternal age distribution curve (Fig. 5-1) which is so characteristic of Down's syndrome could best be accounted for by the assumption that there are two components to the maternal age distribution in Down's syndrome and that the shape of the distribution curve is determined by the proportion of each component. One group (Class A) would contain those cases in which maternal age was not a factor, while the other (Class B) comprises those cases which were maternal age dependent. The maternal age independent cases show a peak frequency of Down's syndrome births at 28.5 years, which corresponds well with the peak frequency of births in the general population. The second curve (Class B) has a peak at about 43 years. Penrose and Smith (1966) have suggested that out of 9441 cases of Down's syndrome, 5683 (60.2%) fall into Class B and 3758 (39.8%) into Class A.

Penrose (1951, 1954, 1961, 1964) has shown that maternal age is reduced both when more than one affected child occurs in a sibship and in families with affected maternal relatives. Penrose and Smith (1966) have argued that the most satisfactory way of assessing the proportion of births which fall into Class A or B is to take the control popu-

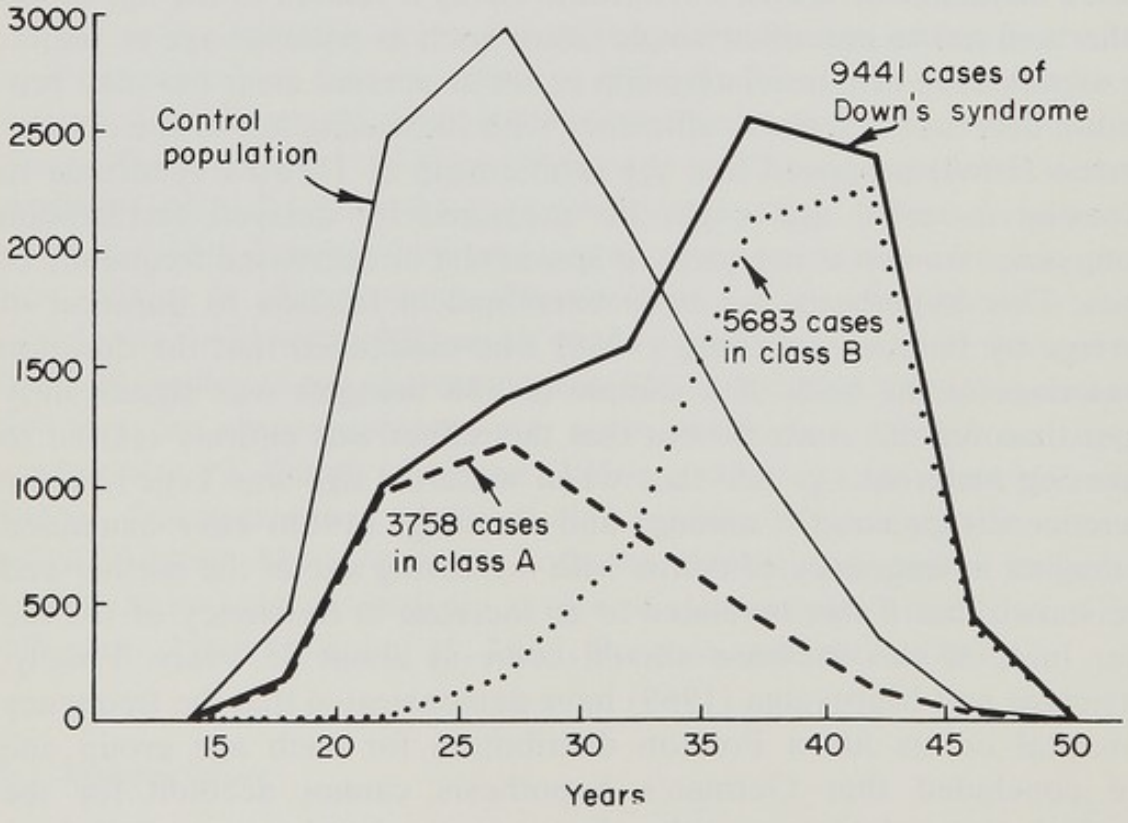


FIG. 5-1. Maternal age distribution of 9441 cases of Down's syndrome with control population. (Reproduced by permission from Penrose and Smith, 1966. J. & A. Churchill.)

TABLE 5-1

Distribution of Down's Syndrome Births by Maternal Age in 11 Countries [a]

Mother's age		Down's (DS) syndrome births	Control (N) births [b]	Ratio DS/N
Group	Center			
<19	18	184	462.4	0.398
20 – 24	22	988	2465.1	0.401
25 – 29	27	1364	2920.7	0.467
30 – 34	32	1569	2082.9	0.753
35 – 39	37	2547	1128.5	2.257
40 – 44	42	2383	353.7	6.737
>45	46	406	27.7	14.657
Total		9,441.	9,441.0	1.000
Mean		34.43	28.17	–
Range of means		33.2–35.1	27.1–28.7	–

[a] Data from Penrose and Smith (1966).
[b] Control births adjusted to give same total as observed number of Down's syndrome births.

lation as 100% Class A and assume that in the youngest age group of Down's syndrome births none are age-dependent. Table 5-1 shows that the youngest age group has the lowest incidence (0.019) of affected births compared with an incidence of 0.05 control births falling into this age group. On these assumptions Class A Down's syndrome comprise about two-fifths of all affected subjects and includes all hereditary cases and some of hypothetical environmental origin, while the remaining three-fifths would be caused by some other process associated with increasing age of the mother.

Penrose (1962) and Penrose and Smith (1966) have suggested that there is a small class of children with a t(GqGq) who show an increased paternal age at birth (Table 5-2), especially where the translocation was transmitted through the father compared to when both parents had a normal karyotype or transmission was through the mother. These data are, however, extremely heterogeneous and based on low numbers of subjects, and additional unselected families are obviously required.

A knowledge of the cytogenetics of Down's syndrome (see Section H, below) indicates that Class B subjects are almost entirely primary trisomics, while Class A subjects include the bulk of secondary trisomics (translocation trisomics). A few primary trisomics which occur in fami-

TABLE 5–2

Parental Age Data in t(GqGq) Down's Syndrome

No. of cases	Mean maternal age	Mean paternal age	Reference
(1) Sporadic t(GqGq)			
10	30.3	35.4	Penrose and Smith, 1966
5	27.0	29.4	Sergovich *et al.*, 1964
10	30.2	32.1	Hamerton *et al.*, 1965, and PRU unpublished data
(2) Father t(GqGq) heterozygote			
4	31.7	42.0	Penrose and Smith, 1966
(3) Mother t(GqGq) heterozygote			
4	27.6	27.5	Shaw, 1962; Pfeiffer, 1963; Yunis *et al.*, 1965; J. F. Jackson and Ashford, 1967

lies in which there may be a genetic predisposition to nondisjunction would, however, be included in Class A (Carter and Evans, 1961; Hamerton *et al.*, 1961a).

2. Incidence

The incidence of Down's syndrome among live births is in the order of 1 in 668 (1.50/1000), and in general the results obtained for widely different populations are in good agreement (Table 5-3).

Collmann and Stoller (1963a), in a very extensive survey of live-born children with Down's syndrome in Australia during the 10-year period 1948-1957, obtained a frequency for all age groups of 0.46/1000 (1/2200) population. This is much lower than most other estimates because of the high mortality rate between 0 and 5 years of age; their estimate for this population at birth was 1.02/1000 compared to 0.7/1000 at 5 years of age. Carter and MacCarthy (1951) showed that the frequency of Down's syndrome was 0.7/1000 births at young maternal ages (< 30) and rose to 3.1/1000 births for older mothers (> 30); it reached a max-

TABLE 5-3

Incidence of Down's Syndrome at Birth in Nine Surveys [a]

Reference	Population	City and/or country	No. of DS	Total births	Incidence	Incidence per 1000
Jenkins, 1933	Hospital	Chicago, Ill.	6	3,818	1:636	1.572
Malpas, 1937	Hospital	Liverpool, England	18	13,964	1:776	1.289
Penrose, 1938	Sibs of non-mongol defectives	England	7	4,374	1:625	1.600
Parker, 1950	Hospital, including Negroes	Washington, D.C.	32	27,931	1:873	1.146
Hug, 1951	Hospital	Zurich, Switzerland	130	67,645	1:520	1.922
Carter and MacCarthy 1951	Hospital	London, England	107	71,521	1:668	1.496
Øster, 1953	Hospital	Copenhagen, Denmark	52	39,788	1:765	1.307
Collmann and Stoller, 1962	General population	Victoria, Australia	1,134	780,168	1:688	1.453
Leck, 1966	General population	Birmingham, England	513	316,954	1:618	1.619
Total			1,999	1,326,163	1:663	1.507

[a] Note: Data from Parker (1950) includes 29 DS subjects in 25,026 Negroes, an incidence of 1:863.

imum of about 1 in 50 births at maternal ages of over 45 years. This increase in incidence with maternal age is shown very clearly in Collmann and Stoller's data (1962), the incidence rising from 1/2300 at maternal ages between 15 and 19 years to 1/46 at over 45 years (Fig. 5-2).

Renkonen (1965) has analyzed the sex of sibs of affected children and has shown a significant increase in risk of Down's syndrome births in families with four or more boys as compared with similar sized families of girls. Hecht *et al.* (1964) have studied the maternal age distribution in 13 sibships with two aneuploid sibs, one of whom had Down's syndrome. They found no increase in maternal age in this series when compared to a sporadic series of patients with primary G-trisomy.

3. Twins

Monozygotic twins usually show concordance for Down's syndrome, although two such twin pairs have been reported in which one

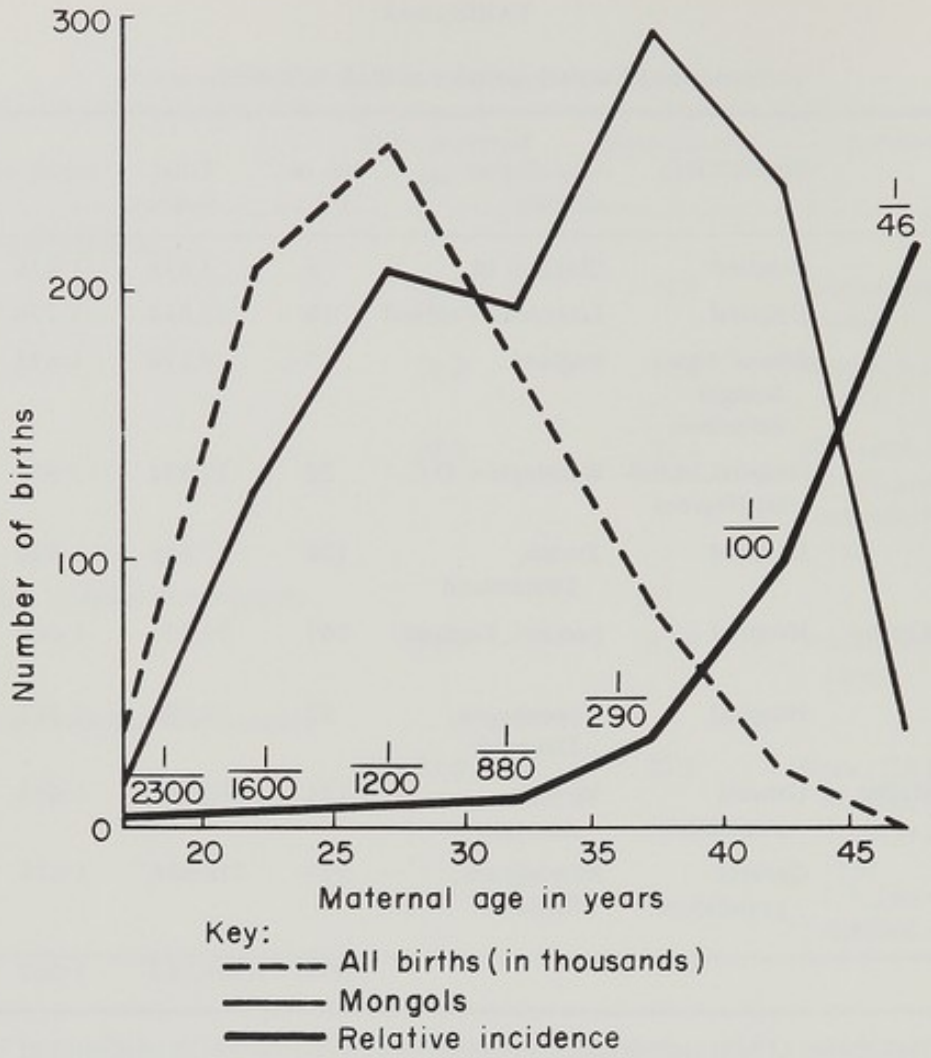


FIG. 5-2. The incidence of Down's syndrome at birth. (From Penrose and Smith, 1966; Collmann and Stoller, 1962.)

twin had Down's syndrome while the other did not (Lejeune *et al.*, 1962; De Wolff *et al.*, 1962; Dekaban, 1965). Dizygotic twins, on the other hand, were thought to show no greater concordance for Down's syndrome than would be expected by chance. However, McDonald (1964) studied 67 pairs of twins in which a diagnosis of Down's syndrome had been made in one or both infants and found two pairs of unlike sex twins who were concordant for Down's syndrome when only 0.14 pairs would have been expected ($P < 0.01$). Five pairs of like sex twins were concordant for Down's syndrome, where 10.5 monozygotic twin pairs might have been expected, which, allowing for the known relationship between maternal age and twinning, represents a deficiency of nearly 50% ($P = 0.065$). This indicates a considerable deficiency of monozygotic twins with Down's syndrome. McDonald suggested that a zygote with abnormal chromosomes might be less likely to split to form

monozygotic twins than a zygote with normal chromosomes. Keay (1958) had suggested that this deficiency might result from the more frequent intrauterine death of one or both members of an affected twin pair. The finding of two pairs of discordant monozygotic twins can now be explained on the basis of the chromosome findings (see Volume I, Fig. 7-12), and several other twin pairs have been described with discordant chromosome findings. Dekaban (1965) described an unequally affected pair of female monozygotic twins, one with a normal karyotype (46,XX) and one with 48,XX,G+, mar+ (mar+ is an additional metacentric chromosome of unknown origin). Rosenkranz *et al.* (1964) reported a pair of like sex twins, one of whom had 47,XY,G+ and the other 47,XXY. Wright *et al.* (1963) reported two families, the first with a pair of twin boys, one with 47,XY,G+ and the other normal (46,XY), while an older sib had 47,XXY chromosomes (Fig. 5-3). A second sibship contained a normal twin pair, one of which was stillborn, and two brothers, one with

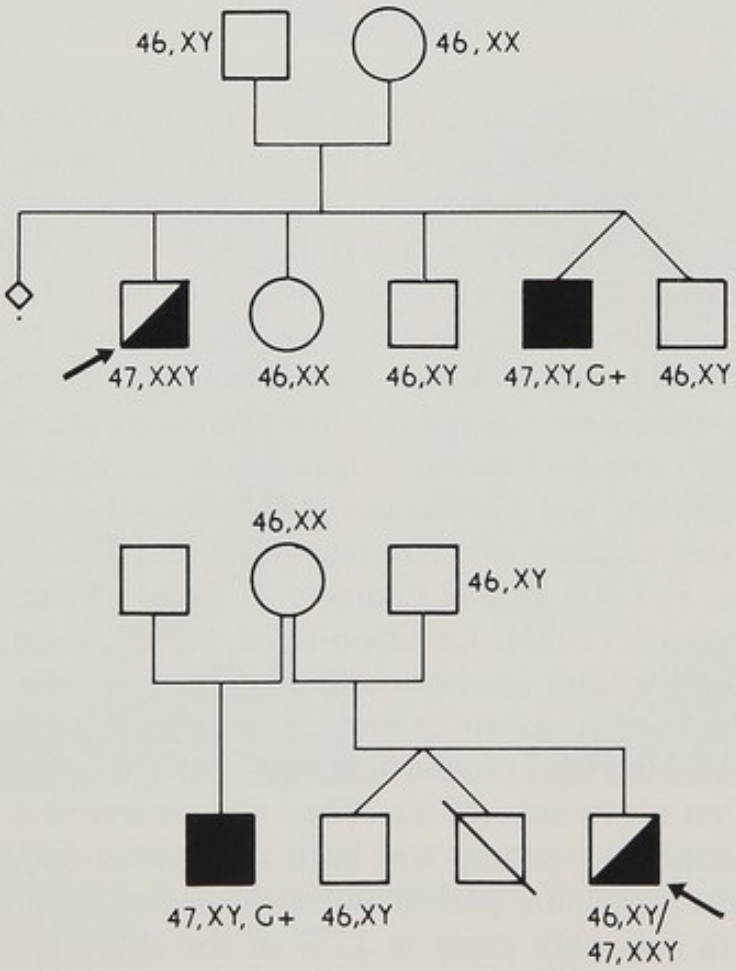


FIG. 5-3. Pedigrees of two families reported by Wright *et al.* (1963) showing sibship concentrations of subjects with aneuploid chromosome complements.

Down's syndrome (47,XY,G+) and the other with 46,XY/47,XXY mixoploidy.

4. Familial Incidence

Although Down's syndrome usually occurs as a sporadic event in a sibship, families and sibships with several affected members have been described (see above). Penrose (1961) pointed out the difficulties of assessing the significance of such familial concentrations in a condition as common as mongolism. He showed that where pairs of first cousins were affected there was a significant increase in the frequency of affected subjects when the parents were sisters rather than when the parents were brother and sister, or brothers. This increase results entirely from young mothers under 30 whose sisters also had mongols.

D. *Clinical Observations*

1. Diagnosis

The clinical features of Down's syndrome have been described many times (Øster, 1953; Penrose, 1961; Hanhart, 1960a; Benda, 1960; Beckman *et al.*, 1962a; Gustavson, 1964; Penrose and Smith, 1966). Carter and MacCarthy (1951) and Hall (1964) have dealt specifically with the features of Down's syndrome in the newborn. Lowe (1949) has described the ophthalmological symptoms, while Rowe (1962) and Rowe and Uchida (1961) among others have discussed the frequency with which Down's syndrome and cardiac malformations are associated.

Øster (1953) listed 10 cardinal signs which can be used in the diagnosis of mongolism, and Gustavson (1964) included in his series 43 mentally retarded patients who had four or more of the 10 cardinal signs listed by Øster, and also scored a further 21 signs. The major diagnostic signs used by Øster (1953), Levinson *et al.* (1955), Gustavson (1964), and Hall (1964) for both newborn and adults are summarized in Table 5-4. The problem of diagnosis at birth is not always easy to solve, and Zappella and Cowie (1962) found that only 74% of subjects were diagnosed in the first six months of life. They also observed a difference according to whether the patient was born at home or in hospital. Sixty-five percent of the hospital patients were diagnosed at birth, while a diagnosis at birth was only made in 12% of the subjects born at home. Figure 5-4 shows typical features of some Down's syndrome patients at various ages. In the final instance, therefore, the satisfactory diagnosis of this condition will, to a large extent, depend on the experience of the



FIG. 5-4. Children with Down's syndrome at various ages. (a) Newborn ♂; (b) ♂ at 12 months; (c) and (d) ♀ at 16 years. (Reproduced by permission of Professor P. E. Polani and Dr. A. I. Taylor.)

observer; however, the value of both quantitative and qualitative traits can be assessed for their discriminative efficiency and the comparative

TABLE 5–4

Frequency of Physical Signs in Down's Syndrome Expressed as Percentage Number of Cases [a]

Signs	Øster 1953 (children and adults)	Levingson *et al.*, 1955 (children and adults)	Gustavson, 1964 (children and adults)	Hall, 1964 (newborn)
Mouth				
Habitually open	67	62	59	–
Fissured lips	–	56	–	–
Small teeth [b]	71	56	65	–
Irregular alignment	71	68	65	–
Large tongue	57	30	–	–
Protruding tongue	49	32	38	68
Furrowed tongue [b]	59	44	44	–
High arched palate [b]	67	74	70	–
Narrow palate	–	–	76	–
Eyes				
Oblique palpebral fissures [b,c]	75	88	86	80
Epicanthic folds [b]	28	50	55	–
Speckled iris	70	30	70	42
Strabismus	23	14	–	–
Nystagmus	12	14	–	–
Blepharitis	–	–	46	–
Ears				
Prominent	47	50	–	–
Malformed	49	48	–	–
Small or absent lobes	82	80	–	57
Folded helix	–	–	28	53
Dysplastic [c]	–	–	–	62

Neck				
Broad and short	39	50	–	–
Abundant skin [c]	–	–	–	81
Abdomen				
Diastasis recti	–	76	–	–
Umbilical hernia	–	4	–	–
Genitalia				
Small penis	98	50	–	–
Cryptorchidism	27	20	–	–
Small scrotum	–	42	–	–
Head				
Flat occiput [b]	74	82	–	–
Round shape	–	–	–	77
Flat facial profile [c]	–	–	–	89
Flat nasal bridge	59	62	62	79
Open fontanelle (>6 months)	–	16	–	–
Cephalic index (83 or >)	–	–	81	–
Chest				
Funnel	5	12	–	–
Pigeon breasted	5	14	–	–
Flat nipples	–	56	–	–
Dorsolumbar kyphosis	–	14	–	–

TABLE 5-4 (cont'd)

Signs	Øster 1953 (children and adults)	Levingson *et al.*, 1955 (children and adults)	Gustavson, 1964 (children and adults)	Hall, 1964 (newborn)
Hands				
Short and broad [b]	69	74	75	–
Short fingers	–	70	–	–
Short fifth finger	57	66	74	–
Curved fifth finger [b]	48	68	52	32
One flexion crease fifth finger	31	10	–	14
Four-finger crease [b,c]	43	48	60	54
Dysplastic middle phalanx fifth finger [c]	–	–	64	58
Feet				
Excessive space between first and second toes	47	44	87	46
Plantar furrow	–	28	–	–
Joints and Muscles				
Hyperextensibility or hyperflexibility [b,c]	47	–	85	77
Hyperabduction of hip	–	–	–	84
Muscular hypotonia [c]	21	–	71.7	77
Weak patella reflexes	–	–	–	84
Dysplastic pelvis [c]	–	–	–	67
Lack of moro reflex [c]	–	–	–	82

[a] After Penrose and Smith (1966). [b] Ten most characteristic signs selected by Øster (1953).

[c] Ten best diagnostic signs in the newborn (Hall, 1964).

values of some metrical and qualitative traits are set out in Tables 5-5 and 5-6 (Penrose and Smith, 1966). From these tables it quickly becomes clear that certain characteristics have a high discriminatory function, for instance, head length, intelligence, maximal atd angle, interpupillary distance, and the presence of a four-finger crease. However, as Penrose and Smith (1966) pointed out, some traits when present give very high probability in favor of a diagnosis of Down's syndrome, but they nevertheless have a low discriminatory index because of their rarity even in Down's syndrome.

2. DERMATOGLYPHICS

The dermatoglyphic pattern on the soles of the feet and the palms of the hands are characteristic in Down's syndrome (Cummins, 1936; N. F. Walker, 1957; Holt, 1964; Penrose, 1961, 1963; Beckman *et al.*, 1962b). Penrose and Smith (1966) have summarized the main dermatoglyphic findings (Fig. 5-5). One feature of the hands is the strong tendency for every finger to possess a loop rather than a whorl or arch. The distribution of radial loops on digits IV and V is unusual as compared with normal people, and the total finger ridge count is less variable. The palmar triradius tends to a central position, giving a maximal atd angle of around 80° as compared with 45° for normal subjects. Hypothenar pat-

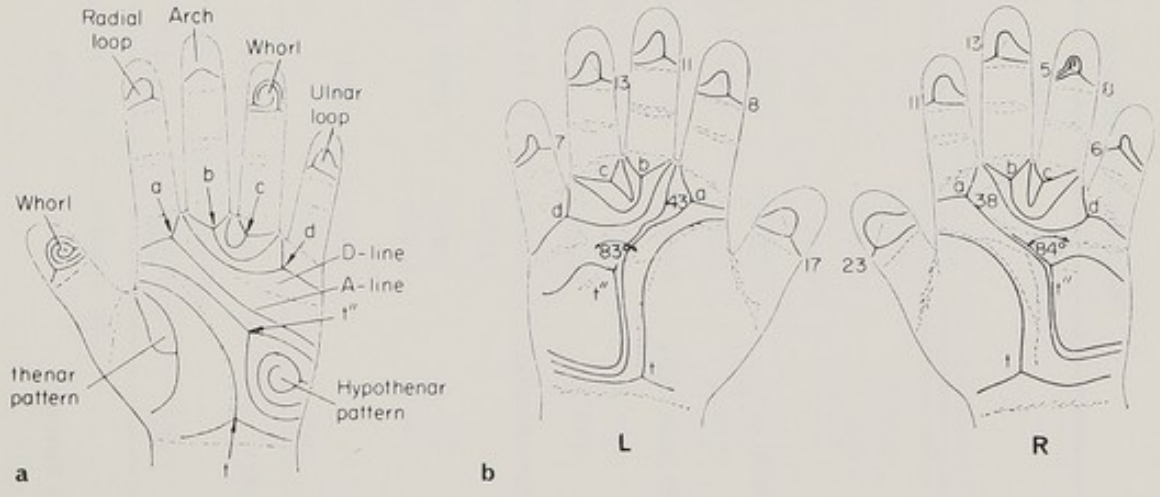


FIG. 5-5. (a) Nomenclature of dermatoglyphics of palms and fingertips; a,b,c,d represent digital triradii; t, the normal position of the palmar triradius; t'', the position of the distal triradius. (b) Tracing of hands of an adult male mongol showing finger pattern ridge count, maximal atd angles, and a-b ridge counts. Note high frequency of loops; central position of the palmar triradius giving a maximal atd angle of 83° (left) and 84° (right); absence of thenar pattern. (From Penrose and Smith, 1966.)

TABLE 5–5

Discriminative Efficiency of Certain Metrical Traits in Down's Syndrome [a]

Characteristic	Unit	Age	Sex	Mongols $\bar{M}$	Controls $\bar{N}$	Difference D	Mean SD $\bar{S}$	Discrimination index $(D/\bar{S})^2$
Birth weight	Pound	0	♂or♀	6.44	7.13	0.69	1.18	0.34
				6.39	7.24	0.85	1.14	0.56
Gestation	Days	0	♂or♀	269.8	281.6	11.8	17.7	0.44
Acetabular angle	Degrees	0–2/12	♂or♀	16	28	12	4.6	6.7
		3/12–11/12		11	22	11	4.2	6.7
Max. atd angle (sum right + left)	Degrees	0–47 year	♂	163.0	92.5	−70.5	21.6	10.6
			♀	162.0	97.5	−64.5	26.6	5.8
Intelligence	Binet IQ	3–9 year	♂or♀	48.4	100.0	51.6	15.5	11.1
Polymorph segmentation	Nuclear lobes	6–12 year	♂or♀	2.34	2.84	0.5	0.35	2.04
Head length	mm	Adult	♂	177	193	16	6.7	5.7
			♀	168	183	15	5.7	6.8
Head breadth	mm	Adult	♂	149	156	7	5.9	1.4
			♀	142	149	7	4.8	2.6
Standing height	mm	Adult	♂	1540	1696	156	67.0	5.3
			♀	1436	1572	136	59.0	5.3
Arm length	mm	Adult	♂	630	778	148	37	16.0
			♀	576	706	170	37	12.2
Interpupillary distance	mm	Adult	♂	54.6	64.3	9.7	3.3	8.4
			♀	55.4	60.6	5.2	3.0	2.9

[a] From Penrose and Smith (1966), who give full references.

TABLE 5–6

Discriminative Efficiency of Some Qualitative Traits in Down's Syndrome [a]

Characteristics	Sex	Frequency in mongols (m)	Frequency in controls (n)	Probability score in favor of mongolism		Index of efficiency (1)
				Presence (+) log exp (m/n)	Absence (−) log exp $[(1-n/(1-m)]$	$(m-n)$ log exp $\left[\frac{m(1-n)}{n(1-m)}\right]$
Ten ulnar loops on fingers	♂or ♀	0.320	0.042	+2.0	−0.3	0.67
Radial loop on digit IV						
Left hand	♂or ♀	0.524	0.070	+2.0	−0.7	1.23
Right hand	♂or ♀	0.454	0.060	+2.0	−0.5	0.99
Distal loop in third interdigital area						
Left hand	♂or ♀	0.540	0.313	+0.5	−0.4	0.22
Right hand	♂or ♀	0.854	0.555	+0.4	−1.1	0.45
Tibial arch on sole						
Left foot	♂or ♀	0.466	0.003	+5.0	−0.6	2.64
Right foot	♂or ♀	0.474	0.003	+5.1	−0.6	2.69
Four-finger crease						
Left hand	♂or ♀	0.656	0.013	+3.9	−1.1	3.22
Right hand	♂or ♀	0.710	0.008	+4.5	−1.2	4.10

[a] From Penrose and Smith (1966), who give full references.

TABLE 5–7

Mean Expectation of Life in Down's Syndrome [a]

Place	Year	Mean survival age in years
London, England	1932	9
London, England	1949	12
Victoria, Australia	1954	10
Victoria, Australia	1963	18

[a] From Penrose and Smith (1966)

terns are common, thenar patterns rare, and a digital loop is nearly always present between the b and c triradii. On the sole of the foot, patterns in the hallucal area are infrequent and an open field is typical.

3. Expectation of Life

Down's syndrome patients tend to have a shorter expectation of life than normal subjects, largely because of a susceptibility to chest infections or bronchial pneumonia. Penrose (1961) suggested that this was likely to result from an abnormal structure of the cells, mucous membranes and other tissues rather than from defective antibody formation. In 1932 the average expectation of life was 9 years; in 1947 it had risen to 12 years, and this rise appears to be continuing, largely because of the effectiveness of modern antibiotics.

Nevertheless a considerable proportion of DS patients die in the first year of life. Collmann and Stoller (1963b) have studied all affected children in Victoria, Australia, and found the mean age of all living Down's syndrome patients to be 18.3 years. At birth they found an expectation of life of 16.2 years. At 1 year it was 22.7 years, and at 5-9 years it was a maximum of 26.7 years, decreasing to 2.5 years for the 50-54 age group; 25, 50, and 75% of all Down's syndrome patients were under the ages of 7, 16, and 27 years, respectively (Tables 5-7 and 5-8).

4. Skeletal and Other Malformations

Several specific skeletal abnormalities have been found in Down's syndrome, and skeletal maturation has been found to be delayed. Poz-

TABLE 5–8

Mortality Rates and Life Table for Live-born Down's Syndrome 1948–1951 [a]

Age period	No. at risk at start	No. dying during period	Mortality rate (%/year)	Life table (% alive at start each period)
Months				
0	729	174	47.8	100.0
6	555	53	19.2	76.1
Years				
1	502	80	15.9	68.9
2	422	28	6.6	57.9
3	394	19	4.8	54.0

[a] From Collmann and Stoller (1963).

sonyi *et al.* (1964) have studied skeletal maturation in 100 Down's syndrome children and found that it was retarded up to 8 years of age and accelerated between 8 and 15 years of age, after which no further maturation was recorded. Another sample of 38 males and 26 female Down's syndrome patients had a retarded bone age of about 3 years at 7–9 years chronological age, which was reduced to 1 year's retardation at a chronological age of 12–14 years (Rarick *et al.*, 1964). These authors also reported the effect of puberty and noted that early sexually maturing children had bone age curves much in advance of the remainder. Other differences from normal are found in variations in the acetabular and iliac angles as measured radiographically and compared with normal controls (Fig. 5-6). In the normals the iliac angle varies from 52–58°, while the acetabular angle varies from 25–28°. In Down's syndrome the figures are around 44° and 19°, respectively. Other common skeletal abnormalities of the hands, feet, and skull occur (Penrose and Smith, 1966).

5. Cardiovascular and Other Malformations

There are many other examples of abnormal or retarded development among Down's syndrome children, and many organs and structures show varying degrees of abnormality (Benda, 1960). Cardiac malformations are the most serious; Rowe and Uchida (1961) studied 184 children with Down's syndrome and found that 40% had cardiac and

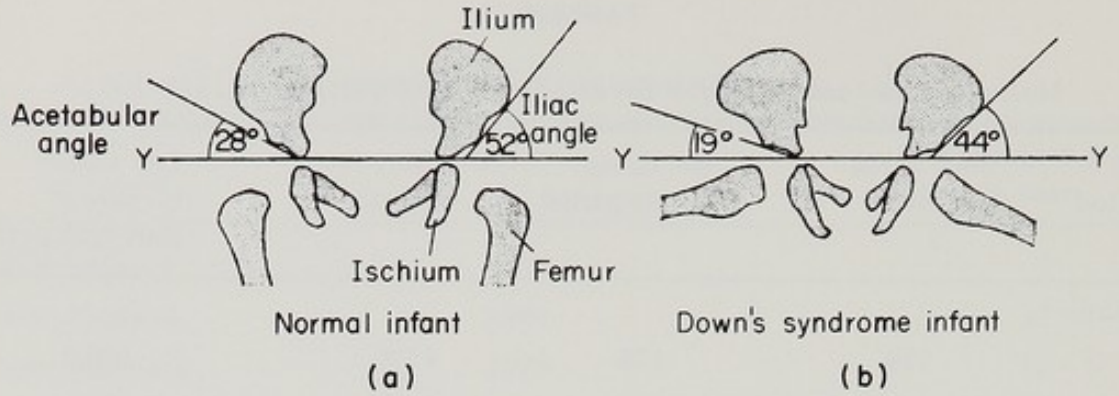


FIG. 5-6. Drawings from X rays showing the measurement of iliac and acetabular angles in (a) normal and (b) Down's syndrome infants. In (b) note the flattening of the lower edges of the ilium and lateral flair of the iliac wings. (From Penrose and Smith, 1966.)

cardiovascular malformations, the most frequent being a common atrioventricular canal and ventricular-septal defects. Less commonly patent ductus arteriosus and atrial-septal defects were observed. Frequently, also, gastrointestinal anomalies were found, notably an annular pancreas, duodenal atresia, and duodenal stenosis.

E. *Reproduction in Affected Females*

There are 13 reports of affected Down's syndrome females with 15 children, including one pair of monozygotic twins. Four of the children were also affected, eight were normal, two were retarded but did not have Down's syndrome, and in 20 and 28 week fetuses the diagnosis was uncertain (Table 5-9). One of the problems in assessing these data is that the same mother-child pair has often been reported several times without adequate reference to previous reports. Reference to Table 5-9 shows that all the affected mothers and their affected children had 47,XX or XY,G+ chromosome complements. The ratio of normal to Down's syndrome children (10:4) shows an excess of normal children, although this is still too small a series for these results to be significant. Examination of Fig. 7-6, Volume I, which illustrates the mechanism of secondary nondisjunction, shows that equal numbers of normal and disomic ova might be expected from a trisomic female and any divergence from this ratio is best accounted for by abnormal chromosome segregation so that the disomic chromosome complement is more frequently included in the polar body (see also Chapter 2, Section IV).

TABLE 5–9

Children of 47,XX,G+ Females

Case No.	Mother's age at birth of child	Sex of child	Down's syndrome in child	Chromosome studies		Reference
				Mother	Child	
1	25	♀	Normal	Not done	Not done	Sawyer, 1949
2	30	♂	Affected	Not done	Not done	Lelong *et al.*, 1949
3	30	♂	Retarded, not affected with DS	47,XX,G+	46,XY	Forssman and Thysell, 1957; Forssman *et al.*, 1961
4	29	♀	Retarded ? DS	Not done	Not done	Schlaug, 1957
5	19	♀	Affected	47,XX,G+	47,XX,G+	Stiles, 1959; Stiles and Goodman, 1961; Rehn and Thomas, 1957; Johnston and Jaslow, 1963
6	21	♀	Affected	47,XX,G+	47,XX,G+	Hanhart *et al.*, 1961
7	23	♂	Affected	47,XX,G+	Not done	Hanhart, 1960b
8	–	♂	Normal	47,XX,G+	46,XY	Levan and Hsu, 1960
9	14	♂ twins stillborn	Normal		46,XY	Thuline and Priest, 1961
		♂	Normal	47,XX,G+	46,XY	Priest *et al.*, 1963
10	21	♂	Normal	Not done	Not done	M.W. Thompson, 1961
11	20	♀ (28 w fetus)	Query	47,XX,G+	Not done	M.W. Thompson, 1962
12	22	♂ (terminated 20 w)	Query	47,XX,G+	Not done	M.W. Thompson, 1962
13	22	♂	Normal	Not done	Not done	Mullins *et al.*, 1960
14	18	♀	Normal	47,XX,G+	46,XX	Foxton *et al.*, 1965
15	27	♀	Normal	47,XX,G+	46,XX	Tagher and Reisman, 1966
Mean	22.93	9 ♂♂, 7 ♀♀	8 Normal, 5 affected, 2 query			

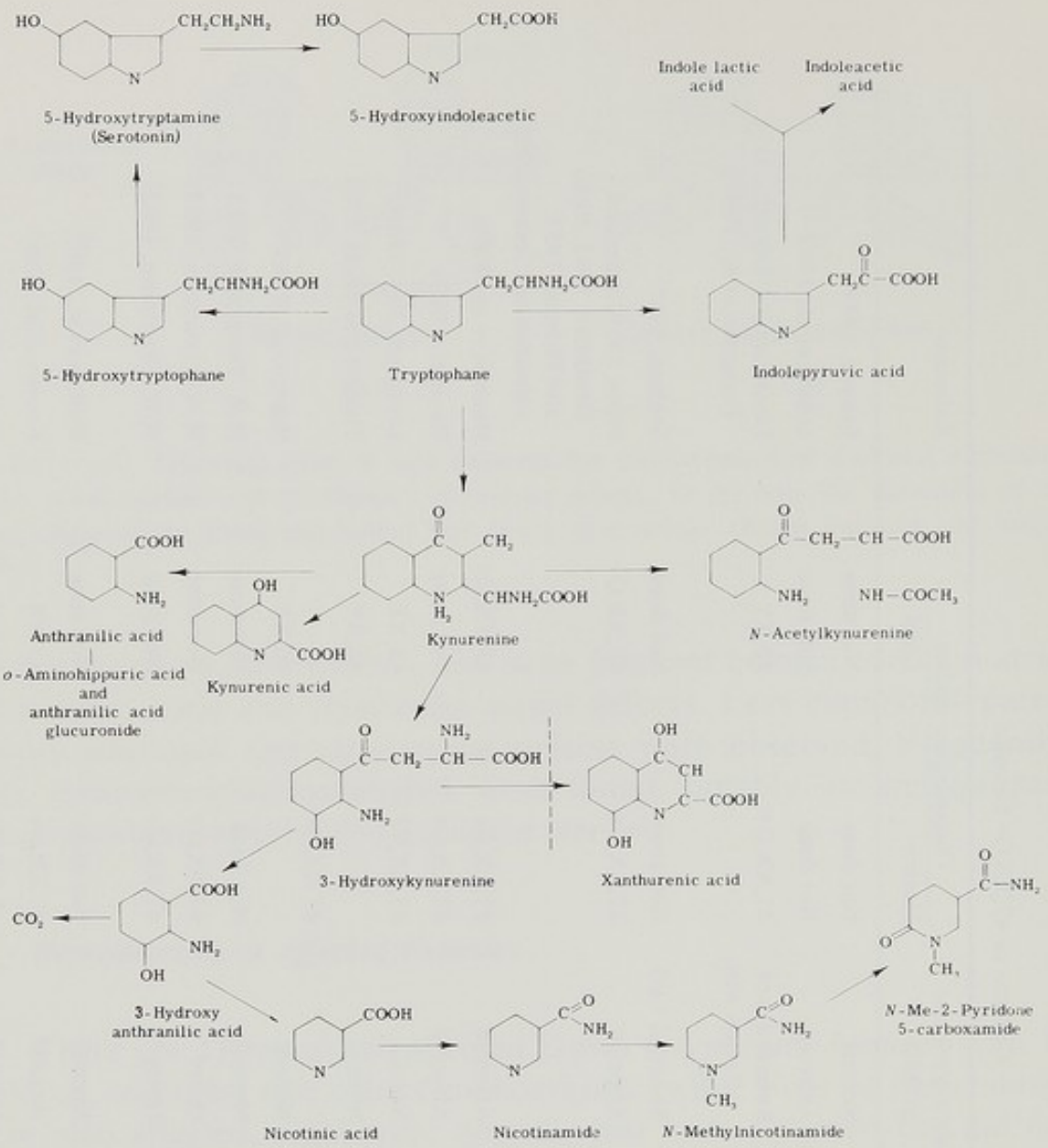


FIG. 5-7. Major pathways of tryptophan metabolism in man. A possible lesion in Down's syndrome is indicated by a broken line (see text). (From O'Brien and Groshek, 1962.)

F. *Biochemical Studies in Down's Syndrome*

The observation that Down's syndrome was caused by autosomal trisomy stimulated several attempts to locate particular gene loci on chromosome 21. These studies have generally been unsuccessful and may perhaps be divided into two categories.

1. METABOLIC LESIONS

Jérôme *et al.* (1960) reported a lowering of the urinary excretion of 5-hydroxyindoleacetic acid, indoleacetic acid, and xanthurenic acid, all

of which are end products of the various pathways of tryptophan metabolism (Fig. 5-7). O'Brien and Groshek (1962) have studied the 7-hr urinary excretion coefficients of 5-hydroxy- 3-indoleacetic acid, kynurenic acid, xanthurenic acid, kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, *N*-methylnicotinamide, 4-pyridoxic acid, and *N*-acetylkynurenine after an oral load of 100 mg/kg of L-tryptophan. The results confirm that in Down's syndrome children there is a reduction in the urinary excretion of xanthurenic acid and *N*-acetylkynurenine. However, calculation of the excretion coefficients indicates that only the reduction in xanthurenic acid excretion is significant (Fig. 5-8). This suggests a specific lesion of hydroxykynurenine transaminase in affected children, which results in a diminished conversion of 3-hydroxykynurenine to xanthurenic acid.

Rosner *et al.* (1965) have shown a significant reduction in the blood serotonin levels in 10 primary trisomic Down's syndrome patients compared with 16 normal controls. Levels in seven patients with translocation Down's syndrome were normal. The level of excretion of the end

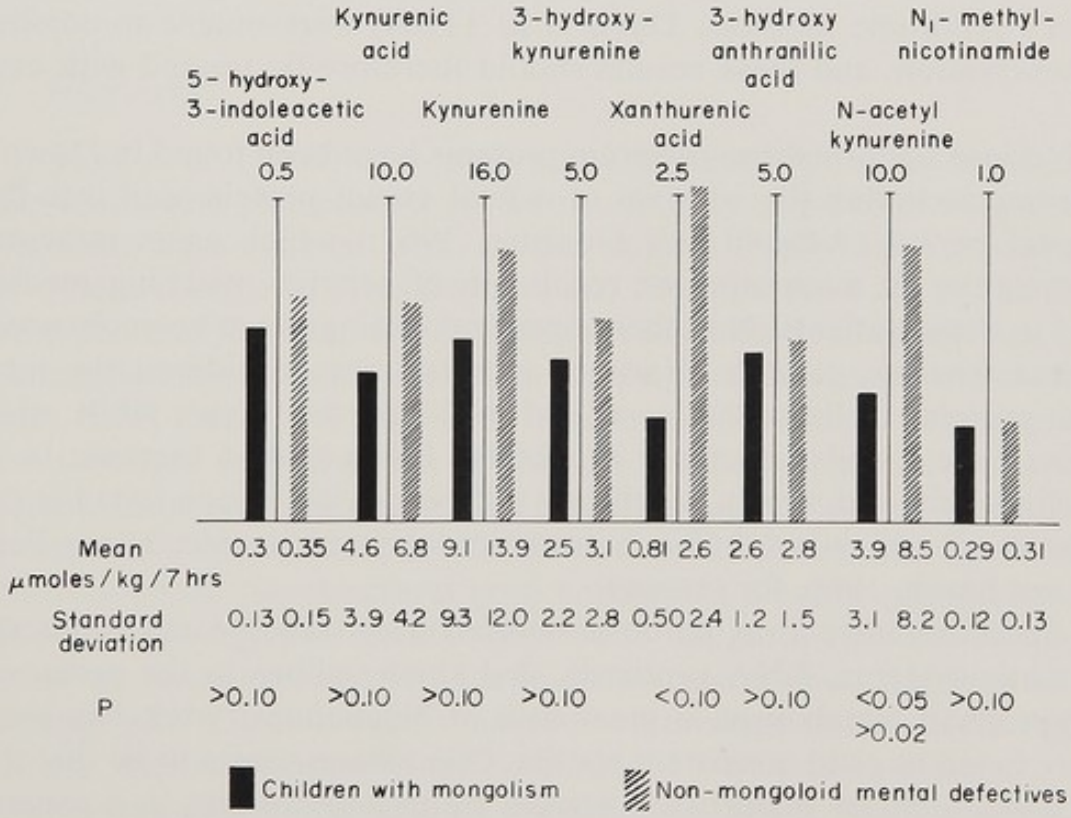


FIG. 5-8. Seven-hour urinary excretion of the various end products of tryptophan metabolism in non-Down's syndrome mental defectives and children affected with Down's syndrome. Significant differences are noted for xanthurenic acid and *N*-acetylkynurenine. (From O'Brien and Groshek, 1962.)

product 5-hydroxyindoleacetic acid was also lowered in the urine after oral tryptophan loads. The actual metabolic lesion is not clear. Recently, Berman *et al.* (1967) have questioned Rosner's findings. They reported high blood levels of serotonin in mentally retarded controls as compared with normal controls and lower levels in patients with Down's syndrome. They found no difference between patients with primary or translocation trisomy, nor was there any difference between the levels in the normal controls and the patients with secondary trisomy although this was perhaps because of one subject with a t(DqGq) with particularly high blood serotonin levels. Bazelon *et al.* (1967) have recently shown that if 5-hydroxytryptophan, the metabolic precursor of serotonin (5-hydroxytryptamine), is fed to infants with Down's syndrome, they showed a reduction of hypotonia.

Steroid excretion has been studied in mothers of Down's syndrome patients and controls. Rundle *et al.* (1961) showed an apparent difference in the urinary steroid excretion pattern of women who, while under the age of 27, had borne a child with Down's syndrome and a control group of normal women. These authors also showed that there was an increase in the excretion of dihydroepiandrosterone in the urine of Down's syndrome mothers. Davis *et al.* (1964) were unable to confirm the observation, and these results should therefore be treated with caution.

Various abnormalities of serum proteins have been found in Down's syndrome including the survival of a fetal serum protein well into the neonatal period (Adinolfi and Gardner, 1967), which again indicates abnormalities in maturation or regulation of genetic switching mechanisms in these patients. No other consistent findings have been observed in these trisomic patients. Various authors have considered the total serum proteins to lie at the lower end of the normal range, while other authors have found a decrease in albumin levels and an increase in γ-globulin levels, and, finally, significant differences have been found in the levels of α-1 and α-2 globulins between mongols and controls (see Penrose and Smith, 1966, for review).

Apart therefore from the observations on erythrocyte and leukocyte enzymatic systems, RNA synthesis, and abnormalities in the pathways of tryptophan metabolism, a great deal of biochemical work has completely failed to yield consistent results. One reason seems to be that the widespread cellular disturbance caused by trisomy results in a general cellular metabolic imbalance rather than in special biochemical lesions.

Various studies on thyroid function have proved inconclusive and are summarized by Penrose and Smith (1966). An interesting and signifi-

cant observation is the finding of thyroid autoantibodies in a proportion of trisomic subjects tested (Mellon *et al.*, 1963; Burgio *et al.*, 1965). Similar findings have also been reported in other aneuploid conditions, and their interpretation is uncertain (Fialkow, 1964; see also Chapter 2). Fialkow *et al.* (1965) have also studied the level of circulating thyroid autoantibodies in the parents of patients with Down's syndrome. They found that 11% of the fathers and 28% of the mothers of Down's syndrome patients were seropositive compared with 9% of the fathers and only 14% of the mothers of controls. They also showed that thyroid autoantibodies were particularly found in young mothers and suggested that these antibodies might be of especial importance in the etiology of the less common chromosome abnormalities, for instance, mosaicism and translocations (Fialkow, 1966, 1967a,b). More recently, studies by Wren *et al.* (1967) showed that there appeared to be rather more clinical thyroid disease among mothers of children affected with Down's syndrome than among mothers of controls. They were, however, unable to show a difference in the incidence of thyroid or other autoantibodies between the two groups of mothers. These results therefore do not support the etiological concept of Fialkow.

2. Enzymes

King *et al.* (1962) have shown a significantly increased level of leukocyte alkaline phosphatase in the neutrophils of patients with Down's syndrome as compared with normal controls, and these observations have been confirmed (Trubowitz *et al.*, 1962; Alter *et al.*, 1962). In the EUE cell line De Carli *et al.* (1964) demonstrated raised alkaline phosphatase levels in clones with high numbers of G chromosomes. However, R. P. Cox (1965) has been unable to show raised levels in fibroblasts derived from the skin of Down's syndrome patients. It has been argued, from the raised levels of alkaline phosphatase in Down's syndrome and the reduced levels in chronic myeloid leukemia (see Chapter 18), that either the structural gene controlling alkaline phosphatase expression or a regulator gene is situated in the particular G chromosome involved. However, the findings in fibroblasts derived from the skin of patients with Down's syndrome and the findings in the EUE cell line suggest that the matter is not so simple. In all probability there is no single locus controlling alkaline phosphatase, and it seems doubtful if a simple dosage effect can account for these findings.

Other red cell enzymes which have been tested include galactose-1-phosphate urydyltransferase (Brandt *et al.*, 1963), galactokinase (Krone

et al., 1965), phosphohexokinase (Baikie *et al.*, 1965a), and erythrocyte glutamic oxalacetic transaminase (Naiman *et al.*, 1965). Baikie *et al.* (1965a) studied 12 other erythrocyte enzymes including hexokinase, phosphohexose isomerase, aldolase, triosephosphate isomerase, glyceraldehyde phosphate dehydrogenase, phosphoglycerate kinase, phosphoglycerate mutase, endolase, pyruvate kinase, lactic dehydrogenase, glucose-6-phosphate dehydrogenase, and glutathione reductase. Of these 12 enzymes, the only enzyme showing increased levels was phosphohexokinase.

Hsia *et al.* (1964) found raised levels of leukocyte galactose-phosphate urydyltransferase (gal-1-put) and glucose-6-phosphate dehydrogenase (G6PD) in Down's syndrome patients. They also showed that the G6PD and gal-1-put activity were positively correlated in both the affected and the control group; since it is well known that the G6PD locus is X-linked, while gal-1-put locus is autosomal, it seems unlikely that the raised enzyme levels found in patients with Down's syndrome necessarily indicate a simple dose response because of triplication of the locus. Benson (1967) has shown that there was an increase in the rate of mRNA synthesis in Down's syndrome and that this was even further increased in a 48,XXX,G+ female. This may reflect an increase in protein synthesis, perhaps because of a less efficient use of enzymes and hence the necessity to produce larger quantities. Twelve Down's syndrome patients showed a raised erythrocyte glutamic oxalacetic transaminase activity (EGOT). This enzyme is a sensitive indicator of red cell age (Naiman *et al.*, 1965), and the finding of raised EGOT levels as well as a significant macrocytosis reflected both as an increased Packed Cell Volume (PCV) and Mean Cell Volume (MCV) when expressed as per 10^6 red blood cells, but not when expressed as per gram of hemoglobin, suggested that the patients with Down's syndrome showed a younger mean red cell age than the controls. This possibility has been considered by Bartels and Kruse (1968) who confirmed the finding of raised levels of phosphohexokinase (PHK) and EGOT in Down's syndrome. They were, however, unable to find any evidence of a younger mean cell age and suggested that the raised level of PHK may be directly related to a gene locus on chromosome 21.

G. *Linkage Studies*

A number of conventional linkage studies have been undertaken to try to establish positively the position of a locus on the trisomic or trans-

location chromosomes. In broad terms these have taken two forms: first, an attempt to show abnormal blood group frequencies in a trisomic population; and, second, the use of "marker" chromosomes in an attempt at direct linkage studies in families in which the marker is transmitted.

1. Blood Group Frequencies

Shaw and Gershowitz (1962) tested 793 patients with Down's syndrome for blood and saliva groups, and their findings suggest that the MNS, P, Kell, Duffy, Kidd, and ABH secretor loci are not closely linked with the centromere of chromosome 21. The ABO frequencies on the other hand showed a deficiency of group O and an excess of groups A and B. They suggest the presence of the ABO locus on the Down's syndrome chromosome as an explanation for these findings. Bateman (1960) and S. Kaplan *et al.* (1964) have discussed the expected frequencies of the different alleles in the trisomic state. Proportionally, the two most striking differences between a trisomic and disomic population should be in the AB frequency which should increase from 2pq to $3pq(1 + r)$, while a significant decrease in the frequency of group O would also be expected in the trisomic group. Group A and B frequencies may not be significantly altered. In the AB group, if the disomic population has a frequency of about 4% then the trisomic group would be expected to have a frequency of about 10%. In group O the change is in the ratio $r^2:r^3 = 1:r$, decreasing by $100(1 - r)\%$. For instance, if $r = 0.675$ in the population then the decrease from disomic O to trisomic O would be 0.5. However, after typing 290 Down's syndrome children, S. Kaplan *et al.* (1964) found no evidence of increase in the AB or decrease in the O group and concluded that it was unlikely that the ABO locus was situated on chromosome 21. A similar finding had been reported by Chown and Lewis (1963) and by Lang-Brown *et al.* (1953).

Confirmation of the suggestion of Shaw and Gershowitz (1962) would be the finding of an AB child from an O father and an AB mother. Their series included one AB mother and child whose father was dead. The series studied by Lang-Brown *et al.* (1953) included one AB Down's syndrome patient, who had an AB mother and A father, and two other AB mothers. One of these had an A and the other a B child with Down's syndrome. Penrose (1957) pointed out that blood groups of Down's syndrome patients were more compatible with those of their mother than with those of their father, and Lawler (1962) interpreted this as a possibility of selection against ABO incompatible offspring. In

conclusion therefore, there is no real evidence for locating the ABO locus on chromosome 21.

A different approach to this problem has been made by R. W. Day *et al.* (1963c). These authors used a quantitative estimation of the D antigen in a group of Down's syndrome patients and controls using ^{131}I-incomplete anti-D and found no evidence of any abnormality, thus confirming that there is no evidence of any Rh abnormality in Down's syndrome. Chown *et al.* (1962) have studied 22 families with a single Down's syndrome child and found three to have a typical inheritance of *fy* and in one there was also an anomaly of the ABO group. These authors (see also Chown *et al.*, 1965) considered a chance concentration of *fy* to be the most likely explanation but questioned whether *fy* is a single entity and considered the possibility that there may be a genetic factor which affects the expression of Duffy or ABO loci and predisposes to the nondisjunction of chromosome No. 21. Chown *et al.* (1965) have now, however, retracted the opinion that there was any association between the blood group anomaly and Down's syndrome since the same anomaly has been found in the same proportions in several other groups who were ascertained differently.

2. The Use of Marker Chromosomes

Shaw and Gershowitz (1963) have summarized the available blood group data on nine mother-Down's syndrome pairs with a t(DqGq) and conclude that the MN and Rh groups can be excluded from chromosome 21, while the evidence for the P, Kell, Duffy, or Kidd groups is insufficient. There is one exception at the ABO locus where an A_1 mother produced an O child. If the ABO locus is on the marker this must represent a crossover.

Examination of a number of other reported families has revealed no suggestion of any linkage between any of the blood group loci or, where studied, the Hp transferrins, Gm or Inv groups, and the centromere of the interchange chromosome (Hutton and Smith, 1964; Penrose and Smith, 1966; Yokoyama, 1966).

H. *Chromosome Studies*

1. Nomenclature

Penrose's (1961) classification into a maternal-age-independent and a maternal-age-dependent class cuts right across cytological types, and although most translocation trisomics fall into the former group so also

do some primary trisomics. In the present section, therefore, the terminology used by Hamerton *et al.* (1965) will be followed and the different cytogenetic types classified as follows:

a. PATIENTS WITH DOWN'S SYNDROME.

i. Primary trisomics (47,XX or XY,21+).

ii. Secondary or translocation trisomics with 46 chromosomes and evidence of the presence of a presumptive translocation or isochromosome. These may be either (*a*) 46,XX or XY,D−,t(DqGq)+, (*b*) 46,XX or XY,G−,t(GqGq)+, or (*c*) 46,XX or XY,G−,Gqi+. It is frequently difficult to differentiate between (*b*) and (*c*) and there are, of course, two categories of (*b*)—46,XX or XY,21−,t(21q21q)+ or 46,XX or XY,22−, t(21q22q)+—which can only be distinguished by their pattern of inheritance (see below).

iii. Primary G tetrasomy (48,XX or XY,G + G +).

iv. Mixoploid subjects with some features of Down's syndrome and two or more cell lines of which one is usually *primary trisomic* and the other normal (46,XX or XY/47,XX or XY,G+, etc.). Rarely normal subjects will be found to have a minor G+ cell line.

b. PHENOTYPICALLY NORMAL SUBJECTS. These usually have 45 chromosomes and carry a presumptive translocation with an effectively balanced chromosome complement. They are balanced translocation heterozygotes. These subjects must have produced or be related to a secondary trisomic with an identical rearrangement in which case they may be either t(DqGq); t(GqGq); the latter may be either t(21q22q) or t(21q21q).

c. DOUBLE TRISOMICS. This is an individual trisomic for two different chromosomes, for instance 48,XXY,G+; 48,XX or XY,E+G+; or 48,XXX,G+. The terms *sporadic* and *inherited* will be used to refer either to a subject with Down's syndrome or to the rearranged chromosome. The term *familial* will, however, be used only to refer to families with more than one affected subject (kinship Down's syndrome) or when a sib of the index case is affected (sibship Down's syndrome).

This classification has the merit of being relatively simple and covers all the known chromosome complements in Down's syndrome which lead to effective 21-trisomy.

2. 47,XX OR XY,21+

The observations of Lejeune *et al.* (1959) (see Section I, A above) were rapidly confirmed (Jacobs *et al.*, 1959b; Ford *et al.*, 1959a; Böök

et al., 1959), and in each case an identical additional small acrocentric chromosome was observed (Fig. 5-9). It was concluded that this was homologous to No. 21 since it was satellited. Böök *et al.* (1959) concluded at this time

> that if the 47th chromosome was found to be causally related to the condition, although it could not be stated with certainty on morphological grounds alone, it was more likely to be homologous to an existing member of the set rather than to be an accessory supernumerary element.

In the intervening 12 years, nothing has occurred to alter this view and much to reinforce it. An editorial in the Lancet as early as 1960 stated that ". . . regular mongolism has now been shown beyond dispute to be caused by trisomy of chromosome No. 21."

The chromosomes of 34 separate series of Down's syndrome subjects have now been recorded, and the results are summarized in Table 5-10, which shows that out of a total of 2594 Down's syndrome subjects 2452 (94.53%) are primary trisomics or mixoploids, while the remaining 142 subjects (5.47%) have one or other class of secondary trisomy. It can therefore now be stated conclusively that Down's syndrome is *caused* by 21-trisomy which results in genetic or chromosomal imbalance and leads to the characteristic phenotype.

Several authors (Hall, 1962, 1963, 1964; V. A. Cowie and Kahn, 1965; Kahn and Cowie, 1965) have tried to show that Down's syndrome can occur either with normal chromosomes or as a result of some other chromosome abnormality. However, in view of the vast body of evidence to the contrary, this requires extensive documentation, both in regard to the clinical as well as the cytogenetic status of the patient. This has not been forthcoming (Hamerton and Polani, 1962; Hamerton, 1965a,b). Neither the child with normal chromosomes described by Hall (1962) nor the other five children described by the same author (1964) could be described as having Down's syndrome; in fact, Hall himself describes them as "pseudo-mongoloids," a term which has little nosological significance. Furthermore, he states that they only resemble patients with Down's syndrome and that only three of these children had even four of Øster's cardinal signs. These subjects therefore hardly provide grounds for a realistic attempt to establish that Down's syndrome can occur without the chromosome error, particularly since it is well known that children with similar phenotypes do occur and may either have normal or mixoploid chromosome complements.

3. Secondary Trisomy

a. Cytology. The first indication that primary trisomy might not be the only chromosome mechanism involved was provided by a

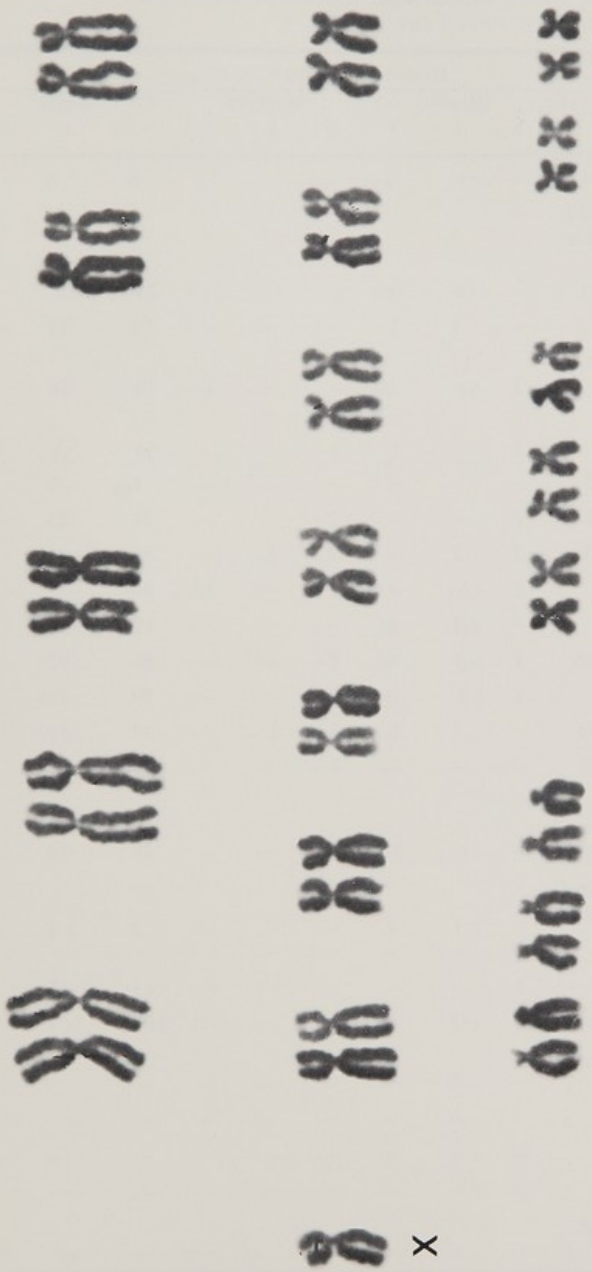


FIG. 5-9. Karyotype of a 47,XY,G+ male with Down's syndrome.

TABLE 5-10

Series	Reference	Maternal age <30 [a]						G+	Total
		t(DqGq)			t(GqGq)				
		S	I	?	S	I	?		
1	Aula and Hjelt, 1964	–	–	–	–	–	–	8	8
2	Benirschke *et al.*, 1963 personal communication (quoted by Polani *et al.*, 1965)	–	–	–	–	–	–	26	26
3	Breg *et al.*, 1962a	–	1	1	–	–	–	10	12
4	Chitham and MacIver, 1965	2	–	1	–	–	1	32	36
5	De Grouchy and Roubin, 1965	1	–	1	3	–	–	32	37
6	Dekaban *et al.*, 1963	–	–	–	–	–	–	5	5
7	Edwards *et al.*, 1963	2	–	–	2	–	–	21	25
8	Giannelli *et al.*, 1965	2	2	–	2	1	–	89	96
9	Gustavson, 1964	1	–	–	1	–	1	30	33
10	Hall, 1964	–	1	–	–	–	–	19	20
11	Hamerton *et al.*, 1965	1	1	–	4	–	–	86	92
12	Hayashi, 1963	1	1	1	–	–	–	29	32
13	Haylock *et al.*, 1963b	–	1	1	3	1	–	22	28
14	Lehmann *et al.*, 1962	–	–	–	1	–	–	44	45
15	Makino *et al.*, 1960 Makino, 1963 (quoted by Polani *et al.*, 1965)	–	–	1	–	–	–	29	30
16	Mellman, 1962 (quoted by Polani *et al.*, 1965)	–	1	–	–	–	–	3	4
17	Pfeiffer, 1966a	–	–	–	–	–	–	–	–
18	Scherz, 1962	1	–	–	–	–	–	13	14
19	Sergovich *et al.*, 1964	3	2	–	4	–	–	100	109
20	Loftus and Mellman, 1965, 1966	–	–	–	–	–	–	–	–
21	A. Bishop, 1965	–	–	–	–	–	–	–	–
22	Ying, 1966	–	–	–	–	–	–	–	–
23	Neu *et al.*, 1966	–	–	–	–	–	–	–	–
24	Buza-Krompotic *et al.*, 1966	–	–	–	–	–	–	–	–

Distribution of Different Chromosome Types in 34 Series of Patients Affected with Down's Syndrome

Maternal age >30								All maternal ages			
t(DqGq)			t(GqGq)			G+	Total	t(DqGq)	t(GqGq)	G+	Total
S	I	?	S	I	?						
–	1	–	–	–	–	14	15				
–	–	–	1	–	–	40	41				
–	–	–	–	–	–	–	–				
–	–	–	–	–	–	68	68				
–	–	–	–	–	–	18	18				
–	–	–	–	–	–	7	7				
–	–	–	–	–	–	–	–				
–	–	–	–	–	–	–	–				
–	–	–	2	–	–	63	65				
–	–	–	–	–	–	38	38				
–	–	–	–	–	–	50	50				
–	–	–	–	–	–	40	40				
–	–	–	–	–	–	–	–				
–	–	–	–	–	–	–	–				
–	–	–	–	–	–	13	13				
–	1	–	–	–	–	7	8				
–	–	–	–	–	–	–	–	11	10	291	312
–	–	–	–	–	–	–	–				
–	–	–	1	–	1	129	131				
–	–	–	–	–	–	–	–	1	3	48	52
–	–	–	–	–	–	–	–	6	–	33	39
–	–	–	–	–	–	–	–	–	3	25	28
–	–	–	–	–	–	–	–	1	1	31	33
–	–	–	–	–	–	–	–	1	–	11	12

TABLE 5-10 (cont'd)

Series	Reference	Maternal age <30 [a]						G+	Total
		t(DqGq)			t(GqGq)				
		S	I	?	S	I	?		
25	Hollowell *et al.*, 1966	–	–	–	–	–	–	–	–
26	Kleisner *et al.*, 1966	–	–	–	–	–	–	–	–
27	Zellweger *et al.*, 1966	–	–	–	–	–	–	–	–
28	Edgren *et al.*, 1966	–	–	–	–	–	–	18	18
29	Kwiterovich *et al.*, 1966	1	–	–	–	–	–	4	5
30	Huang *et al.*, 1967	1	–	–	1	–	–	26	28
31	Mikkelsen, 1967b	3	2	–	4	–	–	84	93
32	B.W. Richards *et al.*, 1965a	–	–	–	–	–	–	–	–
33	Tonomura *et al.*, 1966	–	1	–	2	–	1	64	68
34	Kahn and Abe, 1969	–	–	–	–	–	–	–	–
Total		19	13	6	27	2	3	794	864

[a] Here S stands for sporadic;
I, inherited; and
?, inheritance not certain.

study of the chromosomes of three affected children born at maternal ages of less than 30 years (Polani *et al.*, 1960). One of these children was found to have 46 chromosomes and a t(DqGq) (Fig. 5-10). The parents of this child were subsequently found to have normal chromosomes (Carter *et al.*, 1960) so that in the nomenclature in use here the child may be said to have a sporadic t(DqGq). At about the same time Fraccaro *et al.* (1960e) reported another child with Down's syndrome with 46 chromosomes (Fig. 5-11) with a presumptive t(GqGq) or Gqi. The father in this case had a normal phenotype and was a mixoploid with one cell line having normal chromosomes and the other a similar translocation chromosome (Fraccaro and Lindsten, 1962). These two papers therefore established the existence of secondary trisomy.

This was rapidly confirmed by the simultaneous publication of two families in which t(DqGq) chromosomes were segregating in at least two generations through phenotypically normal balanced heterozygotes and resulted in a familial concentration of patients with Down's syndrome (Carter *et al.*, 1960; Penrose *et al.*, 1960). These observations also established a mechanism by which Down's syndrome could be inherited through balanced phenotypically normal heterozygotes. The conclusive observation, which demonstrated that the additional C-like chromosome

Maternal age >30								All maternal ages			
t(DqGq)			t(GqGq)			G+	Total	t(DqGq)	t(GqGq)	G+	Total
S	I	?	S	I	?						
–	–	–	–	–	–	–	–	1	–	12	13
–	–	–	–	–	–	–	–	6	5	86	97
–	–	–	–	–	–	–	–	2	4	165	171
–	–	–	–	–	–	52	52	–	–	–	–
–	–	–	–	–	–	11	11	–	–	–	–
–	1	–	–	–	–	47	48	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	2	3	219	224
2	–	–	–	–	–	57	59	–	–	–	–
–	–	–	–	–	–	–	–	1	2	83	86
2	3	–	4	–	1	654	664	32	31	1004	1067

found in both the balanced heterozygotes and the secondary trisomics was in fact the product of a t(DqGq) fusion, was provided by the study of meiosis in a balanced heterozygote (Hamerton *et al.*, 1961b) and the finding of a trivalent in the majority of cells (see Fig. 5-11 and Table 5-4, Volume I). This conclusively showed that the t(DqGq) chromosome was homologous with both D and G chromosome material (see Volume I, Chapter 8). The mode of inheritance of Down's syndrome by means of chromosome interchange is now well established and needs no further elaboration (Penrose, 1961; Hamerton, 1962, 1966, 1968a, 1969; Penrose and Smith, 1966; Polani *et al.*, 1965), and the various different chromosome complements which most frequently cause Down's syndrome are shown in Fig. 5-12. The origin, behavior, and segregation of these and similar structural changes have already been discussed (Chapter 8), so that here we shall be concerned solely with their clinical and genetic significance.

b. FREQUENCY OF SECONDARY TRISOMICS. i. *Among patients with Down's syndrome* Data on chromosome studies in Down's syndrome are now available from 34 separate series comprising a total of 2594 affected subjects (Table 5-10); 94.53% of these patients were

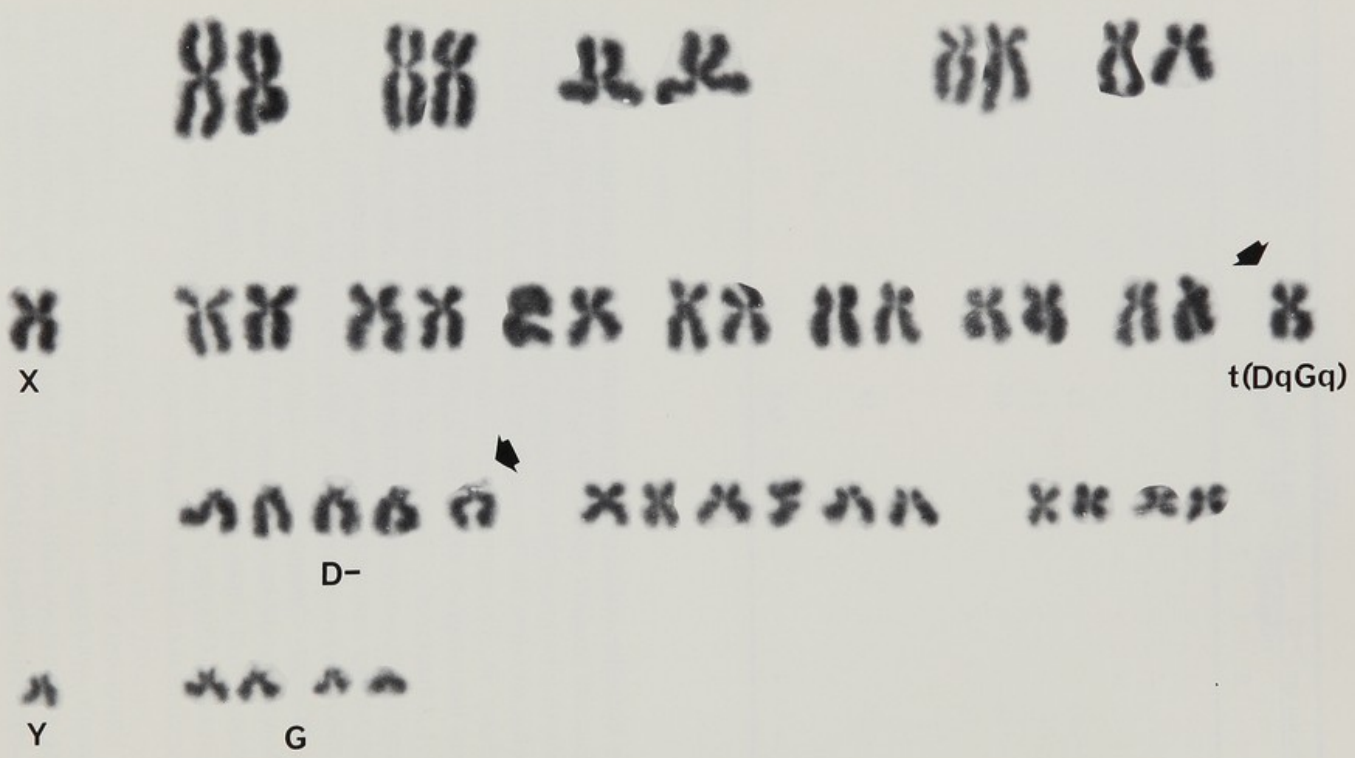


FIG. 5-10. Karyotype of a 46,XY,D−,t(DqGq)+ male with Down's syndrome.

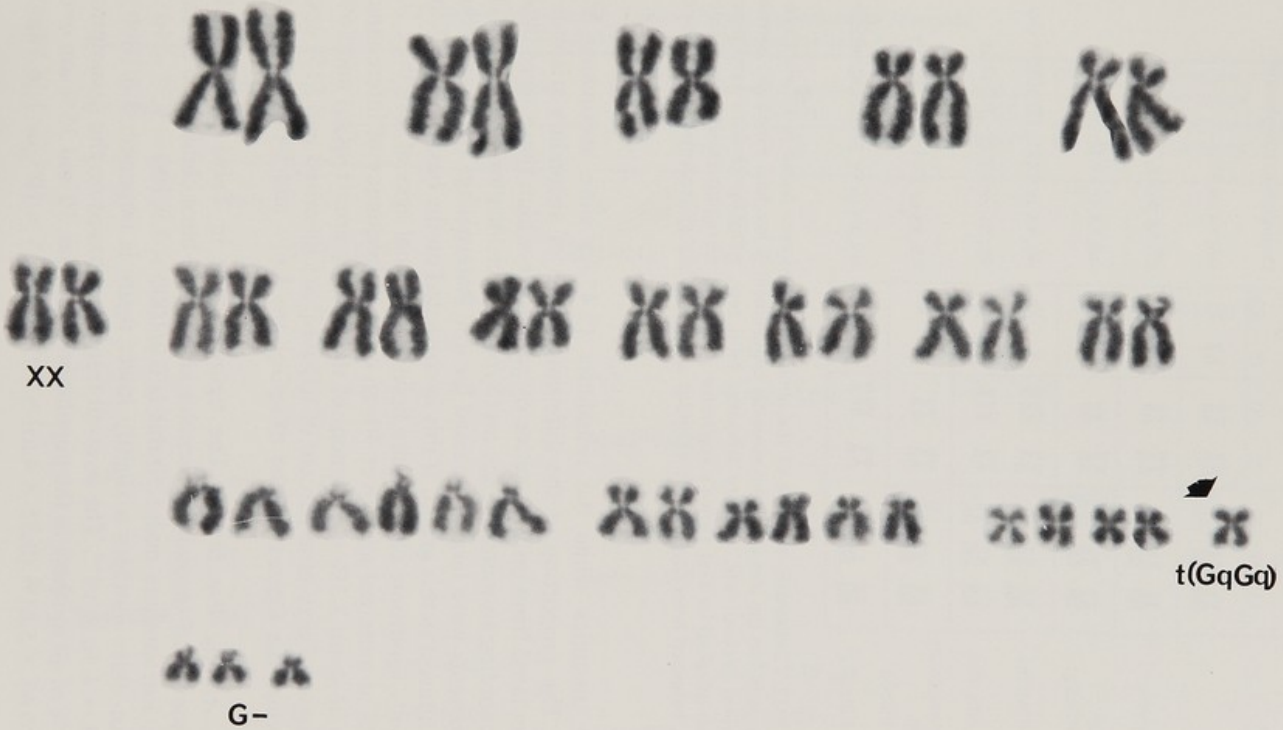


FIG. 5-11. Karyotype of a 46,XX,G–,t(GqGq)+ or Gqi female with Down's syndrome.

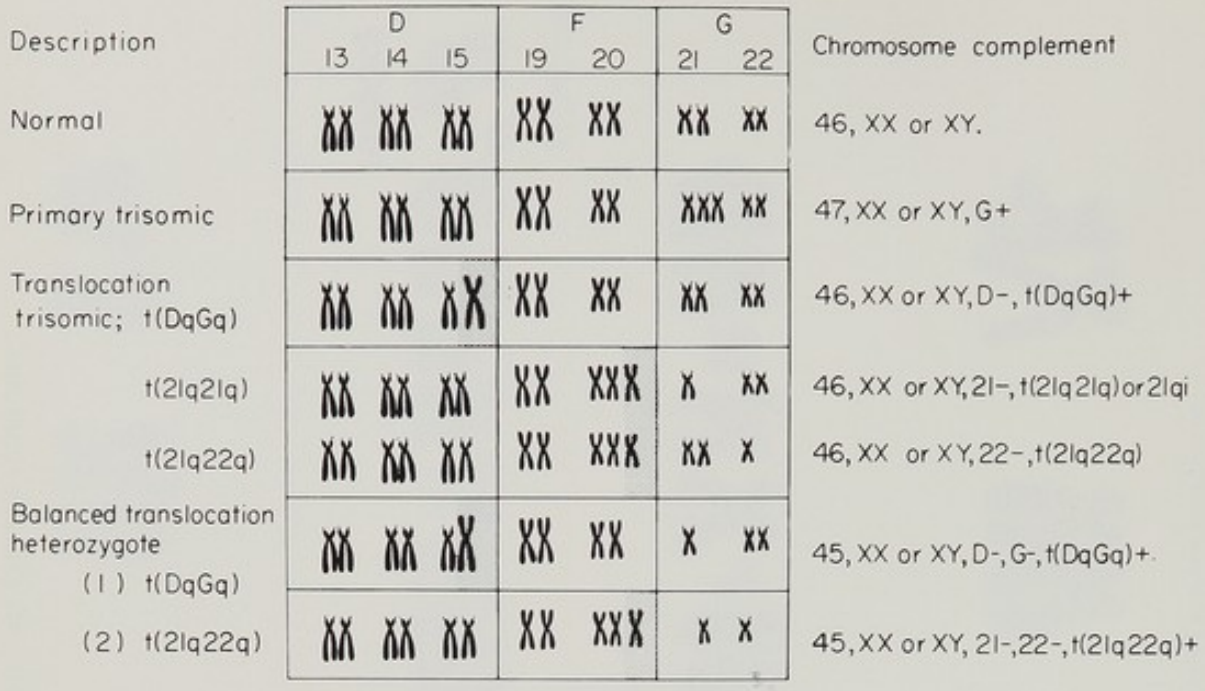


FIG. 5-12. Schematic diagram of the abnormal karyotypes found in Down's syndrome. In each line the abnormal chromosome complement is hatched. First row, normal chromosomes; second row, primary trisomic; third row, t(DqGq) Down's syndrome; fourth row, t(GqGq) or Gqi Down's syndrome; fifth row, t(21q22q) Down's syndrome; sixth row, balanced heterozygotes (1) t(DqGq) and (2) t(21q22q). Redrawn from Hamerton (1962).

primary trisomics while the remainder (5.47%) were secondary trisomics. The proportion of the different classes of secondary trisomics was calculated from only 23 series of patients in which these were classified according to maternal age and type of translocation (Table 5-11). These patients were largely selected for low maternal age because of the greater interest in this group. If this is corrected on the basis that 35% of all Down's syndrome children are born at maternal ages of less than 30, and 65% at maternal ages over 30, an over-all frequency of interchange trisomy of about 3.5% is obtained; of these, 44% are t(DqGq) and 56% are t(GqGq). Forty-nine percent of t(DqGq) are inherited and 51% sporadic, while the figures for the t(GqGq) are 5.6% and 94.4%, respectively.

ii. *Among live births* The figures given in Table 5-11 enable the frequency of secondary trisomics among live-born children to be calculated. For mothers under 30 this is $0.7/1000 \times 7.9/100 = 5.53 \times 10^{-5}$, while for older mothers a slightly lower figure is obtained: $3.0/1000 \times 1.5/100 = 4.50 \times 10^{-5}$. The over-all frequency based on the assumption that 65% of all mothers in the population are under 30 and 35% are over 30 is $[(0.65 \times 5.6) + (0.35 \times 4.5)] \times 10^{-5} = 5.215 \times 10^{-5}$, or 1 in 18,000

TABLE 5-11

Frequency of Secondary Trisomic Patients (Translocation Trisomics) in the 34 Series of Patients Summarized in Table 5-10

Maternal age	Total probands	Secondary trisomics t(DqGq) S	I	?	Secondary trisomics t(GqGq) S	I	?	Assumed percent in DS population[a]	DS frequency per 1000 live births[b]	Frequency secondary trisomics among live births[c]
<30	863	19	13	6	27	1	3			
		19/32=0.59		13/32=0.41	27/28=0.96					
			38			31		28	0.7	5.53×10^{-5}
			38/69=0.55			31/69=0.45				
			38/863=0.044			31/863=0.036				
				69/863=0.0799						
>30	664	2	3	–	4	–	1	72	3.0	4.5×10^{-5}
			5/664=0.0075			5/664=0.0075				
				10/664=0.015						
Unspecified	1067		32			31				
			32/63=0.51			31/63=0.49				
			32/1067=0.03			31/1067=0.03				
				63/1067=0.06						
Total	2594		75	142/2594=0.055 (0.0547)		67		100	–	5.22×10^{-5} [d]

[a] From Carter and Evans (1961). [b] From Collmann and Stoller (1962).
[c] Down's syndrome frequency per 1000 live births times frequency of secondary trisomics in DS populations.
[d] Assuming 65% mothers <30 and 35%>30 (Registrar General, 1955).

live births in the general population at all age groups, which can be compared with an incidence of Down's syndrome generally of about 1:660 live births.

Polani *et al.* (1965) have calculated that the new mutation rate of translocations of all types related to Down's syndrome is 2.71×10^{-5} chromosomes 21 per gamete per generation. This figure is based on certain assumptions and is given with a full realization that the data on which it is based are not ideal. It does however compare favorably with other calculated mutation rates.

4. Familial Down's Syndrome

The occurrence of more than one child affected with Down's syndrome in a kinship or sibship is a relatively rare event in comparison to the frequency with which single isolated affected births occur. It is important to have an estimate of the risk that a sibship concentration of Down's syndrome births might occur after the birth of a single affected child. The demonstration in 1960 that some of these high risk families result from an inherited translocation has provided the basis for a study of some of the mechanisms which lead to such concentrations of affected children.

a. Early Data. Penrose (1934b) studied 217 families with an affected index patient, seven of which also had an affected sib, but in 1949 wrote ". . . that with such a common defect it is difficult to produce convincing evidence that the familial cases are due to familial concentration and not to chance sampling." In a study of 526 patients, Øster (1953, 1956), found seven index patients with affected sibs, four of whom were younger than their respective index patients and three older; on the basis of this he concluded that the risk of a second affected child was no greater than the random risk based on maternal age. Carter and Evans (1961) studied 642 families with an affected index patient (Table 5-12). They found that these 642 index patients had 927 sibs born before the index patients, of whom four were also affected, whereas about 1.5 would have been expected. While of the 312 sibs born after the index patient, five were affected, whereas only one would have been expected. They found that the risk of a second affected sib is much influenced by maternal age, and that for mothers under 25 the risk of a second affected child is fiftyfold over the random risk based on maternal age, while for the 10-year age period 25-34, the increase is fivefold. Above a maternal age of 35 there is no increase in risk over and above that expected due to increasing maternal age.

Chromosome studies on the nine families with more than one affected sib showed that three out of the five families with younger af-

TABLE 5–12

Relative Prevalence of Down's Syndrome among Sibs of Affected Probands [a]

	Maternal age (years) at birth of index patient			Total
	15–24	25–34	35	
Total children	130	341	768	1239
Translocation trisomy	3	–	–	3
Primary trisomy	1	3	2	6
Expected DS	0.068	0.606	1.741	2.415
Obs./Exp.	59.82	4.950	1.149	3.727

[a] From Carter and Evans (1961) and Hamerton *et al.* (1961a).

fected sibs carried a translocation, while in the two remaining families the affected children were primary trisomics. In the four families in which the affected sibs were born after the index patients, all the affected children were primary trisomics. This indicates that high-risk translocation families can account for much, but not all, of the increased risk at younger maternal ages since there is still about a fivefold increase in the risk of a second affected child at maternal ages of less than 35, even after elimination of families carrying a translocation.

A study of families with more than one affected sib (Table 5-13) shows that 25.6% of these have a translocation while only 12.5% of families with more distant relatives affected carried a translocation. Four families with two affected members had one primary and one sporadic secondary trisomic, an incidence of 5%. This may be a chance association or may indicate a predisposition in these families to nondisjunction

TABLE 5–13

Frequency of Translocations in Families With More Than One Affected Subject [a]

Relationship of affected subjects	No. of families	Primary trisomics	Secondary trisomics	Primary and secondary trisomy	Incidence (%) secondary trisomy (translocation)
Sibs	39	28	10	1	25.6
Other relatives	32	25	4	3	12.5
Total	71	53	14	4	19.7

[a] Giannelli *et al.*(1965), Soltan *et al.* (1964), Forssmann and Lehmann (1962), Hamerton *et al.*(1965), and Mikkelsen (1966).

or chromosome breakage. Several families are reported in which a primary or secondary trisomic may be associated with a marker chromosome (Dp+;Gp+Yq+), either in the same individual or in other members of the family (Mikkelsen, 1967b; Hamerton *et al.*, 1965a; Huang *et al.*, 1967). This type of association may be too frequent to be accounted for entirely by chance so that the presence of one of these minor anomalies may indicate a predisposition to nondisjunction or structural rearrangement.

These data indicate that only a proportion of the "high-risk families" can be accounted for by a chromosome translocation. The presence of more than one affected subject with primary trisomy in a family may result from chance, and it is impossible at present to separate chance events from events for which there is some predisposition, particularly when dealing with a condition which is as common as Down's syndrome. If all the evidence is considered, however, it seems probable that there is some form of genetic control over nondisjunction. There is little doubt, for instance, that double trisomics occur with greater frequency than would be expected by chance; furthermore, it seems likely that an extension of the study of Carter and Evans (1961) and Hamerton *et al.* (1961a) would reveal a significant excess of families with more than one affected primary trisomic subject. The existence of families with Down's syndrome and another aneuploid condition in the same sibship may also be evidence of some form of predisposition for nondisjunction. The mechanism involved is not clear. It is, however, certain that the risk is greater if the index patient is born at a maternal age of less than 30 and is still appreciable up to maternal ages of 35.

b. High Risk Translocation Families and Family Data. Families in which a segregating translocation has been identified present an entirely different picture, and the risk depends upon a number of intrinsic factors which have already been discussed (Volume I, Chapter 8); this section is concerned entirely with conclusions which may be drawn from this study and with a consideration of the risk of further affected births in these families.

i. *t(DqGq)*[15]. There are three possible translocation types t(13q21q), t(14q21q), and t(15q21q), and autoradiographic studies suggest that the chromosome involved is usually No. 14, rarely No. 15, and never No. 13 (F. Hecht *et al.*, 1968). For the purposes of this discussion, therefore, all these families will be considered as one class. They fall into two groups: the first, in which the translocation is transmitted by the mother (sibships with maternal transmission), and the second, where the

[15]See Chapter 8, Volume I, and Addendum to Volume I.

father is a balanced translocation heterozygote (sibships with paternal transmission) (Hamerton *et al.*, 1961b; Hamerton and Steinberg, 1962; Giannelli *et al.*, 1965; Hamerton, 1966, 1968a, 1969).

Sibships with maternal transmission: The data for 62 sibships have been summarized (see Volume I, Chapter 8, Table 8-11) and suggest that for any further pregnancy there is about an 89% chance of a normal child or a balanced heterozygote and only about a 10% chance of an affected child. There may also be an increased risk of abortion, although these data are less easy to assess. These figures may be biased by an inadequate correction for ascertainment since children born both before and after the index patient are included, and this may result in too high a frequency of normal or balanced children. There is, however, little doubt that the theoretical expected figure of 33% affected children is not obtained.

Sibships with paternal transmission: The data for 32 sibships have been summarized (Volume I, Table 8-11) and these showed an even lower frequency of affected subjects (2.4%) compared with 97.6% who had either normal chromosomes or were balanced heterozygotes, so that the risk of an affected child when the translocation is patroclinous is probably less than 5% while there would seem to be an excess of heterozygotes.

ii. *t(GqGq)*. There are three types of rearrangement which fall into this category, each must be dealt with separately since its genetic consequences are quite different. Compared to the t(DqGq) only 5.6% of this type of structural change is inherited, while the remainder arises *de novo*. The three types are t(21q22q), t(21q21q), and 21qi. The cytogenetics of these three rearrangements have been discussed by Hamerton (1962, 1966). The t(21q22q) is considered to behave in a similar way to other Robertsonian translocations [the t(DqGq) and t(DqDq)], and families with this type of inherited structural change can be recognized by the presence of balanced heterozygous sibs as well as affected children. The other two types of t(GqGq) cannot produce balanced heterozygous children and must usually arise sporadically. A few families are, however, known with a presumptive t(21q21q) heterozygous parent; such heterozygotes can only arise from a postfertilization mitotic error of a normal zygote. The gametes formed by a t(21q21q) heterozygote must be either disomic or nullisomic-21 and after fertilization the respective zygotes either trisomic or monosomic-21 (Fig. 5-13). Hamerton *et al.* (1961a) reported a family with two Down's syndrome sibs and an abortion in the same sibship, while the mother had 45 chromosomes and a presumptive t(21q21q). Dallaire and Fraser (1964) reported a sibship with four Down's syndrome patients, one abortion, and one still-

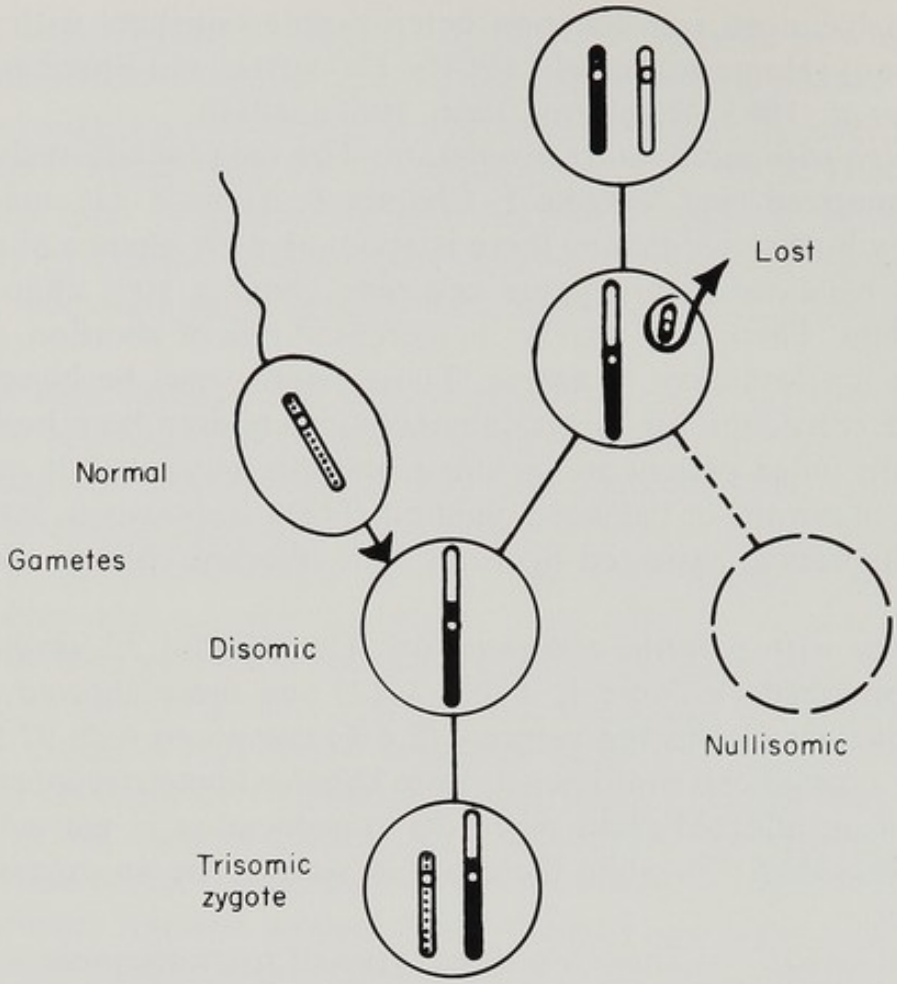


FIG. 5-13. Gametes produced by t(21q21q) or 21qi heterozygotes; heterozygotes for this translocation can only produce disomic or nullisomic gametes resulting in either monosomic or trisomic zygotes. (From Hamerton, 1962.)

birth. Three of the four sibs with Down's syndrome were found to have 46 chromosomes and t(GqGq). The father had 45 chromosomes and carried a similar structural change. Both families could be accounted for if the rearrangement were a t(21q21q).

21qi formation is the result of centromere misdivision at the second meiotic division or at the first division through the intermediate stage of an unstable telocentric chromosome (see Volume I, Fig. 8-6) and must result in the formation of a disomic gamete and therefore a trisomic zygote. The origin of a balanced 21qi heterozygote is more difficult to understand (see Chapter 8, Section II, C). The isochromosome could be formed during gametogenesis in a normal subject and if followed by postzygotic nondisjunction could produce a zygote with both a normal and a secondary trisomic cell line (see Volume I, Fig. 8-6). Two such families have been described with a phenotypically normal mixoploid father and an isotrisomic son (Fraccaro *et al.*, 1960e; Fraccaro and Lindsten, 1962; Hamerton *et al.*, 1961a).

Four t(21q22q) families are known. These have been recognized by the presence of balanced heterozygous sibs as well as normal and affected offspring. Examination of the data suggests that a balanced heterozygote has an approximately equal chance of producing chromosomally normal and heterozygous offspring, while there may be a deficiency of affected children similar to that observed with the t(DqGq) (see also Volume I, Chapter 8; Table 8-15). There are, however, insufficient data on the segregation of this rearrangement to reach any firm conclusion about the frequencies of the different types of progeny. Soudek *et al.* (1966, 1968) reported a family (Fig. 5-14) with a presump-

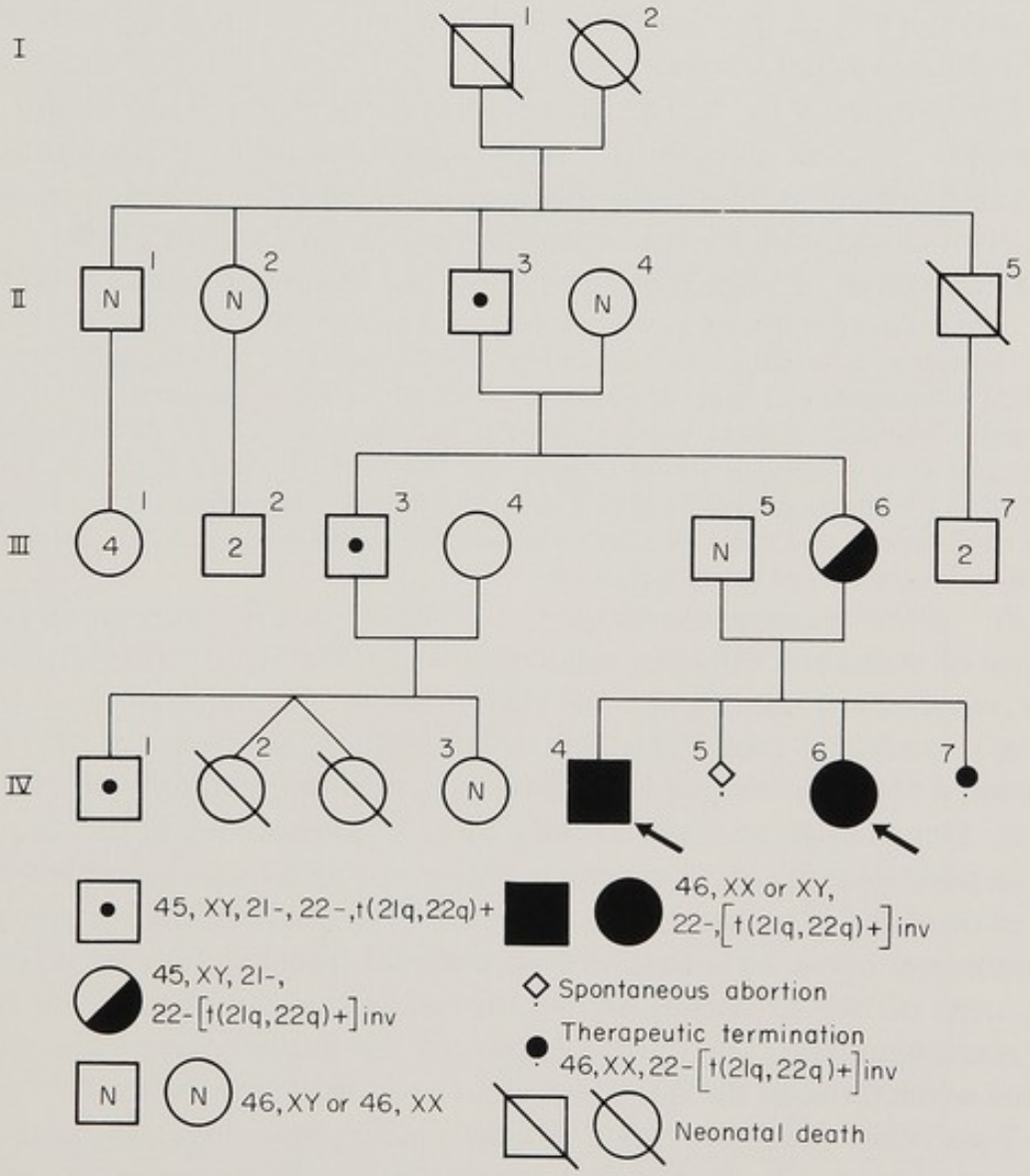


FIG. 5-14. Pedigree of family reported by Soudek *et al.* (1966, 1968) in which a t(21q22q) and an inversion of the translocated chromosome is segregating. Note that chromosome imbalance only occurs in the branch of the family in which the inverted chromosome is present (III-6, IV-6, IV-4, IV-7).

tive t(21q22q) in one sib [45,XY,21−,22−,t(21q22q)+]. His sister also had 45 chromosomes, but instead of the typical F-like chromosome, an acrocentric chromosome of similar length was observed. This was thought to have arisen by means of a pericentric inversion of the original translocation chromosome [45,XX,21−,22−,t(21q22q)inv+] (Fig. 5-15). The propositus and his sister both had Down's syndrome and carried the same longer acrocentric chromosome [46,XY,22−,t(21q22q)inv+]; two abortions (one therapeutic) had also occurred in the same sibship. There were no abnormal children or abortions in the remainder of the family in which the noninverted t(21q22q) was segregating (Fig. 5-14). This suggested that the pericentric inversion had caused a disturbance in pairing and segregation to give an increased frequency of progeny with unbalanced chromosome complements.

The prognosis for t(21q21q) heterozygotes is likely to be very poor since only trisomic affected or monosomic children can be produced. The same argument applies to the 21qi heterozygote, although in theory both normal and primary trisomic offspring can arise from 21qi.

Giannelli *et al.* (1965) have summarized these findings as follows:

> If the father or mother as well as the patient has a G_{21}/G interchange, the risk of recurrence is probably higher than with a D/G_{21} because of the possibility of a 21/21 interchange and iso-L-21 formation. This higher risk is supported by the few families available. If there is evidence that the translocation is of the type 21/22 because there is already a balanced sib, the two families available (Shaw, 1962; Pfeiffer, 1963) suggest that the risk may be less than the theoretical 1:3, but it must be remembered that these families were selected by the presence of a phenotypically normal balanced heterozygous sib.

iii. *Other structural changes.* There are a few reports in the literature of structural changes other than the t(DqGq) or t(GqGq) which have resulted in an excess of chromosome 21 material and hence Down's syndrome (see Table 8-8, this volume). Zellweger *et al.* (1963) reported a 5½-year-old girl with Down's syndrome with only 46 chromosomes. Her karyotype showed only three chromosomes in the G group and an additional larger acrocentric chromosome which resembled chromosomes of the D group. It was suggested that the abnormal acrocentric chromosome arose as a result of an unequal translocation between the long arms of two G chromosomes instead of the more usual long-short arm rearrangement. The chromosomes of the mother were ' the mother normal while those of the father were not examined (Fig. 5-16).

Two other families with a similar Gq;Gq translocation have been reported (Fig. 5-17). In the first family (B. W. Richards *et al.*, 1965b) the propositus was a 41-year-old adult Down's syndrome female who was a mosaic with two cell lines (Fig. 5-16). The majority of cells had 45 chromosomes, two G chromosomes, and an additional long acrocentric

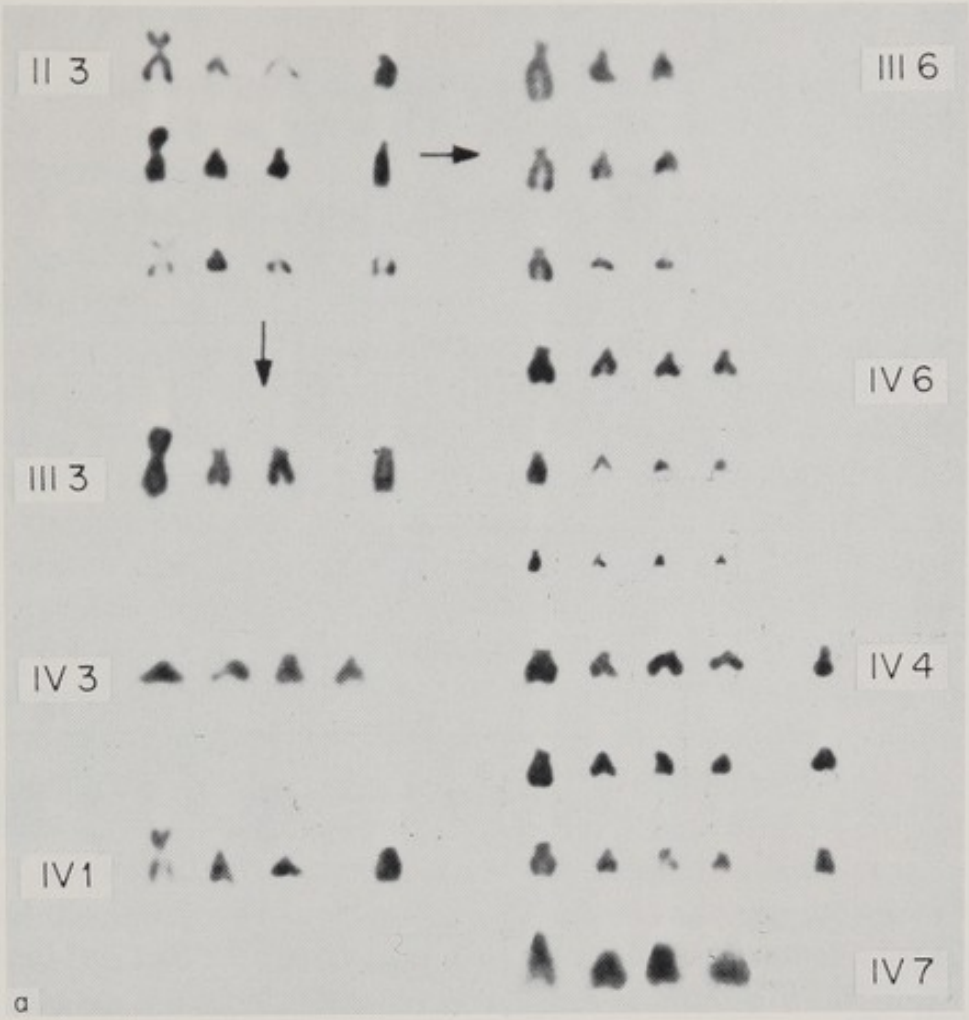


FIG. 5-15. (a) Partial karyotypes of chromosomally studied subjects in family reported by Soudek (1966, 1968). Note t(21q22q) in II-3; III-3; IV-3 and IV-1, and t(21q22q)inv in III-6; IV-6; IV-4 and IV-7. (b) The probable mode of origin of the translocation (left) and the inverted translocated chromosome (right).

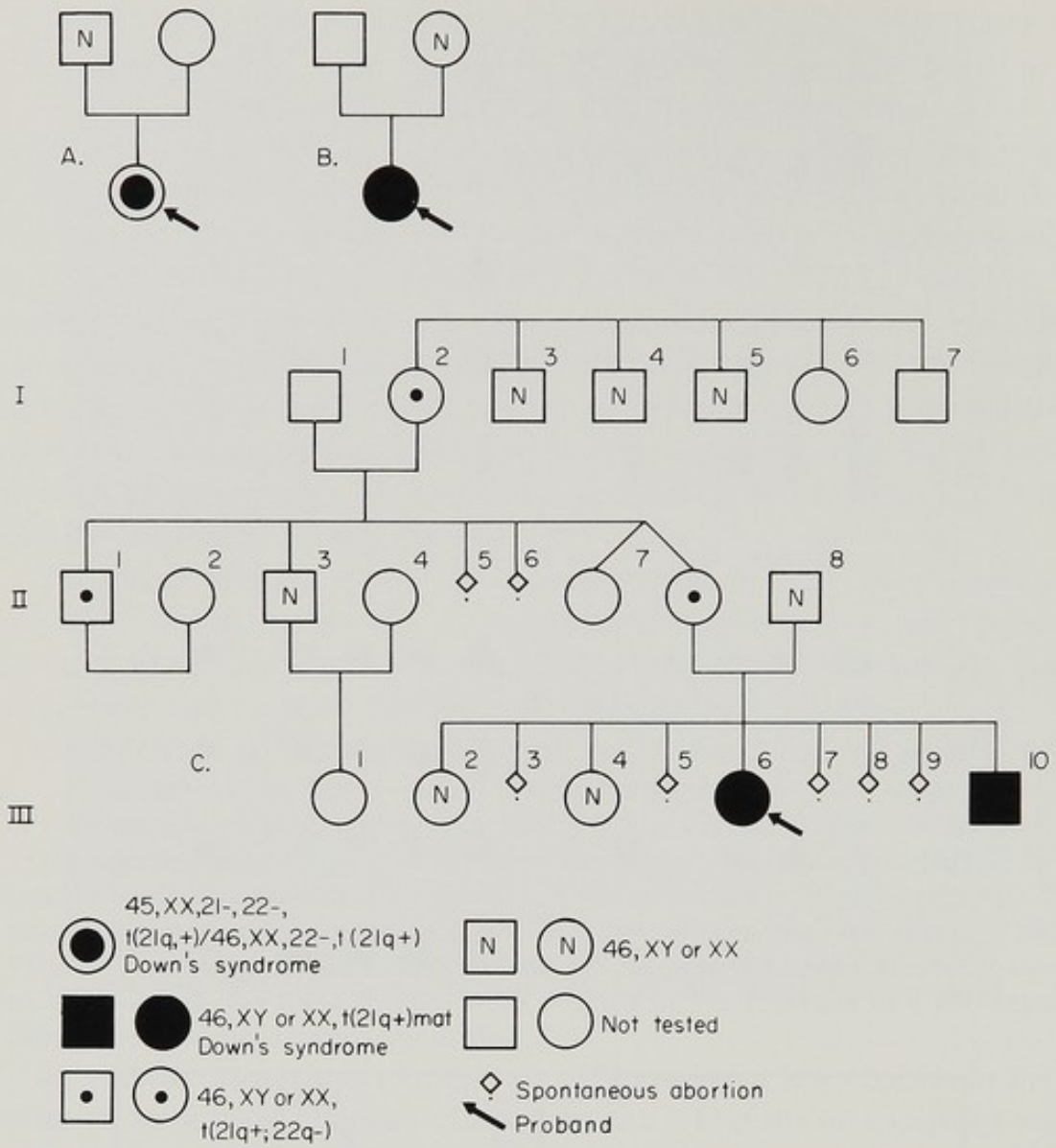


FIG. 5-16. Pedigrees of three families in which a t(21q+;22q−) has been observed: (a) B. W. Richards *et al.* (1965b), (b) Zellweger *et al.* (1963), and (c) Cohen and Davidson (1967).

D-like chromosome. The remaining cells of the second cell line had three G chromosomes and the same D-like chromosome [45,XX,G−,G−, t(Gq+)/46,XX,G−,t(Gq+)]. The proband had typical features of Down's syndrome, and in this connection it is interesting to note that while 7.4% of the lymphocytes were unbalanced and 92.6% balanced, 55.6% of fibroblasts were unbalanced and only 44.4% balanced. The second family in which a similar translocation was present (Fig. 5-16) (Cohen and Davidson, 1967) contained two cases of Down's syndrome together with multiple spontaneous abortions in the same sibship. The mother, an uncle, and maternal grandmother of the propositus were all balanced heterozygotes (Fig. 5-16).

5. Mixoploids

A proportion of patients who are only mildly affected with Down's syndrome proved to be mixoploids, usually with both a primary trisomic and a normal cell line.

C. M. Clarke *et al.* (1961) described the first 46,XX/47,XX,G+ girl as ". . . an intelligent child with some mongoloid characters"; and at 11 months the over-all clinical picture ". . . was thought to be against a diagnosis of mongolism." This child had Brushfield's spots and characteristic palm prints as well as other features of Down's syndrome. On the other hand, she was very advanced both mentally and developmentally compared to the average child of her age affected with Down's syndrome. In this instance the proportion of trisomic cells was relatively low in skin (Table 5-14), and this might account for the relatively mild phenotype and high intelligence. Equally important in relation to the degree of phenotypic involvement are the tissues affected by trisomic cells as well as their proportions. It is, therefore, theoretically possible for a phenotypically normal subject to carry a primary trisomic cell line involving perhaps only a single tissue such as the gonads, and this could explain an otherwise inexplicable sibship concentration of patients with Down's syndrome. Several subjects are known. Blank *et al.* (1962) reported the mother of a child with Down's syndrome who was herself mixoploid (46,XX/47,XX,G+). She had a few stigmata of Down's syndrome and an IQ of 62. Only 14% of cells in culture were trisomic. D. W. Smith *et al.* (1962b) reported a phenotypically normal woman who was the mother of two affected boys. Twenty seven per cent of her cells were found to be G+. Verresen *et al.* (1964) reported a 17-year-old female with 14% trisomic cells who was the mother of a child with Down's syndrome and another young mother with a primary trisomic child who was found to be 46,XX/47,XX,G+ (Table 5-15); a further 11 mixoploids, eight infants and three adults, two of whom were mothers of mongols were reported by Taylor (1968b) (Tables 5-14 and 5-15). It is perhaps therefore as important to determine which tissues have extensive trisomy as it is to establish the proportion of trisomic cells in culture. For instance, if the central nervous system is wholly or largely trisomic, extensive impairment of mental development may be expected, leading perhaps to an expression of the Down's syndrome phenotype. On the other hand, the presence of trisomic germ cells could result in several trisomic births as the result of secondary nondisjunction. This can be illustrated by chromosome studies which were carried out on the mother of two affected children who had a very low frequency of trisomic cells in both blood and skin, while a culture established from an

(a)

(b)

ovarian biopsy was almost exclusively trisomic (Jagiello and Taylor, 1969).

Table 5-14 summarizes some data on the chromosome analysis of 41 46,XX or XY/47,XX or XY,G+ mixoploids. This shows extensive individual variation which makes it difficult to generalize about these results; one fact which does however stand out is that fibroblast cultures frequently have a higher proportion of trisomic cells than lymphocytes or bone marrow. Ford (1964) suggested that this implied that normal cells had a selective advantage over trisomic cells and therefore replaced the aneuploid cells in the more rapidly dividing tissues. In this connection it is interesting to note that the child originally reported by C. M. Clarke *et al.* (1961) was further studied by the same authors (1963) and both lymphocytes and bone marrow contained a lower proportion of aneuploid cells (14 and 17%) than the original fibroblast cultures (32 and 38%). There are, of course, a number of reasons for this variation and it is not possible to determine the exact cause. There may be variation in the proportion of the different cell types in different tissues when the cultures were started and these may be maintained *in vitro*; alternatively, a given cell type may have a selective advantage *in vitro* in which case the proportions *in vitro* would differ from those found *in vivo*; and, finally, we may have a situation which is seen in some sex chromosome mixoploids in which the different cell types are found nearly exclusively in different tissues. The proportions of the different cell types *in vivo* may be affected by cell selection or the proportions of stem cells of the different types may vary from tissue to tissue. Recently, Taylor (1968b) studied the frequency of normal and trisomic cells in 11 mixoploids (46,XX or XY/47,XX or XY,G+) comprising eight infants, seven of whom had Down's syndrome while the eighth did not, and three adults, two phenotypically normal mothers of affected children and one adult with Down's syndrome. The infants were studied for various periods ranging from 6 to 42 months. These results have already been discussed (Volume I, Chapter 7, Section II; Figs. 7-22, 23 and 24) and do not suggest any consistent difference either between different tissues as postulated by Ford (1964) or between normal and trisomic cells.

Other mixoploid combinations are known, and some of these are summarized in Table 5-16. All of these patients have Down's syndrome, although two subjects with a Gq− chromosome have minimal stigmata. The two pairs of discordant monozygotic twins have already been dis-

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FIG. 5-17. (a) Karyotype of balanced t(21q+;22q−) heterozygote (see Fig. 5-16c, II-1, II-7, and I-2). (b) Karyotype of proband with Down's syndrome t(21q+) effectively trisomic for most of the 21q (see Fig. 5-16c).

TABLE 5–14

Chromosome Findings in 41 Patients Affected with Down's Syndrome with a Mixoploid Chromosome Complement

Case No.	Sex	Age (years)	Trisomic cells (%)		Parental ages at birth		Reference
			Lymphocytes	Fibroblasts	Mother	Father	
1	♀	–	20	67	19	–	Nichols *et al.*, 1962
2	♀	2 3/12 4 4/12	– 14,17 (bone marrow)	32,38 –	26	26	C.M. Clarke *et al.*, 1961, 1963
3	♀	–	63	29	38	29	Lindsten *et al.*, 1962
4	♀	–	5	75	32	34	Hinden, 1961[a]
5	♀	–	67	99	25	29	Edwards, 1963[a]
6	♂	–	–	70	24	29	Gustavson and Ek, 1961
7	♂	–	50	–	17	–	Hayashi *et al.*, 1962
8	♂	–	–	40	32	25	Bonham Carter, 1962[a]
9	♂	–	58	–	38	–	Fitzgerald and Lycette, 1961
10	♂	–	2	98	45	45	Ridler *et al.*, 1965
11	♂	–	18	–	27	31	Gerald, 1963[a]
12	♀	–	16	–	36	39	Gerald, 1963[a]
13	♀	–	17	–	31	40	Gerald, 1963[a]
14	♂	–	65	–	25	26	Warkany *et al.*, 1964
15	♂	–	0	19	23	24	Warkany *et al.*, 1964
16	♀	10	24	69	40	53	Lord *et al.*, 1964
17	♂	6	45 (bone marrow)	–	32	33	Tsuboi *et al.*, 1968

			85	(bone marrow)			
18	♂	10/12	79	–	42	38	Biscatti, 1964
19 (3088)	♀	6 1/2	4	–	28	28	Hamerton *et al.*, 1965
20 (3576)	♀	2 5/12	44	–	29	31	Hamerton *et al.*, 1965
21 (2985)	♂	10	22	18	26	27	Hamerton *et al.*, 1965
22 (2316)	♂	6	23	–	35	30	Hamerton *et al.*, 1965
23 (3107)	♀	2 1/12	73	–	32	30	Hamerton *et al.*, 1965
24	♀	2/12	35	–	30	34	Taylor, 1968b
170467/6200		4/12	18	–			
		7/12	10	–			
		10/12	6	26			
		12/8	8	–			
25	♀	1/12	83	–	30	36	Taylor, 1968b
280266/5246		4/12	–	82			
		10/12	59	–			
		12/12	60	–			
		20/12	40	–			
		25/12	46	–			
26	♀	1/52	77	–	43	53	Taylor, 1968b
281165/5061		3/12	90	–			
		6/12	59	95			
		9/12	79	–			
		11/12	68	–			
		16/12	60	–			

TABLE 5–14 (cont'd)

Case No.	Sex	Age (years)	Trisomic cells (%)		Parental ages at birth		Reference
			Lymphocytes	Fibroblasts	Mother	Father	
26 (Continued)		18/12	58	–			
27	♀	1/36	30	–	22	21	Taylor, 1968b
120866/5599		2/12	–	27			
		13/12	8	–			
		19/12	2	–			
		22/12	1	–			
28	♀	2/52	14	–	21	20	Taylor, 1968b
091064/4379		31/12	6	–			
		37/12	3	–			
		42/12	3	–			
29	♂	4/12	92	–	32	37	Taylor, 1968b
201266/6091		7/12	66	–			
		8/12	86	–			
		10/12	90	–			
		18/12	95	–			
30	♀	4/12	75	–	34	38	Taylor, 1968b

040567/6313		8/12	92	–			
		12/12	98	–			
31	♂	4/52	72	–			
091067/6421		3/12	99	–	26	33	Taylor, 1968b
		6/12	106	–			
32	♀	16	18	–			
080549/4791		16.3	14	–	32	29	Taylor, 1968b
		16.5	20	–			
		16.8	16	–			
		17.8	18	–			
33 (1)	♂	–	36	–	32	–	Van Gelderen *et al.*, 1967
34 (2)	♀	–	6.5	–	32	–	Van Gelderen *et al.*, 1967
35 (3)	♀	–	9.0	–	30	–	Van Gelderen *et al.*, 1967
36 (4)	♂	–	9.0	–	43	–	Van Gelderen *et al.*, 1967
37 (5)	♀	–	7.0	–	39	–	Van Gelderen *et al.*, 1967
38 (6)	♀	–	13.0	–	27	–	Van Gelderen *et al.*, 1967
39 (7)	♀	–	15.0	–	37	–	Van Gelderen *et al.*, 1967
40 (8)	♀	–	30.0	–	36	–	Van Gelderen *et al.*, 1967
41 (9)	♀	–	40.0	–	24	–	Van Gelderen *et al.*, 1967
Mean ages					30.24	32.68	

[a] Quoted by Penrose and Smith (1966).

TABLE 5–15

Chromosome Findings in Six Phenotypically Normal Mothers of Children Affected with Down's Syndrome Who Were Mixoploid

Age at birth of DS proband	No. of DS children	Age at birth of parent [a]		No. of cells		Proportion G+	Mongoloid features in mother	References
		M.A.	P.A.	46,XX	46,XX,G+			
19	2	–	–	–	–	0.27	Dermal ridge pattern	D.W. Smith *et al.*, 1962b
28	1	40	42	95	15	0.14	IQ 60; Brushfield's spots; Fissured tongue; Palmar and digital ridge patterns	Blank *et al.*, 1962
30	1	34	–	128	15	0.10	Nil. Radial loop IV right hand	Verresen *et al.*, 1964
17	1	39	–	122	26	0.18	? Brushfield's spots	E.D. Weinstein and Warkany, 1963
–	–	23	–	285	15	0.05	Normal phenotype	Taylor, 1968b – 35/5883
–	–	38	–	243	3	0.01	Normal phenotype	Taylor, 1968b – 250829/4126
Mean 23.5 (4)		34.8	–					

[a] Here M.A. stands for maternal age and P.A. for paternal age.

TABLE 5–16

Chromosome Complements and Phenotype in Some G+ Mixoploids and One Mildly Affected Patient

Chromosome complement [a]	Phenotype	Reference
46,XY/47,XY,G+/48,XY,G+,?Gqi+	Down's syndrome	Gustavson and Ek, 1961
46,XY/47,XY,G+/48,XY,G+G+	Down's syndrome	Fitzgerald and Lycette, 1961
47,XY,G+/48,XY,G+G+	Down's syndrome	Hamerton *et al.*, 1965
47,XY,G+/49,XY,G+,G+,G+	Down's syndrome	Piazzi and Rondinini, 1961
46,XY/47,XY(Gq−)+	A few features of DS	Ilbery *et al.*, 1961
46,XY//47,XY,G+	Monozygotic twins discordant for DS	Lejeune *et al.*, 1962
46,XX//48,XX,G+,G+	Monozygotic twins discordant for DS	Dekaban, 1965
47,XY,(Gq−)+	Minimal features of DS	Dent *et al.*, 1963

[a] Here // indicates that the two cell lines are contained in separate zygotes.

cussed (see above; see also Volume I, Chapter 7). The origin of this type of mixoploidy is depicted in Fig. 7-12, Volume I.

FREQUENCY OF MIXOPLOIDS. i. *Among children with Down's syndrome or suspected Down's syndrome.* The frequency of 46,XX or XY/47,XX or XY,G+ mixoploids among patients confidently diagnosed as having Down's syndrome is low, probably of the order of 1% (Hamerton *et al.*, 1965) but reaches about 10% among patients in whom the diagnosis is in doubt. Four out of the six mixoploid patients reported by Hamerton *et al.* (1965) were referred for diagnosis, while the other two had the usual Down's syndrome phenotype. One of these was a 47,XY,G+/48,XY,G+,G+ mixoploid. Gustavson (1964) found two mixoploids among 103 index patients. In his case one of these was the 46/47/48 mixoploid referred to in Table 5-16 (Gustavson and Ek, 1961), and the other was a 46,XX or XY/47,XX or XY,G+ subject.

ii. *Among phenotypically normal subjects.* The six females who have been shown to be mixoploid and who have minimal stigmata of Down's syndrome raise the question of the frequency with which parental mixoploidy contributes to sibship Down's syndrome. The study by Giannelli *et al.* (1965) of 96 index patients with Down's syndrome born to young mothers did not reveal a single instance of mixoploidy among the parents, and there are only a few reports (see above) of mixoploid

mothers of primary trisomic sibs. It is probable that in many of the studies, including the one by Giannelli *et al.* (1965), low level mixoploidy would not have been detected because of the relatively few cells studied in the parents. It must, however, be clear from the relatively low frequency of mixoploids that this phenomenon cannot account for more than a small proportion of high-risk families.

I. *Association of Down's Syndrome with Other Conditions*

The frequency with which Down's syndrome is found to be associated with leukemia and Klinefelter's syndrome is greater than would be expected by chance. There have also been reports of association with the Ehlers Danlos syndrome and Albright's syndrome.

1. Leukemia

A. Stewart *et al.* (1958) showed that 2.6% (17/667) of childhood deaths from leukemia between 1953 and 1955 were associated with Down's syndrome. Tough *et al.* (1961) pointed out that the frequency of Down's syndrome at birth is of the order of 1.6/1000 and that on the assumption that all these survive, the incidence of children with Down's syndrome developing leukemia was a minimum of 15 times the incidence of leukemia in the general population, and, in view of the early deaths of many patients with Down's syndrome from other causes, probably considerably higher.

Krivit and Good (1957) found a minimum of 34 cases of an association of leukemia with Down's syndrome in the 0–4-year age group in the United States between 1952 and 1955 compared with an expectation of 12.3 cases. This is a threefold increase over the incidence of leukemia in the general population. They also reported a ninefold increase in the incidence of congenital leukemia among newborn Down's syndrome patients. Wald *et al.* (1961) analyzed the incidence of the association of Down's syndrome and leukemia over all ages and found a raised incidence in all age groups. R. W. Miller (1963) showed that the incidence of Down's syndrome among six probands with leukemia was higher than expected, both as a direct association and among sibs. Holland *et al.* (1962) followed 2033 probands with Down's syndrome for periods ranging from 1–14 years. During this period seven index patients died of leukemia and seven from other forms of cancer. The death rate from leukemia was 18 times greater in the Down's syndrome population than in the general population, while that from other types of cancer was 2.6 times above the national rate. From these data there can be no doubt

that the frequency with which Down's syndrome and leukemia are associated is considerably greater than would be expected by chance.

Cytogenetic studies throw little light on this association, and the only consistent abnormality which has been found in these patients has been G-trisomy. Several subjects with congenital leukemia and Down's syndrome have had normal chromosomes except for the presence of G-trisomy. Ten Down's syndrome patients with acute leukemia were all G-trisomics and also had various nonspecific chromosome abnormalities. This suggests that there is some connection between chromosome No. 21 and a spectrum of events linking Down's syndrome, the neutrophil leukocytes and leukemia. These can be summarized as follows: (1) chronic myeloid leukemia (CML) and a Gq− chromosome (Ph^1), (2) Down's syndrome and G-trisomy, (3) reduced polymorph lobulation in Down's syndrome, (4) raised leukocyte alkaline phosphatase in Down's syndrome and reduced levels in CML, and (5) an increased association of Down's syndrome with leukemia generally. The reduced polymorph lobulation indicates immature circulating neutrophils. It has been suggested that chromosome 21 carries loci, which, if not controlling, at least affect leukopoiesis. Anomalies at these loci can lead to leukemia, while trisomy causes Down's syndrome and may in some instances predispose a leukemic change (Tough *et al.*, 1961).

2. Double Aneuploidy and Association of Aneuploid Conditions

Various double aneuploid associations are summarized in Table 5-17. The most frequently reported type of double aneuploid is the 48,XXY,G+; other types include 48,XXX,G+ and 48,XYY,G+. Several mixoploids have also been reported. In general, the double aneuploids which involve the sex chromosomes as well as G-trisomy have phenotypic features representative of both aneuploid conditions. A few double autosomal aneuploids have been reported. These usually have the features of both conditions although the more serious condition usually masks the less serious. Several reports of children affected with Down's syndrome and associated in the same family or sibship with subjects having a different chromosome abnormality have also been reported (Table 5-18) (see also Chapter 1; and see, for instance, Fig. 5-3, above).

Hamerton *et al.* (1965) have summarized the data on the frequency of 48,XXY,G+ males and concluded that the expected incidence of double trisomics based on chance association should be about 0.31×10^{-5} live-born males. They observed three double trisomics in a series of 616 primary G-trisomics, and concluded that, based on a maternal age

Some Examples of Double Aneuploidy in Patients Affected with Down's Syndrome

Chromosome complement	Phenotype	Maternal age (years)	Paternal age (years)	Reference
48,XXY,G+	Klinefelter/Down's syndrome	42	40	Ford *et al.*, 1959a; Harnden *et al.*, 1960; Court Brown *et al.*, 1964a
48,XXY,G+	Klinefelter/Down's syndrome	20	–	Lanman *et al.*, 1960
48,XXY,G+	Klinefelter/Down's syndrome	41	–	Lehmann and Forssman, 1960
48,XXY,G+	Klinefelter/Down's syndrome			Pfeiffer, 1964a
48,XXY,G+ 48,XXY,G+ (twins)	Klinefelter/Down's syndrome	43	–	Hustinx *et al.*, 1961
48,XXY,G+	Klinefelter/Down's syndrome	19	–	Van Gelderen and Hustinx, 1961
48,XXY,G+	Klinefelter/Down's syndrome	43	43	Hamerton *et al.*, 1962
48,XXY,G+	Klinefelter/Down's syndrome	35	38	Milcu and Maicanescu, 1963
48,XXY,G+	Chromatin +ve DS infant	24	25	Hamerton *et al.*, 1965
48,XXY,G+	Chromatin +ve DS (2 years)	40	41	Court Brown *et al.*, 1964a
48,XXY,G+	DS prepubertal; small penis and scrotum; testes not palpable.	42	49	Court Brown *et al.*, 1964a

48,XXY,G+	Chromatin +ve infant with DS			Taylor and Moores, 1967
48,XXY,G+	Chromatin +ve infant with DS			Taylor and Moores, 1967
48,XXY,G+				De Grouchy *et al.*, 1965a
48,XXX,G+	Double chromatin positive female with DS	20	19	R.W. Day *et al.*, 1963b
48,XXX,G+	Double chromatin positive female with DS	47	45	Yunis *et al.*, 1964b
48,XYY,G+	DS infant	22	33?	Uchida *et al.*, 1966
48,XYY,G+	DS	27	28	Migeon, 1965a
48,XYY,G+	DS	35	44	Verresen and Van den Berghe, 1965
46,X,G+/47,XX,G+	DS infant	42	44	Root *et al.*, 1964b
46,X,G+/47,XX,G+/48,XXX,G+	DS child	26	26	Zergollern and Hoefnagel, 1964
46,X,G+/47,XX,G+	DS	26	28	Van Wijck *et al.*, 1964
48,XY,E+,G+	Congenital malformations	22	22	Gagnon *et al.*, 1961
48,XY,D+,G+	Congenital malformations	39	46	K.L. Becker *et al.*, 1963
46,XX/48,XX,E+,G+	Edwards' syndrome >DS	44	48	L.Y.F. Hsu *et al.*, 1965
46,XY/48,XY,E+,G+	Edwards' syndrome >DS	19	23	Tolksdorf *et al.*, 1965a
46,XY/48,XY,E+,G+	DS	20	22	Tolksdorf *et al.*, 1965a
46,XX,D-,D-,G+,t(DqDq)+	DS	24	27	Hustinx, 1966
46,XY,D-,D-,G+,t(DqDq)+	DS	30	29	Zergollern *et al.*, 1964
47,XX or XY, t(Cp+;Dq-),Gqi+	DS			Ruffie *et al.*, 1966a

TABLE 5–18

Examples of Other Chromosome Abnormalities Found in Close Relatives of Patients Affected with Down's Syndrome

Chromosomes in DS proband	Other abnormalities in family	Relationship to DS proband	Reference
21 +	47,XXY	Sib	Mosier *et al.*, 1960
21 +	47,XXY	Sib	Mosier *et al.*, 1960
21 +	45,X	Sib	Zellweger and Mikamo, 1961
21 +	49,XXXXY	Paternal aunt and ♀ first cousin	O.J. Miller *et al.*, 1961
t(GqGq)+ [a]	47,XXY	Sib	Benirschke *et al.*, 1962a
21 +	47,XYY	Daughter	Hauschka *et al.*, 1962
21 +	47,XXX	Sib	Breg *et al.*, 1962b
21 +	47,XXX	Sib	Breg *et al.*, 1962b
21 +	48,XXXX	Daughter	Bergemann, 1962a,b
21 +	46,XX/47,XXX	Granddaughter, daughter, niece, or sister	Bergemann, 1962a,b
21 +	45,X	Sib	Johnston and Petrakis, 1963
21 +	47,XXY	Sib	Wright *et al.*, 1963
21 +	47,XXY	Sib	Wright *et al.*, 1963
21 +	E+ (?18)	Sib	F. Hecht *et al.*, 1964
21 +	E+ (?18)	Sib	B. Turner *et al.*, 1964
21 +	Mar + [b]	Sib	Gustavson *et al.*, 1964c
21 +	69,XXY (Fetus)	Maternal aunt and distant relatives (two)	Penrose and Delhanty, 1961
21 +	t(DqDq)	Son	Hamerton *et al.*, 1963
21 +	t(DqDq)	Son	Gerald, personal communication, quoted by Hamerton, 1968a
t(DqGq)+ [a]	t(DqDq)	Son	Gerald, personal communication, quoted by Hamerton, 1968a
21 +	46,XY/49,XY,mar+,[c] mar+,[c] mar+,[c]	Daughter	Sergovich *et al.*, 1967

[a] Sporadic translocations.
[b] Here mar stands for extra-metacentric in male.
[c] Here mar stands for three small metacentric satellited chromosomes with satellites on both arms; a few cells with 47 and 48 chromosomes are also present.

estimate, these 616 patients represent 5.7×10^5 males. On this basis the incidence of double trisomics was 0.53×10^{-5} males. In six sex chromatin surveys of the newborn (see Taylor and Moores, 1967, for references) 23,229 live-born males were studied; 47 of these were chromatin positive and two were double trisomics (48,XXY,G+), an incidence of 8.62×10^{-5}. This was 18 times higher than the indirect estimate for the general population and 30 times higher than the expected frequency based on chance association (Table 5-19). These figures suggested that there was a much higher incidence of double trisomics at birth than would be expected by chance; the most satisfactory explanation for the reduced incidence among older groups was that double trisomics had a much higher mortality during the early years of life than the primary trisomics (see also Chapter 1, Section I).

The association of Klinefelter's syndrome and Down's syndrome in the same sibships has already been referred to (see Chapter 1) and would appear to occur more frequently than would be expected by chance although this is more difficult to establish.

3. Association of Miscellaneous Chromosome Anomalies with Down's Syndrome

Court Brown *et al.* (1965, 1966) and Court Brown (1967) have reported that about 2% of the general population may carry a variety of minor chromosome anomalies not associated with any known specific condition. These include minor changes involving the short arms of the D and G groups or involving the lengths of the long arm of No. 16 and the occurrence of satellites on a member of the 17-18 group. Finally, between 2 and 3% of males studied possessed a Y chromosome of unusual length (see Volume I, Chapter 4, Section III).

Hamerton *et al.* (1965) reported 7 out of 208 families in which similar anomalies occurred, an incidence of 3.5%. Three of the index patients had Down's syndrome with primary G-trisomy, two had Down's syndrome but had died before chromosome studies could be done, and two had normal chromosomes. In two of these families with a Down's syndrome index patient the father had an elongated Y chromosome, while in the other three families anomalies were seen in the satellite region of either a D or a G chromosome. In the two families in which the index patients had normal chromosomes D or G short arm anomalies were seen. In one of these the G chromosome had duplicated satellites and was transmitted through three generations. A family similar to this was reported by Therkelsen (1964b) where an anomaly of the short arm of a G chromosome inherited through three generations is associated

TABLE 5–19

Estimates of the Frequency with Which Other Chromosome Abnormalities Are Found To Be Associated with Down's Syndrome in One Individual

Type of double aneuploid	Incidence of DS	Incidence of other condition	Expected incidence of association assuming independent origin of both events	Observed	
				In newborn	In adults
48,XXY,G+	1:660	1:480 [a]	1:316,800	1:10,700 [b]	1:190,381 [b]
48,XXX,G+	1:660	1:1471 [c]	1:970,860	No data	No data
45,X,G+	1:660	1:2500 [d]	1:1,650,000	No data	No data
48,XX or XY, D+,G+	1:660	1:7602 [e]	1:5,017,320	No data	No data
48,XX or XY,E+,G+	1:660	1:6766 [e]	1:4,465,560	No data	No data

[a] See Chapter 1.
[b] Hamerton *et al.* (1965a); also Chapter 1.
[c] See Chapter 2.
[d] Maclean *et al.* (1964).
[e] Taylor (1968a).

TABLE 5–20

The Frequency with Which Y Chromosome Anomalies Are Found in Patients with Down's Syndrome

Population and reference	No. studied	No. of Y chromosome variants	Percent
Males with Down's syndrome			
Hall, 1964	31	2	
Edgren *et al.*, 1966	43	7	
Total	74	9	12.2
Fathers of DS patients			
Mikkelsen, 1967b	78	4	
Kahn and Abe, 1969	75	1	
Hamerton *et al.*, 1965	80	2	
Total	233	7	3.00
Total males with DS and fathers of DS patients	307	16	5.20
Males in general population			
Court Brown *et al.*, 1966	385	10	2.60

$\chi^2 = 3.15$ Df. 1. $0.1 > P > 0.05$

with Down's syndrome. The frequency of these minor anomalies both among patients with Down's syndrome and their parents is summarized and compared with findings in the general population in Tables 5-20 and 5-21. The autosomal variants are found twice as frequently among parents of affected children as they are in the general population. The frequency of Y chromosome variants does not, however, differ as between fathers of patients with Down's syndrome and males in the general population, although the frequency is significantly higher among affected males. The finding of a significant excess of autosomal variants in Down's syndrome populations and among Down's syndrome parents suggests that these anomalies may in some way affect the frequency of nondisjunction. They may be true structural rearrangements and hence directly affect pairing and segregation or they may represent an increased or decreased amount of heterochromatin which might affect nondisjunction (see Volume I, Chapter 7, Section II).

TABLE 5–21

The Frequency with Which Minor Autosomal Anomalies Are Found in Families with a Down's Syndrome Proband

Reference	Study population	No. of individuals	No. of autosomal variants	Per cent
Mikkelsen, 1967b	Down's syndrome	91	5	
Edgren *et al.*, 1966	Down's syndrome	73	5	
Hamerton *et al.*, 1965	Down's syndrome	173	5	
Kahn and Abe, 1969	Down's syndrome	86	4	
Total		423	19	4.49
Mikkelsen, 1967b	Parents of Down's syndrome	155	9	
Kahn and Abe, 1969	Parents of Down's syndrome	160	4	
Total		315	13	4.12
Court Brown *et al.*, 1966	Random population	756	17	2.25
$\chi^2 = 4.66$ Df.1.				$0.05 > P > 0.025$

J. *Summary and Conclusions—Chromosome No. 21 and Down's Syndrome*

The data available on the cytogenetics of Down's syndrome have been reviewed. No convincing case of Down's syndrome in the absence of G-trisomy has been reported. The phenotypic expression of the condition is relatively constant and shows a typical constellation of signs which is characteristic of chromosome trisomy, and it shows the same range of variation irrespective of whether the additional chromosome material is present as a separate chromosome (primary trisomy) or involved in a structural rearrangement (secondary trisomy).

An intermediate phenotype ranging from the full expression to an almost normal phenotype has been reported in mixoploids and would seem to depend on the proportion of cells involved and on their distribution. Similar partial phenotypic expression has been reported when part of the G chromosome is present in triplicate because of a deletion or other structural change. Chromosome trisomy enables hypotheses to be

tested regarding maternal age, twinning, etc., and the presence of translocations accounts for only some of the maternal age independent group. Evidence in other cases for a genetic predisposition to nondisjunction is becoming more definite.

We have moved far in our knowledge of this condition since Benda (1960) wrote:

> We are far from knowing whether the mitotic anomalies are the cause of mongolism as is so often claimed now or are another symptom at the cellular level . . . . I also believe that the optimism of some scientists who claim that the cause of mongolism is discovered and of a genetic nature is rather premature.

Clearly all the evidence reviewed and summarized above leads to the inescapable conclusion that trisomy of one of the G-group autosomes defined as No. 21 is the cause of Down's syndrome and that this condition is genetically determined and in some cases can be inherited. We are, however, still as far as ever from a knowledge of how the additional autosome acts to give the abnormal phenotype. There is no evidence of a specific biochemical lesion but more of a generalized imbalance in all cells. Various features suggest that Down's syndrome along with the other trisomic states results in developmental retardation and perhaps abnormalities of some switching mechanisms controlling cellular differentiation, and it is studies in this direction which might give useful results in the near future.

II. G-Trisomy Not Associated with Down's Syndrome

There have been a number of reports of children who do not have Down's syndrome but who do have an additional chromosome which resembles one of the G group autosomes (Table 5-22). The clinical features are variable, and there is insufficient evidence to implicate trisomy of chromosome 22. In general the parents have normal chromosomes, but in one instance the mother is a 46,XX/47,XX,G+ mixoploid.

These additional acrocentric chromosomes could originate from one of several mechanisms including nondisjunction and structural change, or they may simply be supernumerary chromosomes which occur as normal variants in some subjects. This, however, is perhaps less likely. There are 16 subjects (Table 5-22) in which primary 22-trisomy is a possible, though in most instances an unlikely, explanation. Three of these have subsequently been identified as possible 47,XYY males. Ten subjects may be divided as follows: two are schizoid mental defectives, one is mentally retarded without other gross malformations, three have mental retardation as well as various other congenital malformations, three subjects have a combination of coloboma and anal

TABLE 5-22

Case No.	Author	Date	Chromosome analysis	Author's conclusion
1	Hayward and Bower	1960	47,XY,?G+	22-Trisomy
2	B. Turner and Jennings	1961	47,XY,?G+	22-Trisomy
3	Dunn *et al.*	1961	47,XY,?G+	22-Trisomy or XYY
4	Biesele *et al.*	1962	47,XX,G+	22-Trisomy
5	Biesele *et al.*	1962	47,XX,G+	
6	Koulischer and Perier	1962	47,XX,G+ 46,XX/47,XX,G+	22-Trisomy Mother
7	Gustavson *et al.*	1962a	47,XX,?G+s-	Probably 18q- or compound chromosome
8	Gustavson *et al.*	1962a	47,XX,?G+s- (one G chromosome larger than remainder)	
9	Ferguson and Pitt	1963	47,XX,?G+	?22-Trisomy

Clinical Features of Non-Down's Syndrome G-Trisomics

Clinical features [a]	Comment
Sturge Weber (SW) syndrome	This condition is considered to be an example of dominant inheritance with low penetrance (Zellweger and Mikamo, 1961); 18 additional cases of SW show no chromosome abnormality. McKusick (1966) considered no clear-cut inheritance pattern established. Conclusion: Almost certainly not 22-trisomy or if so not associated with condition. Possibly XYY (Dent *et al.*, 1963).
Five years old. Destructive, anti-social and defiant. Some facial anomalies including retrognathia, flat occiput, and wide nostrils. Dull-normal intelligence. Schizoid	?XYY or fragment
Benign hypotonia. Developmental retardation. Microcephalic. Mentally retarded. Downward slant palpebral fissures. No other mongoloid signs. Retrognathia. Limited hip abduction. Fingers long and thin. Feeding difficulties. Cryptorchid with small penis, scrotum.	Possibly XYY or fragment
Twins – schizoid. Mental retardation. Otherwise no malformations. No mongoloid characteristics.	Origin of extra chromosome uncertain. Variable chromosome abnormalities have been found in schizophrenia.
CHD (Eisenmenger's complex). Sclerosis of bronchial arteries, hepatomegaly. Generalized hypotonia. Developed retardation. Small left ovary; right ovary absent. Attenuation of the cranial vault.	Mother mosaic primarily normal cells. Authors considered this to be 22-trisomy and that few cases are reported because of the high degree of lethality of the heart condition.
No mongoloid features. Mental retardation. Multiple malformations. Hypotonia. Microcephaly. Hearing impairment. Cleft palate. Micrognathia. Low set malformed ears. Absent E.A.M. A.S.D. secundum defect. Absent flection of fingers and hands.	Authors speculated whether this is an abnormal deleted 18 with part of the long arms missing, possibly a compound chromosome resulting from translocation in the mother or father but not detectable in somatic cells. Absence of satellites and increase in size suggests it is not a G.
M.A. 30. P.A. 34. Micrognathia. Enlarged malformed ears. Hypoplastic clavicles. Hemangioma. Left hip dislocated. Valgus feet. Developed retardation. Mental retardation. Hypotonia. Cardiovascular system normal. Urino-genital system normal.	No evidence for origin of additional chromosome. Possibly 22-trisomy or partial trisomy for 13-15.

TABLE 5-22 (cont'd)

Case No.	Author	Date	Chromosome analysis	Author's conclusion
10	Zaremba *et al.*	1966	47,XX,?G+	?22-Trisomy
11	Schachenmann *et al.*	1965	47,XX,?G+	Considered abnormal chromosome to be the product of a rearrangement, perhaps between two acrocentrics. No evidence as to type or which chromosome.
12	Schachenmann *et al.*	1965	47,XX,?G+	
13	Schachenmann *et al.*	1965	47,XX,?G+	
14	Schachenmann *et al.*	1965	47,XX,?G+	
15	Punnett and Vaughan	1966	47,XX,G+	?22-Trisomy
16	Townes and Ziegler	1964	46,XX,?G–,t(GqGq)+	Possible translocation 22-trisomy Parental chromosomes normal
17	Crawfurd and Lele	1965	46,XX,G–,t(GqGq)+	?Translocation 22-trisomy

Clinical features [a]	Comment
Eight years old. Low grade mental retardation. Mother has history of several spontaneous abortions and premature deliveries.	Abnormal chromosome probably not No. 22; may be a compound chromosome resulting from a translocation. This might account for the recurrent abortions.
M.A. 27. P.A. 40. Bilateral coloboma iridis and choroid microphthalmia. Anal atresia. Bilateral preauricular fistulae; rectal fistula opening into the vestibulum, behind the introitic vagina.	The additional chromosome is smaller than the G group and has a submedian centromere. Satellites and satellite association noted.
M.A. 34. P.A. 40. No mental retardation. Bilateral coloboma. Hypertelorism. Slight antimongoloid slant. Anal atresia with rectal fistula opening as in Case 11.	
M.A. 30. P.A. 29. Bilateral congenital dislocation of the hip. Coloboma iridis and choroid on left. Strabismus, hypertelorism. Imperforate anus with rectovestibular fistula. Mental retardation. Peculiar facies.	Chromosome mosaicism noted in brother of propositus and maternal uncle and maternal grandfather.
Mother of Case 13 – bilateral coloboma iridis. Cataract of left lens. Slight mental retardation.	Almost certainly not 22-trisomy.
Absence of pericardium. A.S.D. abnormal genitalia and Pierre Robin syndrome. Micrognathia, glossoptosis, cleft palate, bilateral eye defects.	Chromosome indistinguishable from G group.
M.A. 23. No signs of DS. Failure to thrive. Motor retardation. Hyperextensibility of hips. Short middle phalanx. Cervical ribs. A sixth lumbar vertebra and questionable subclinical A.S.D. No evidence of mental retardation.	Mild congenital malformations. Possible 22-trisomy. Alternatively a t(?;G).
Hyperextensibility of legs and neck at birth. Limited moro reflex. Occipitocephalic hematoma. No residual CNS deficit. Very slight developed retardation. M.A. 22. P.A. 23. Transverse flection crease on right hand. Single flection crease on both fourth fingers. Atd angles: R, 46°; L, 42°. Normal progress by 4 months. Possibly no mental retardation. No mongoloid stigmata.	21- or 22- monosomyand 16-trisomy unlikely. Abnormal chromosome too large to be an F. 21- or 22-monosomy and 18-trisomy, with pericentric inversion unlikely. Abnormalities at birth likely to result from birth trauma, except nasal stenosis. The possibility that this is an XXY karyotype with a t(Y;G) eliminating the short arms of the Y and hence the male determinants cannot be excluded. Chromosomal appearance is that of a Gqi. Completely symmetrical arms of non Y type.

TABLE 5-22 (cont'd)

Case No.	Author	Date	Chromosome analysis	Author's conclusion
18	Koulischer *et al.*	1966	46,XY,G-,t(GqGq)+	
19	Becak *et al.*	1963a	47,XY,?G+	

[a] Here M.A. stands for maternal age, P.A. for paternal age.

atresia; the mother of one of these patients has bilateral colobomata with cataract of the left lens and also has the abnormal chromosome complement. In the latter four subjects the additional chromosome is smaller than the other G autosomes and has a slightly more submedian centromere; it does, however, have satellites and associates with the other chromosomes in the G and D groups. The authors do not consider this chromosome to be No. 22 but feel that a more likely explanation is that it is the product of a structural rearrangement between two acrocentric chromosomes. A variety of chromosome abnormalities have been found in schizoid subjects (J. M. Anders *et al.*, 1968), and it seems unlikely that 22-trisomy would result only in schizophrenia or mental retardation without other congenital malformations. The additional chromosome in the two patients with schizophrenia is probably, therefore, a structurally rearranged chromosome leading to a small duplication or deficiency.

Three other patients with mental retardation and congenital malformation might be examples of 22-trisomy but the phenotype is insufficiently distinctive to merit the establishment of a new clinical entity (Table 5-22). (Koulischer and Perier, 1962; Ferguson and Pitt, 1963; Punnett and Vaughan, 1966.) Two patients (Gustavson *et al.*, 1962a) who have an atypical G-like chromosome which was slightly too large, lacked satellites, and could be an 18q−, in which case the phenotype might represent partial 18-trisomy (Chapter 6).

The three remaining subjects listed in Table 5-22 have a 46,XX or XY,G−,t(GqGq)+ chromosome complement. These could all be ac-

Clinical features [a]	Comment
M.A. 34. P.A. 36. Low birth weight (1900 gm). Developed retardation. Ptosis left eyelid. Large nose, broad base. Hypertelorism. Retrognathia. Clubfoot. Inguinal hernia. Scrotal right, inguinal left, testes. Supplementary hemivertebrae. Spina bifida. Bone age normal. Congenital heart disease. ? A.S.D. with enlarged pulmonary artery. Hypertonia. Single palmar crease. Atd $<57^{\circ}$. Axial triradius in position t.	Too great malformations to consider XYY. Features of DS insufficient to suggest translocation 21-trisomy. Possibly translocation 22-trisomy or 22qi. Authors considered possibility that this case and that reported in 1962 have the same chromosome complement (Case 6).
Hemangioma. Thrombocytopenia. Minor skeletal anomalies.	? XYY

counted for by a 21- or 22-monosomy and F-trisomy. The most likely explanation, however, is that the additional F group chromosome results from a translocation of the "Robertsonian" type (centric fusion) between the long arms of two G chromosomes. However, none of these subjects has more than extremely minor stigmata of Down's syndrome so it is unlikely that there is imbalance of chromosome 21. The two most interesting subjects are those reported by Townes and Ziegler (1964) and Koulischer *et al.* (1966). Both had multiple malformations including congenital heart disease and skeletal anomalies and might be said to resemble the patient with presumptive 22-trisomy reported in 1962 by Koulischer and Perier. The possibility therefore remains that these two patients had either a 22qi, t(21q22q), or t(22q22q). Finally, in this group there was one patient with an identical karyotype but with minimal malformations and very slight developmental and mental retardation (Crawfurd and Lele, 1965). The abnormal chromosome resembled a Gqi, but it is difficult to explain the minimal clinical features if this amount of duplicated autosomal material is present. It is possible that the zygote was 47,XXY and that early in cleavage a translocation occurred between the long arm of the Y and the short arm of a G autosome, resulting in a deletion of the short arm of the Y, which is thought to carry the male determining factors (see Chapters 1, 3, and 4), so that the resulting phenotype would be female and the karyotype balanced. This would account for the relatively mild malformations observed.

Recently, M. K. Moore and Engel (1968) have reported five chil-

dren with G-trisomy who were mentally retarded but who had only minimal features of Down's syndrome. Four out of the five could be classified as having atypical Down's syndrome. These may possibly be explained as mixoploids in which selection has favored the trisomic cell line to the exclusion of any normal cells. It seemed most likely that chromosome 21 was involved in four of these children. The fifth child had features of Patau's syndrome (Chapter 7) and the additional chromosome was considered to be a Dq−.

Van Gelderen *et al.* (1967) reported nine 46,XX or XY/47,XX or XY,G+ mixoploids with the frequency of the trisomic cell line ranging from 7 to 40% (see Table 5-14). The features of Down's syndrome were minimal but sufficient to suggest that chromosome 21 was involved, especially if the variable phenotype which has been shown to be associated with mixoploidy is considered.

There is still, therefore, no evidence for a clinical syndrome associated with 22-trisomy and most of the subjects who have been reported with this karyotype can be explained by other hypotheses.

III. G Group Deletions

Deletions of the short arm of a G chromosome (Gp−) occur as a variant of the normal karyotype with a frequency of about 1% in the general population. Deletion of the long arm of a G chromosome (Gq−) occurs in many cases of chronic myeloid leukemia. Recently, there have been nine patients reported who have a deficiency of group G material because of deletions resulting from ring chromosome formation, monosomy, or both (Table 5-23). The first of these subjects was described by Lejeune *et al.* (1964) who considered that the chromosome involved was the same as in Down's syndrome and that the clinical features were the antithesis of Down's syndrome; they referred to the condition as "*le contre type des stigmates de la trisomie 21*," and subsequently the term *antimongolism* has been coined (Reisman *et al.*, 1966). However, there seems little justification for this usage which implies first that these patients are the opposite of Down's syndrome and second that the chromosome involved is the same as that in Down's syndrome for which there is little evidence. There is little doubt that these patients have sufficient phenotypic features in common to be included in a clinical entity of their own (Fig. 5-18; Tables 5-23 and 5-24). Two of them are mixoploids (45,XY,G−/46,XY, Gr) (Fig. 5-19) while three have 46 chromosomes and only one cell line (46,XX or XY, Gr). Two patients have only 45 chromosomes and lack one G chromosome (45,XX or XY,

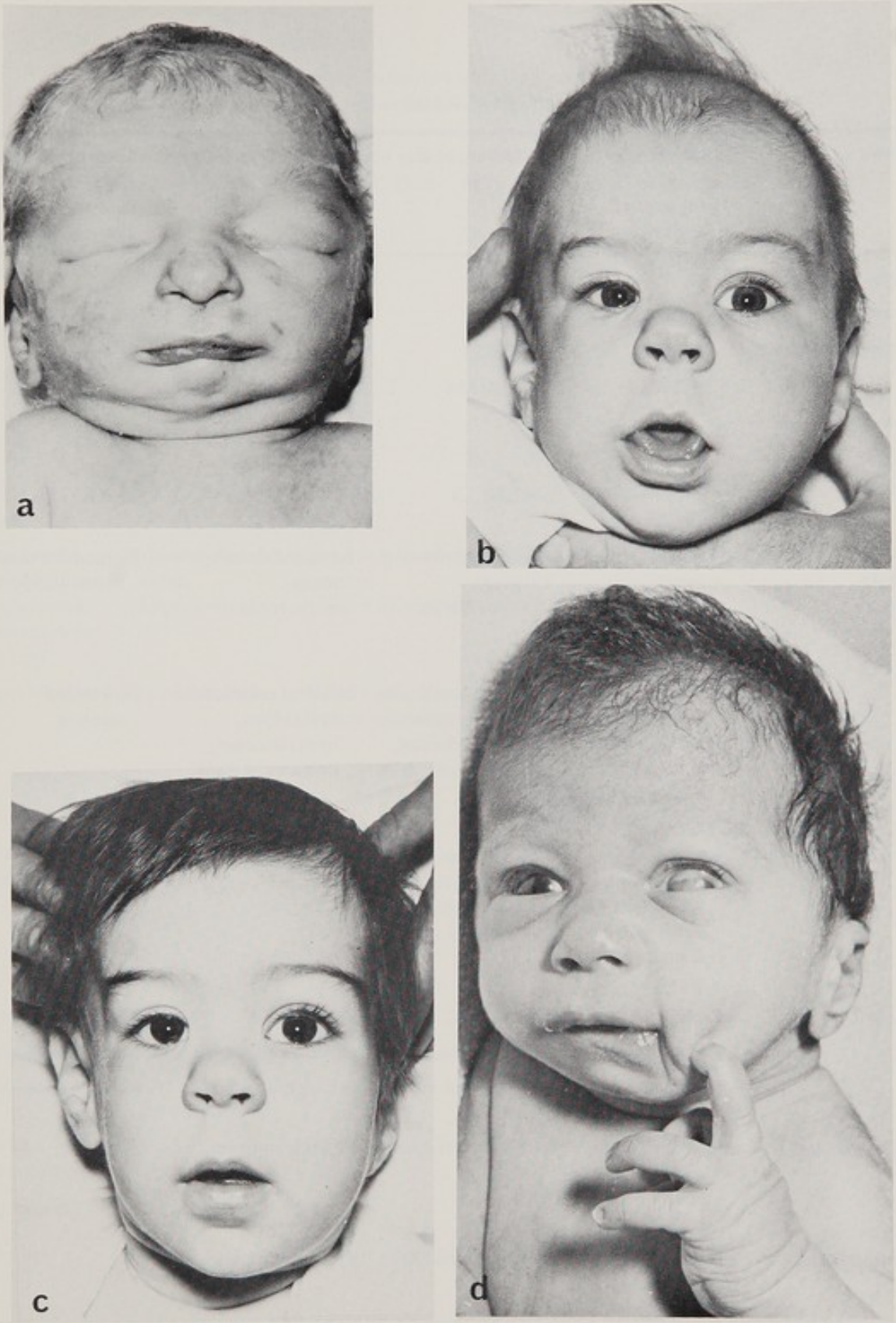


FIG. 5-18. Children with G group deletions: (a) patient reported by Reisman *et al.* (1966) (46,XY,Gr); (b) patient reported by Hoefnagel *et al.* (1967), age 5 months; (c) age 18 months (46,XX,Gr); (d) patient reported by Challacombe and Taylor (1969), (45,XY,G−/46,XY,Gr) (see Table 5-23 for clinical details).

TABLE 5-23

Feature	Lejeune *et al.*, 1964 Broyer *et al.*, 1966	Reisman *et al.*, 1966	Challacombe and Taylor, 1969	German and Bearn, 1966, quoted by Penrose and Smith 1966; German 1969.
Maternal age	27	18	23	37
Paternal age	28	23	40	47
Birth weight (gm)	2100	2035	2100	3647
Age	6/12	4/364	1/364	11 years
Age at death	–	–	–	–
Sex	♂	♂	♂	♀
Karyotype	45,XY,G–/46, XY,Gr	46,XY,Gr	45,XY,G–/46,XY, Gr	46,XX,G?r
Central Nervous System	Retarded development, hypertonia.	Retarded development, hypertonia.	Retarded development, hypertonia.	Normal development, IQ65.
Eyes	Pupillary membrane present. Bilateral cataracts, blepharochalasis, downward slant.	Bilateral cataracts, blepharochalasis, hypertelorism, downward slant.	Bilateral cataracts. epicanthus, hypertelorism, downward slant.	Downward slanting
Ears	Large, low-set, malformed. Asymmetrical with wide external auditory meatus.	Large, low-set, malformed; wide external auditory meatus.	Large, low-set	Prominent
Nasal bridge	Prominent	Prominent	Prominent	Prominent
Skull	Microcephalic	Microcephalic	Dolicocephalic	Dolicocephalic
Jaw	Micro- and retrognathia	Micro- and retrognathia	Micrognathia	Retrognathia
Cardio-Vascular System	Systolic murmur	Systolic murmur	Systolic murmur	–
Gastrointestinal	Meckel's diverticulum, pyloric stenosis.	Pyloric stenosis	Pyloric stenosis	–

Clinical Features of Nine Patients with a Deficiency of G-Chromosome Material because of Deletion or Monosomy

Engel *et al.*, 1966	Hoefnagel *et al.*, 1967	Thorburn and Johnson, 1966	Hall *et al.*, 1967	Hindle (quoted by Challacombe and Taylor, 1969)	Mean
22	24	18	30	43	26.89
27	23	–	32	–	31.4
–	2858	–	2660	2150	2507.1
12 years	5/12	12/12	Birth	20/12	
–	–	12/12	1/12	–	
♀	♀	♀	♂	♂	5 ♂4 ♀
46,XX,Bp-,G?-,Gr+	46,XX,Gr	45,XX,G-	45,XY,G-	46,XY,?Gr	
Retarded development, hypertonia, mental retardation	Retarded development, hypertonia.	Retarded development, slight hypertonia.	Development normal, hypertonia.	Retarded development, hypertonia.	
Hypertelorism	Epicanthic folds	Downward slanting	Blepharochalasis, downward slanting eccentric pupils.	Downward slanting	
Asymmetrical and rotated	Normal	Large, low-set, malformed	Dysplastic	Low-set misshapen helix of left ear.	
Prominent	Prominent	Prominent	Prominent	Prominent	
Microcephalic	Microcephalic	–	Normal	–	
Retrognathia	Mandibular asymmetry	–	Micro- and retrognathia	Micrognathia	
? Patent ductus arteriosis	–	Normal	Multiple congenital heart defects.	Systolic murmur	
Normal	–	Normal pylorus	Normal	Pylorus normal, ? achalasia of cardia.	

TABLE 5-23 (cont'd)

Feature	Lejeune *et al.*, 1964 Broyer *et al.*, 1966	Reisman *et al.*, 1966	Challacombe and Taylor, 1969	German and Bearn, 1966, quoted by Penrose and Smith 1966;German, 1969
Genitourinary	Bilateral inguinal herniae, renal agenesis, hypospadias.	Undescended testes, renal agenesis, hypospadias.	Right inguinal hernia, undescended testes, hypospadias.	Normal
Skeleton	Thirteenth rib acetabular and iliac indices normal. Growth retarded	Iliac indices normal. Sacral hemivertebrae; retarded growth.	Retarded growth. Normal skeleton.	Normal
Hands and feet	Small index finger. Koilonychia.	Flextion deformity. Koilonychia.	Flextion deformity. Retroflectible thumbs. Abnormal feet; "rocker bottom."	Long fingers and toes
Blood Leuocyte	Raised	Normal	Normal	–
Alkaline Phosphatase				
5-Hydroxy-Indole Acetic Acid/ Kynurenine Ratio.	Raised	–	Normal	–
Hypo-γ-globulin	Present	–	–	–
$\gamma^A \gamma^m$	Normal	–	–	–
Thrombocytopenia	Present	Present	Present	–
Granulocyte lobe count	2.66	Normal	–	–

G–). The phenotype of these children consists of relatively severe congenital malformations presumably resulting from monosomy or deletion. Some of the features appear to be the antithesis of those malformations seen in Down's syndrome. The term *antimongolism* is, however, misleading, at least until it is established that the chromosomes involved are the same.

Two older and less malformed children have also been described (Table 5-23). Both have one cell line; in the first the chromosome complement was 46,XX,Gr, while in the second there was also a B chromosome deletion (Bp–) as well as a G chromosome deletion (46,XX,Bp–, G?– or Gr). She had some features of the *cri du chat* as well as features associated with a deletion of a G group chromosome. The two older children had less severe malformations than the seven infants, and this may be associated with the fact that four of the infants had a substantial

Engel *et al.*, 1966	Hoefnagel *et al.*, 1967	Thorburn and Johnson, 1966	Hall *et al.*, 1967	Hindle (quoted by Challacombe and Taylor, 1969)	Mean
No palpable uterus, normal kidney.	–	Normal	Inguinal hernia, scrotal dysplasia, testes in inguinal canal.	Undescended testes, scrotal dysplasia.	
Hypermobile joints	Skeleton abnormal	Normal skeleton	Skeleton abnormal	Retarded growth, iliac angles normal. Sixth lumb. vert. thirteenth rib.	
Long fingers. Deformed little finger.		Slight flextion deformed retroflex thumbs	Koilonychia. Hyperconvex nails.	Normal	
Normal	Normal	–	Normal	Normal	
–	–	–	–	–	
–	–	–	–	–	
–	–	–	–	–	
Present	–	–	–	Platelets normal	
Normal	3.23	–	–	–	

monosomic cell line. The main phenotypic features of these nine children are contrasted with the features of Down's syndrome in Table 5-24.

It is interesting that in contrast to Down's syndrome there is a reduction in maternal age in these patients. This is surprising, especially if the G-monosomic gametes were produced as a complement to the trisomic gametes, which would imply that the primary event was nondisjunction. It can therefore be argued that the origin of these subjects was by way of a postzygotic structural change followed by chromosome loss rather than by meiotic nondisjunction followed by structural change.

The most likely hypothesis suggests the formation of a ring chromosome (see Fig. 8-2, Volume I) followed by loss of the ring from some cells. The well-known instability of ring chromosomes might suggest that the Gr line is constantly throwing off G− cells and this might account for the two G− subjects. Alternatively a few of these subjects may re-

TABLE 5-24

A Generalized Comparison between the G+ and G del Phenotype

Characteristics	46,XX or XY,Gr or 46,XX or XY,G- or 45,XY,G-/46,XY,Gr (nine cases)	47,XX or XY,G+ (numerous cases)
Mean maternal age (years)	26.9	34.43
Mean paternal age (years)	31.4	–
Gestation	Normal	Normal or slightly reduced
Male sex	5/9	No variation in sex ratio
Birth weight (gm)	2507	Normal or slightly reduced
Central nervous system	Retarded	Retarded
Muscular system	Hypertonic	Hypotonic
Eyes	Blepharochalasis. Downward sloping palpebral fissure; bilateral cataracts; persistent pupillary membrane, hypertelorism, abnormal facies.	Outward mongoloid slant to palpebral fissure. Epicanthic folds. Brushfield's spots. Abnormal facies.
Ears	Large, low-set, malformed	Usually small with small external auditory meatus.
Nose	Prominant nasal bridge	Usually depressed, often small.
Skull	Microcephalic, often dolicocephalic	Reduced cephalic index resulting from brachycephaly.
Jaw	Micrognathia and retrognathia	Often slight retrognathia.
Heart	Usually a systolic murmur. Two subjects with congenital heart disease.	Congenital heart disease common. Often auriculo-ventricula defects.
Gastro-intestinal system	Meckels diverticulum or pyloric stenosis (3/5)	Duodenal atresia common.
Limbs, hands and feet	Often abnormal with long fingers and toes and abnormal nails. Axial triradius in *t* position. Normal palmar creases.	Fingers and toes short and stubby. Distal axial triradius (t″), short fifth finger, single palmar crease.
Skeleton	Normal or increased iliac index; retarded growth.	Absence of rib. Decreased iliac index. Retarded growth.
Genitourinary	Renal agenesis, cryptorchidism, hypospadias, inguinal hernia.	Infantile genitalia, small penis, some cryptorchidism.
Blood	Thrombocytopenia, normal lobe count, Leuocyte Alkaline Phosphatase normal, hypo γ-globulinemia.	Reduced lobe count, increased LAP, hyper γ-globulinemia.

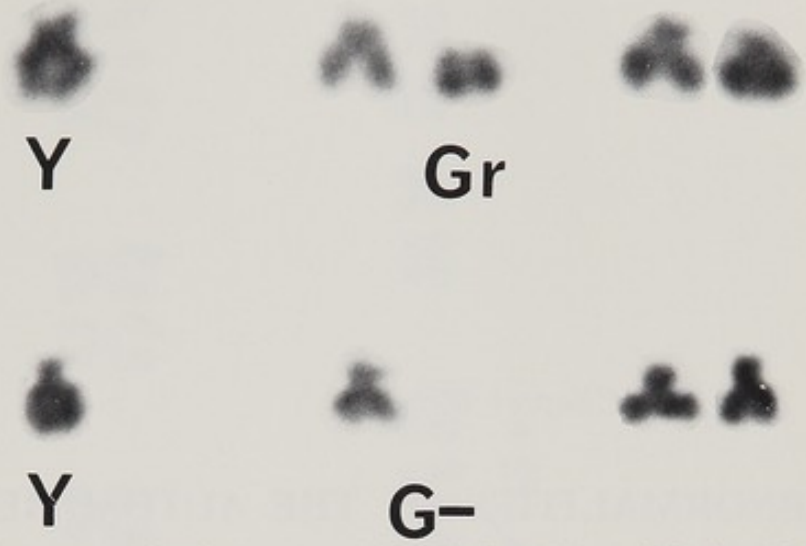


FIG. 5-19. Partial karyotype of patient reported by Challacombe and Taylor (1969) showing one cell line with a Gr and the other with a missing G chromosome (G–) (× 4000 aceto orcein). (Courtesy of Dr. A. I. Taylor.)

sult from nondisjunction, giving a simple monosomic cell line. The variability of the phenotype is hardly surprising when some subjects carry a partial deletion while others are wholly monosomic; the latter, as expected, being the more grossly malformed. The size of the deletion may vary, and there is also the possibility of duplication as the result of doubling of the ring.

In conclusion, both trisomy and monosomy of a G chromosome lead to characteristic phenotypes. These both show the characteristic hallmark of chromosome imbalance, mental and developmental retardation combined with congenital malformation.

Chapter 6

ABNORMALITIES OF THE AUTOSOMES—GROUP E (16-18 GROUP—DENVER CONFERENCE)

I. Edwards' Syndrome (47,XX or XY,18+)

A. *Nonmixoploid*

In 1960 Edwards and his colleagues described the first patient with multiple congenital anomalies and E-trisomy; they considered that on morphological grounds the extra chromosome was homologous to No. 17. At almost the same time, Patau *et al.* (1960) reported a similar patient also with E-trisomy and they identified the extra chromosome as homologous to No. 18; subsequently, the Wisconsin group reported several additional cases all of which they concluded had 18-trisomy (Fig. 6-1) (D. W. Smith *et al.*, 1960; Patau *et al.*, 1961a). The syndromes described by both groups of investigators were clinically similar, and despite various suggestions to the contrary it seems likely that they are caused by trisomy of the same autosome. It is sometimes possible to separate the 17-18 group into two pairs according to their morphology: one of these chromosomes is longer and more mediocentric while the other is shorter and less mediocentric. The presence of a fifth chromosome in this group usually makes this separation more difficult, and it is less easy to assign the additional chromosome to one or the other pair on morphological grounds alone. Autoradiographic studies have shown that the chromosome involved in E-trisomy is the one which completes

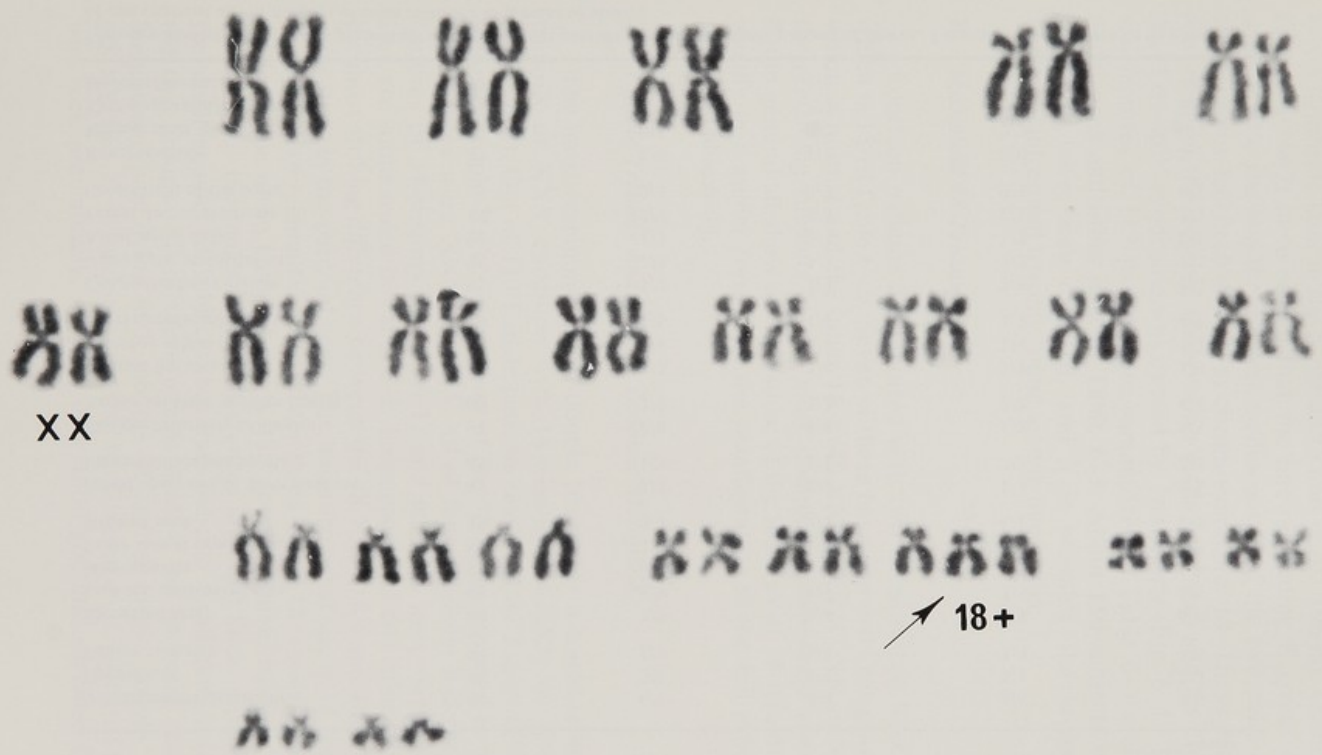


FIG. 6-1. Karyotype of female patient with primary E-trisomy.

TABLE 6-1

Clinical Features of E-Trisomy

Major clinical features	47,XX or XY,E+ (*a*) (119 cases)	Mixoploids (*a*, *b*) (14 cases)	48,XXX,18+(*a*, *b*) (4 cases)	48,XXY,18+(*a*, *b*) (3 cases)	Translocation trisomics (*a*, *b*) (6 cases)
Developmental retardation	100	6/7	4/4	1/1	6/6
Hypertonia	75	3/5	1/1	1/1	2/3
Failure to thrive	97	5/7	4/4	3/3	3/5
Elongated skull	88	7/8	4/4	3/3	6/6
Low-set, malformed ears	99	8/9	4/4	3/3	6/6
Micrognathia	97	6/6	3/3	3/3	5/6
Extra skin at nape of neck	50	2/5	2/2	3/3	3/3
Webbed neck	25	0/3	0/1	1/1	2/3
Shield chest and/or short sternum	87	6/7	2/3	1/1	5/5
Inguinal/umbilical hernia	45	1/3	1/2	2/2	2/2
Flexion deformity of fingers	94	8/8	4/4	1/2	5/5
Arches on three or more fingers	100	2/2	2/2	2/2	4/4
Limited hip abduction	87	3/3	3/4	2/2	3/3
Calcaneo valgus feet	63	6/6	3/3	1/1	3/3
Short dorsiflexed hallux	79	4/5	4/4	2/3	4/4
Congenital heart disease	>95	5/7	3/3	2/3	4/4
Ventricular septal defect	96	2/3	3/3	2/2	2/2
Atrial septal defect	22	1/3	0/3	1/2	0/1
Patent ductus arteriosis	69	2/2	0/3	0/1	2/2
Coarctation of the aorta	9	0/3	0/3	0/1	0/1
Renal anomaly	57	4/4	1/2	0/0	2/2
Normal renal tract	37	0/3	0/2	2/2	0/1
Thin diaphragm/eventration	35	0/1	1/2	0/1	0/0
Meckels Diverticulum	46	1/1	1/2	0/0	0/0

[a] Primary 18+-trisomy given as percentage calculated from number of cases definitely present or absent. In smaller groups given as number of cases present out of number of cases recorded as present or absent.

[b] References and chromosome complement given in Table 6-2.

DNA synthesis later in the S period (Yunis *et al.*, 1964a). Giannelli and Howlett (1967) have shown that the late-replicating E group chromosome is also the shorter and less mediocentric of the two pairs and this chromosome has been defined as chromosome No. 18. These data therefore confirm the original observation made by Patau and his colleagues that Edwards' syndrome was caused by 18-trisomy (Fig. 6-1). The clinical features of 119 patients are summarized in Table 6-1 and the parental ages and other data in Table 6-3. About 150 subjects with this condition have been reported, and it is probably the second most common autosomal trisomy found among live births.

B. *Mixoploid 18-Trisomy*

Fourteen patients are reported with two or more cell lines, one of which is 18+ (Table 6-2). Seven of these have two cell lines only, one of which is normal and the other 18+ (46,XX or XY/47,XX or XY,E+); the remaining subjects have a more complex chromosome constitution but in general all show at least some of the features of 18-trisomy, albeit usually in a milder form than the manifestation in the full primary trisomics (Table 6-1).

C. *Double Trisomy and Double Trisomic Mixoploidy*

The most common form of double trisomy is a combination of the triplo-X or XXY condition with 18-trisomy (48,XXX or XXY,18+) (Table 6-2). Out of 113 female patients reviewed by Taylor (1970) four were also triplo-X (3.5%), and out of the 30 males reported in the same paper, three were XXY (10.0%). All of these patients had the clinical features of 18-trisomy (Table 6-1) and parental ages, survival times, etc., are summarized in Table 6-3. Examination of this table shows that the most striking difference between the 48,XXX,18+ and 48,XXY,18+ subjects is in the parental ages. The mean maternal age is 31.5 years for four XXX,18+ females and 43.3 for three XXY,18+ males, while surprisingly the mean paternal age is 28.5 for the double trisomic females and 45.0 for the males. These differences are most likely a reflection of the small number of subjects, but may indicate a different etiology for the two groups. All of these infants died in the neonatal period, the longest survivor dying at 2 months of age. A single double trisomic (48,XY,18+,21+) has been reported by Gagnon *et al.* (1961). This child was born prematurely, weighed only 1500 gm, and survived for 8 hr.

TABLE 6-2

Chromosome Findings in Some Cases of Variant E-Trisomy

Chromosome constitution	No. of cases	Reference
Mixoploids		
46,XX/47,XX,18+	6	Koulischer *et al.*, 1963; Hook and Yunis, 1965; U. Wolf *et al.*, 1965b; Warkany *et al.*, 1964; De Toni *et al.*, 1966
46,XY/46,XY,18+	1	Kulakowski *et al.*, 1966
46,XX/47,XX,18+/48,XX,18+,18+	1	Taylor, 1968a
47,XX,18+/48,XX,18+,18+	1	Taylor and Polani, 1964
47,XXX/48,XXX,18+	1	Engel *et al.*, 1965c
46,XX/48,XX,18+,21+	1	L. Y. F. Hsu *et al.*, 1965
47,XY,18+/48,XY,18+,21+	1	Tolksdorf *et al.*, 1965a
47,XX,D+/47,XX,E+	1	Baikie *et al.*, 1965b
46,XY,D−,t(DqGq)+/46,XY,D−,G−, t(DqGq)+,E+/47,XY,D−,t(DqGq+),E+	1	Porter and Brown, 1966
Double Trisomics		
48,XXX,18+	4	Uchida and Bowman, 1961; Uchida *et al.*, 1962a; Ricci and Borgatti, 1963; Taylor, 1968a; Haas and Lewis, 1966
48,XXY,18+	3	Taylor, 1968a; Pfeiffer, 1964b; Haylock *et al.*, 1963a
48,XY,18+,21+	1	Gagnon *et al.*, 1961
Translocations and Structural Variants		
46,XY,Dq+mat proband	1	Brodie and Dallaire, 1962
45,XX,t(Dq+;Eq−) mother	1	Dallaire, 1969
46,XX,D−,t(DqEq)	1	F. Hecht *et al.*, 1963
46,XX,E−,t(EqEq)	1	Rohde *et al.*, 1963
47,XX,?E?i+	1	J. Q. Miller *et al.*, 1965
46,XX,Ds+mat,18−,?18p+q+	1	Taylor, 1968a
46,XX,4q+	1	Gagnon *et al.*, 1963a

The clinical features were described as a mixture of Down's syndrome and 17-18 trisomy with the latter predominating. There are several double trisomic mixoploid subjects with various chromosome complements (Table 6-2). The phenotype in these cases is usually milder than the full 18-trisomy, and these children usually survive longer than either primary 18-trisomics or double trisomics.

TABLE 6-3

Data on Some Patients with Numerical and Structural Abnormalities of an E Group Chromosome[a]

	18+	Mixoploids	XXX,18+	XXY,18+	Structural trisomy	18p−	18q−	18r
Mean maternal age at birth (years)	31.7±0.7	28.9 (9)	31.5 (4)	43.3 (3)	23.2 (6)	32.4 (18)	30.4 (10)	26.1 (8)
Mean paternal age at birth (years)	34.9±0.8	33.0 (9)	28.5 (4)	45.0 (3)	30.5 (6)	35.0 (17)	34.1 (10)	29.5 (6)
Gestation age (weeks)	42.2±0.8	39.7 (4)	42.0 (3)	40.0 (2)	39.2 (6)	Term	Term	Term
Birth weight (gms) (mean)	2242±35	2167 (8)	2213 (3)	2557 (3)	2312 (6)	2946 (9)	2977 (9)	3019 (5)
Mean age at death (days)	70.85 (variance > mean)	174 (range 42-395)	45	7.3	48-111	Variable > 16 years	Variable > 15 years	Variable > 13.5 years
Sex ratio females/total	113/143	11/14	–	–	5/6	12/17	7/12	3/6
Total No. of subjects	153	14	4	3	6	18	15	9

Summary

	Maternal age	Paternal age	
Aneuploids	35.5	36.1	(including double aneuploids)
Mixoploids	28.9	33.0	
Structural anomalies	27.6	31.8	
Birth weight:			
E duplication	2298 gm.		
E deletion	2981 gm.		

[a]Figures in parentheses represent number of subjects.

D. *Structural Chromosome Rearrangements Resulting in 18-Trisomy*

Six subjects have been reported (Table 6-2), five of whom had presumptive translocations which had resulted in duplication of the larger part of the long arm of an E chromosome; the sixth was a secondary trisomic with a presumptive isochromosome. The clinical findings are given in Table 6-1 and other data in Table 6-3. Examination of Table 6-1 indicates that the clinical features of these translocation trisomics are indistinguishable from primary 18-trisomy despite a presumptive deletion of the short arms and centromeric region of the third E chromosome which must have taken place during the structural rearrangement. With the single exception of the subject reported by Brodie and Dallaire (1962) in which the mother was a balanced heterozygote (Fig. 6-2) all the remaining subjects had sporadic translocations while the chromosomes of the parents were normal[16]; therefore, the translocations can only be con-

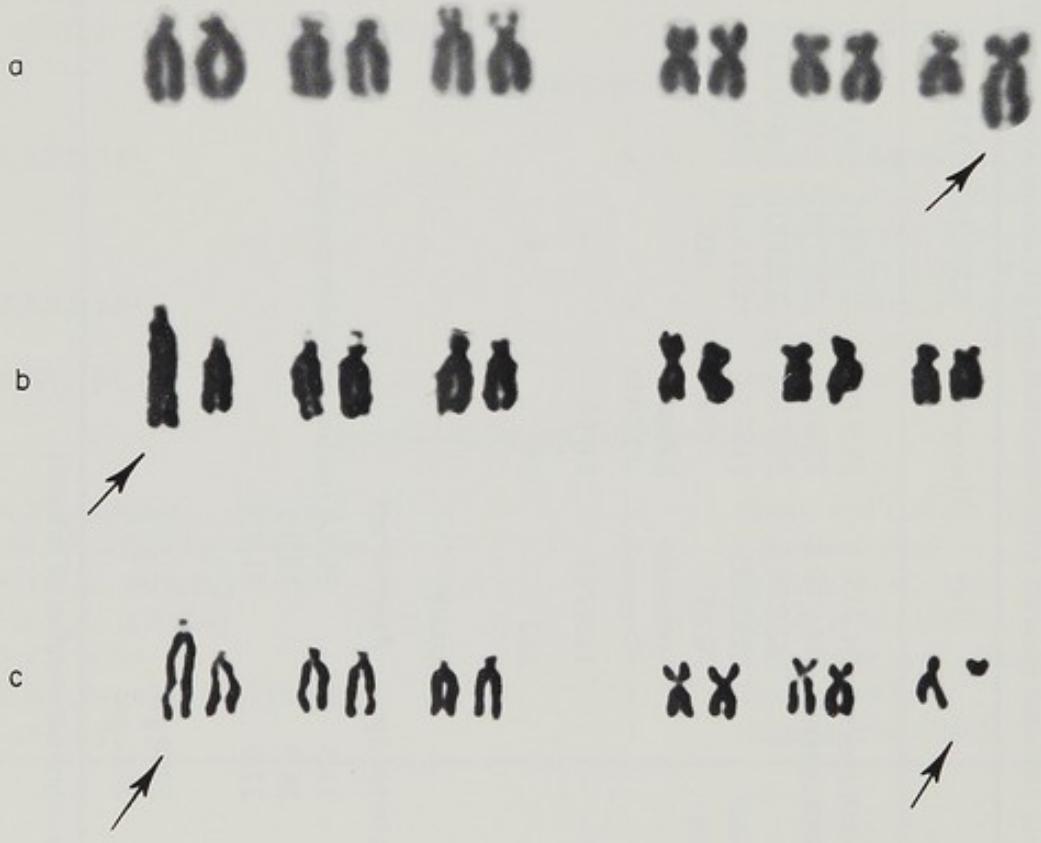


FIG. 6-2. (a) Partial karyotype of a patient with ?EP+q+ and clinical E-trisomy reported by Taylor (1967, 1968a) (b) Partial karyotype of patient reported by Brodie and Dallaire (1962) with a t(Dq+) and (c) the balanced karyotype found in his mother t(Dq+; Eq−).

[16]Two additional children have been born in this family; both are phenotypically normal and have an identical karyotype to their mother (balanced heterozygotes) (Dallaire, 1969).

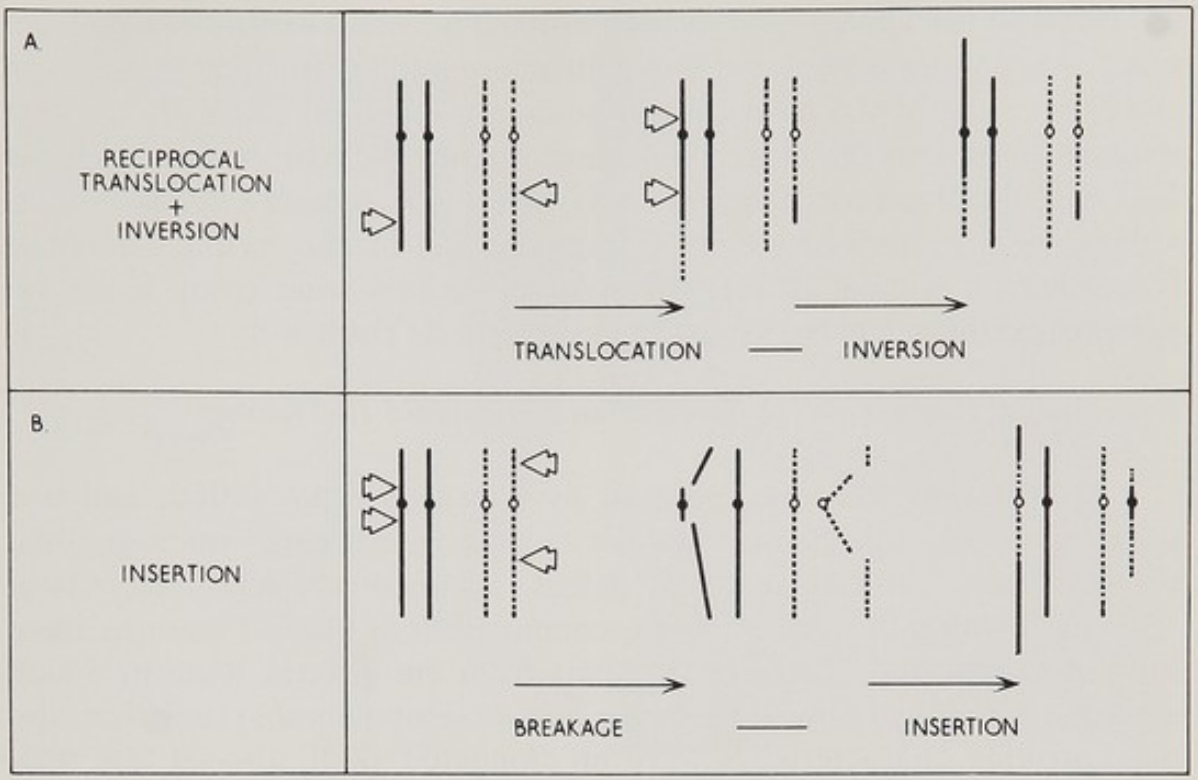


FIG. 6-3. Two possible mechanisms by which the ?Ep+q+ chromosome shown in Fig. 6-2a might have arisen: (a) reciprocal translocation and inversion and (b) double insertion type of rearrangement (see text).

sidered to be presumptive. Two of these translocations involved a D and an E group chromosome (Brodie and Dallaire, 1962; F. Hecht *et al.*, 1963), two involved two E group chromosomes (Rohde *et al.*, 1963; Taylor, 1967, 1968a), while a third had a presumptive isochromosome for the long arm of one E (J. Q. Miller *et al.*, 1965) and so was effectively a tetrasomic. The sixth subject (Gagnon *et al.*, 1963a) had a presumptive t(Y;E) which has resulted in duplication of E group material.

The product of the presumptive t(E;E) reported by Taylor (1967, 1968a) was an abnormal chromosome which could not have resulted from a simple reciprocal translocation between the long arms of two E group chromosomes (Fig. 6-2) since it had both elongated long and short arms. Two possible mechanisms are illustrated (Fig. 6-3), the first involves a reciprocal translocation between the long arms of two E chromosomes with breaks in the distal region of one and the proximal region of the other. This is then followed by a pericentric inversion which shifts the centromere to a more median position. The second mechanism postulates an insertion which requires four breaks in two E chromosomes: one break in the short arm and one in the long arm of one E chromosome close to the centromere, while in the other chromosome the breaks

are distal to the centromere in both arms. The small centric region from one chromosome is lost, and the centromere and greater part of the long and short arms of the other chromosome are inserted. Formally the first explanation seems the most likely since it is the simpler and involves the loss of a small centric fragment only, while the second explanation involves the loss both of a centric fragment and of two terminal acentric fragments. A number of other translocations involving group E are reported, and these will be discussed in Chapter 8 (Table 8-8).

E. *Clinical Features of 18-Trisomy and Mixoploid 18-Trisomy*

The first subject was reported by Edwards *et al.* (1960) and had developmental retardation, low-set and pointed ears, micrognathia, webbed neck, ventricular septal defect, and neonatal hepatitis. About 150 cases which fit into this basic combination of clinical features have now been reported (Table 6-1). Apart from the general features which included a uniform failure to thrive and developmental retardation, the most striking characteristics were an elongated skull, low-set and malformed ears, and micrognathia (Fig. 6-4). Shield-shaped chest and short sternum were common as well as various joint abnormalities including a flexion deformity of the fingers and limited hip abduction; most subjects had some abnormality of the feet and limbs (Fig. 6-5). Congenital heart disease was common in most affected subjects; this was usually a ventricular septal defect while 69% of patients had a patent ductus arteriosus (Taylor, 1967, 1968a). Most subjects had simple arches on all or nearly all of the digits (Fig. 6-6). Uchida *et al.* (1962b) found a minimum of three arches in one and a maximum of 10 arches in seven of their 15 patients. Three out of the remaining seven patients had nine arches, one eight, two seven, and one six arches; while 82.9% of the controls had no arches on their fingertips, a difference which is highly significant. Most of these patients had very short fifth digits with only a single crease. These findings have been confirmed by Penrose (1963) who stated that there was no obvious abnormality of the palms which had relatively normal axial tri-radii and a normal crease pattern. The hallucal areas of the soles had fairly wide open fields, and arches were found on the toes (Fig. 6-6).

The clinical features of the seven 46,XX or XY/47,XX, or XY,18+ mixoploids together with one XXX,18+ mixoploid, two mixoploid double trisomics, and one trisomic/tetrasomic-18 mixoploid have been contrasted with the full primary trisomics in Table 6-1; it can be seen that while the main features were similar, the phenotype of the mixo-

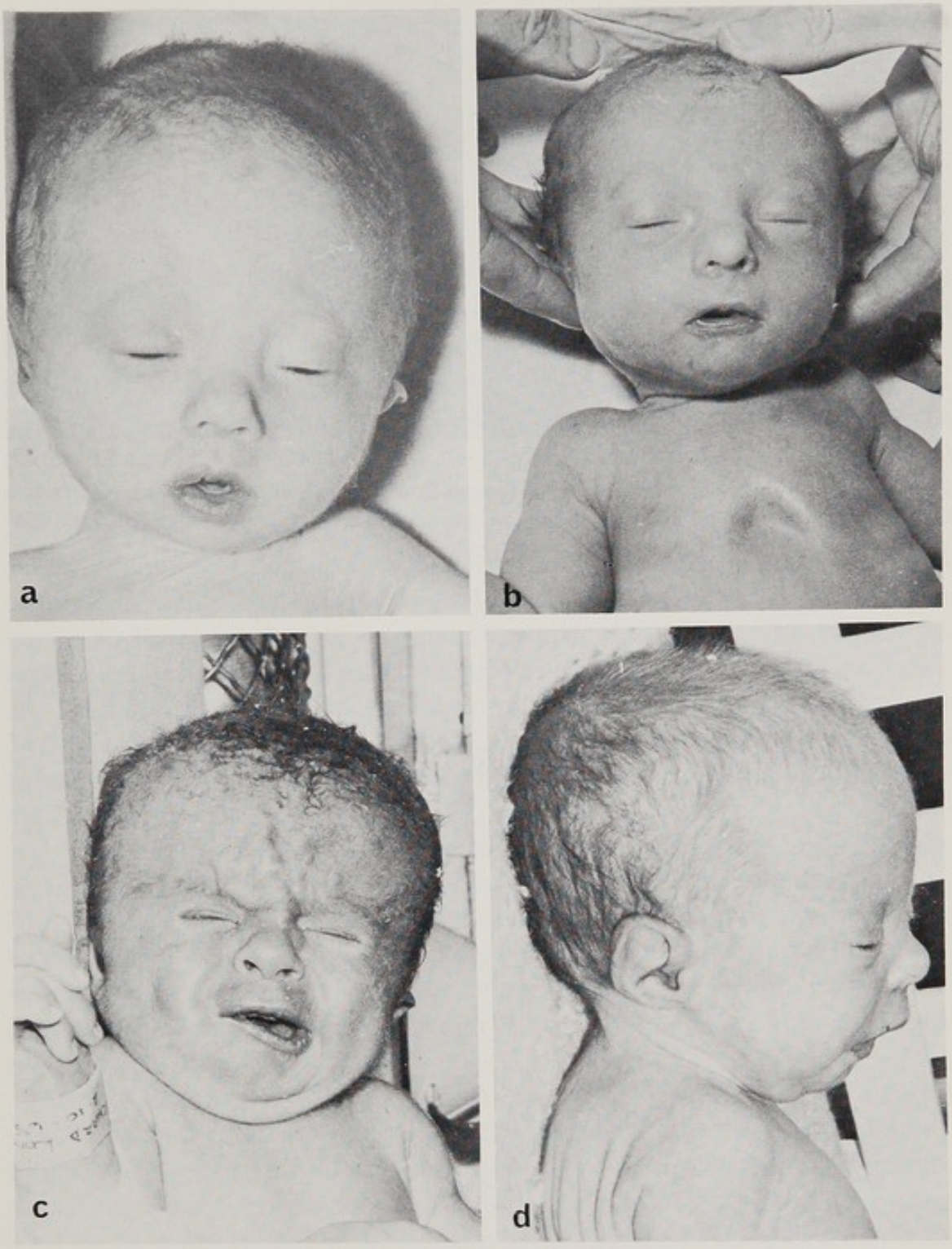


FIG. 6-4. Some clinical features of Edwards' syndrome showing: (a) round face, microophthalmia, and microstomia; (b) abnormally short sternum; (c) low-set ears and unilateral facial palsy; (d) micrognathia, primitive ears, and redundant skin folds of neck and back. (Reproduced by courtesy of Dr. A. I. Taylor.)



FIG. 6-5. Foot and hand abnormalities in Edwards' syndrome showing: (a) flexion deformity of the fingers and (b) hypoplastic big toe and syndactyly of second and third toes. (Reproduced by courtesy of Dr. A. I. Taylor.)

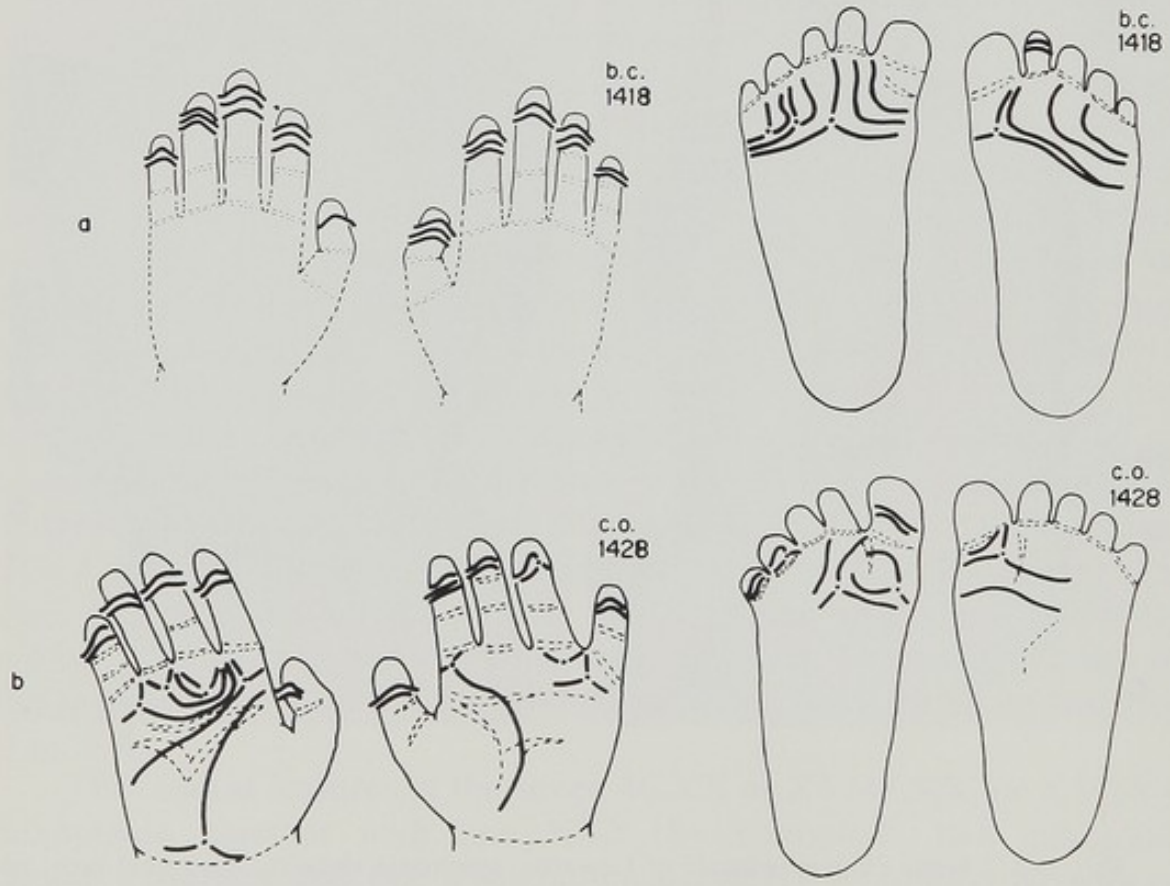


FIG. 6-6. Dermatoglyphic findings in two patients with E-trisomy. Note high frequency of simple arches, normal palmar patterns, open fields in hallucal areas of soles, and simple arches on toes. (From Taylor and Polani, 1964.)

ploids was much milder and the mean survival time much greater (Table 6-3).

F. *Anamnestic and Epidemiological Data in 18-Trisomy*

1. Parental Age

The mean maternal age for 153 18-trisomics was 31.7±0.7 years compared with the age for the general population of 28.0 years (Table 6-3). The maternal age distribution curve (Fig. 6-7) is apparently bimodal, although the numbers on which this is based are small. This is similar to the observation made by Penrose (1961) on the bimodality of the maternal age distribution curve in Down's syndrome (see Chapter 5), which he considered indicated a maternal age independent group and a maternal age dependent group of Down's syndrome patients. There are, as yet, insufficient data to indicate whether two similar subgroups of 18-trisomic patients exist; the bimodality of the maternal age distribution curve is, however, highly suggestive, particularly since the modes fall between 21 and 25 years and 36 and 40 years. However, additional data are required to confirm these observations. The mean paternal age is 34.9 (Table 6-3) compared with a control mean for the general population of 31.7 years. This, however, probably simply reflects the increased maternal age.

The mean maternal age at the birth of nine mixoploid subjects with an E-trisomic cell line was 28.9 years, while the mean paternal age was 33.0 years (Table 6-3). These data showed a lowering of the mean maternal age at birth of the mixoploids as compared to the primary trisomics. This suggested that some of the mixoploids resulted from nondisjunction during the early cleavage of a normal zygote rather than from a trisomic zygote.

Five patients (Table 6-3) with the clinical features of Edwards' syndrome had presumptive reciprocal translocations involving either a D and an E group chromosome or two E group chromosomes. One had a presumptive isochromosome for the long arm of one E chromosome. The mean maternal age in this group was reduced to 23.2 years and the paternal age to 30.5 years. The extreme difference between the maternal and paternal ages in this group was significant as well as the reduction in maternal age when compared to the controls. In five out of these six cases the translocation was sporadic while in one the mother was a balanced heterozygote.

Examination of the maternal and paternal ages in the small group of double trisomics indicated an extreme age effect. The mean maternal age

at the birth of these patients was 37.4 years while the paternal age was 36.8 years. This increase was almost entirely accounted for by the very high parental ages found in 48,XXY,18+ subjects (see above and also Table 6-3). The maternal age distribution curves (Fig. 6-7) were made up entirely from the data on primary E-trisomics. If data from both the translocation and the double trisomic subjects were to be included this would both accentuate the lower and the higher peak. The situation therefore seems to be very similar to that found in Down's syndrome where the maternal age independent group comprised the majority, if not all, of the subjects with translocations as well as a small proportion of the primary

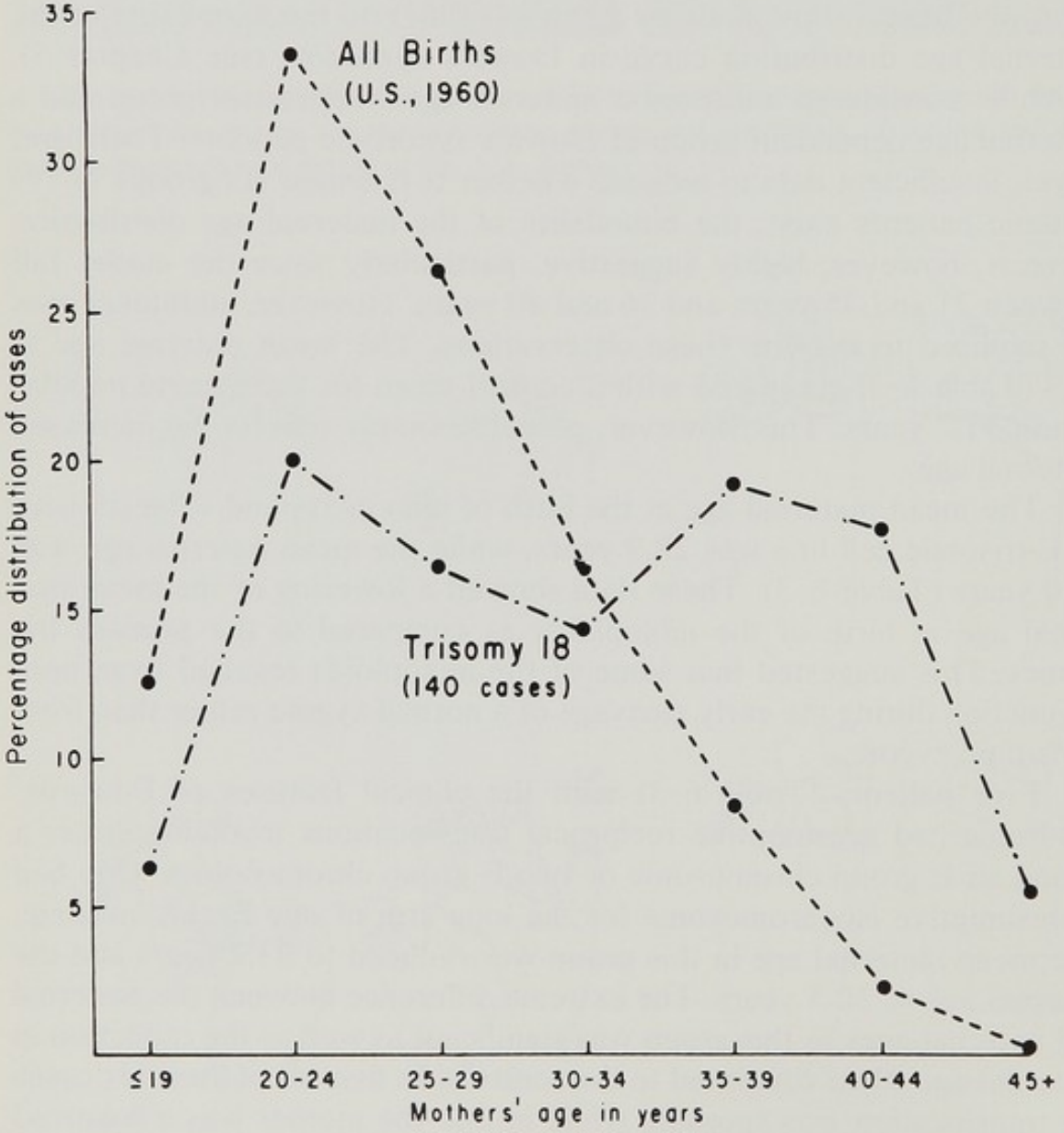


FIG. 6-7. Maternal age distribution curve for 140 cases of 18-trisomy and controls. Note slight bimodality of trisomic curve. (Modified from Magnenis *et al.*, 1968.)

trisomics in which the nondisjunctional events may have been under genetic control.

2. Sex Ratio in 18-Trisomic Live Births

A most striking feature of 18-trisomy was the grossly disturbed sex ratio which was observed among live births. Taylor (1968a, 1970) reviewed 153 subjects and showed that out of 143 in which the sex was stated 113 were female (79.02%) and only 30 (20.98%) were male. As already mentioned above, four (3.5%) out of the 113 females were 48,XXX,18+ while three (10.0%) of the 30 males were 48,XXY,18+.

This gross disturbance of the sex ratio has not yet been explained; possibly male trisomic fetuses are more at risk than female trisomics. If so, abortion of males must occur very early in gestation, before the time at which most abortions have been collected for study (Chapter 9). Most abortions have been studied in the first or second trimester (10–15 weeks) without finding any excess of E+ males. Alternatively, loss of the male 18-trisomics occurs much later in pregnancy as stillbirths (see Section D below). Finally, a possible explanation might be selective fertilization; if so, then the haplo-E+,X-bearing sperm must have an advantage over the haplo-E+Y-bearing sperm. Selective fertilization has been reported in the mouse to account for abnormal segregation ratios at the T locus, but other reported examples have proved not to be conclusive (see Volume I, Chapter 5 and Addendum). The second most interesting observation was the relatively high frequency of double trisomy compared to Down's syndrome, and this will be discussed at greater length below.

3. Frequency of 18-Trisomy

It has proved difficult until recently to obtain a reliable estimate of population frequency of E-trisomy. However, there have now been two distinct approaches (Table 6-4); the first was based on three surveys of hospital newborns (F. Hecht *et al.*, 1963; Marden *et al.*, 1964; Taylor and Moores, 1967), which included a hospital population of just over 21,000 births, and in this group six subjects with Edwards' syndrome were found, giving an over-all minimum frequency of about 1 in 3500 live births.

The second approach (Conen and Erkman, 1966a) was based on the population of York County, Ontario, Canada from August 1962 to the end of 1963. During this period there were 89,309 live births in the

TABLE 6-4

Frequency of Clinical Edwards' Syndrome in Various Population Groups

Reference	No. Studied	No. Edwards' syndrome	Per 1000 births	
(a) In Newborn Hospital Populations				
F. Hecht *et al.*, 1963	999	2	2.00	
Marden *et al.*, 1964	10,345	3	0.29	
Taylor and Moores, 1967	9,688	1	0.10	
Total	21,032	6	0.29	1 : 3,505
(b) In Ascertained Newborns in General Populations				
Conen and Erkman, 1966a (Canada)	89,309	8	Obs. 0.0009	1 : 11,164
			Calc. 0.22	1 : 4,500
Taylor and Fraser Roberts (quoted by Talor, 1968a) (England)	94,000	11	0.00012	1 : 8,545
Over-all total	204,341	25		1 : 8,174

study population and eight of these were 18-trisomics, an incidence of 8.9×10^{-5} live births (90% Poisson confidence limits of $3.98 - 14.43 \times 10^{-5}$). These authors then estimated the loss resulting from either non-transfer to hospital or from a failure to recognize the condition in hospital and obtained a maximum estimate of 3.6×10^{-4} and a minimum estimate of 1.6×10^{-4} (90% confidence limits of $6.5 \times 10^{-4} - 7.9 \times 10^{-5}$). They considered the most likely estimate to be 2.2×10^{-4} or about 1 in 4545 live births, a figure which agrees very well with that obtained from hospital surveys of the newborn. Taylor and Fraser Roberts (1969), in an attempt at complete ascertainment of E- and D-trisomics in southeast England, found 11 E-trisomics in 94,000 births, an incidence of 1/8545 newborns. This must be a minimum estimate since a proportion of affected children will have died before ascertainment or will not have been referred. Pooling these data gave twenty-five 18-trisomics in 204,350 newborns, an incidence of 1/8174. This estimate is probably too low because of the type of ascertainment loss referred to above, and an incidence nearer to 1/4000 may be more likely if it can be assumed that fewer ascertainment losses occur in the hospital. Conen and Erkman (1966a) showed that there were indications of clustering of 18-trisomic births among their patients and that out of 16 patients, 13 were born in the first half of the year and only three in the second half. On the other hand, Taylor (1968a) showed that the majority of the 18+ patients (18/27 – 66.7%) were born between the first of June and the thirtieth of November. It is not immediately possible to reconcile the two sets of data, but it seems likely that when a sufficiently large series of patients is available

births are likely to be found to be random over the year. A different form of clustering has been reported by Heinrichs *et al.* (1963) who reported three apparent clusters of Down's syndrome patients from January 1, 1954 through to February 28, 1963. In this period 20 children with Down's syndrome were born in the hospital concerned out of a total of 6929 deliveries, and 19 of these fell into three clusters of births. The first from September 23, 1954 to May 24, 1956; the second from June 30, 1958 to June 6, 1960; and the third from December 17, 1961 to February 8, 1963. Furthermore, in the 1962 cluster there were also two E+ births. A similar clustering of Down's syndrome births were reported from Australia (Collmann and Stoller, 1963a). The significance of clusters in relation to the etiology of the trisomic conditions is not clear. It has been suggested that they may be related to virus epidemics or to some other etiological factor, and in an extensive study A. Robinson and Puck (1965) found a clustering of sex chromatin abnormalities during three six-month periods from December 1962 to May 1964. A significant increase in frequency of Down's syndrome and of the sex chromosome anomalies were found in one of the periods only, correlating with the occurrence of a severe rubella epidemic about 9 months previously. Evidence is thus beginning to accumulate that this type of cluster may have some biological significance; further data of this type are obviously needed in order to settle this point and to establish what factors are concerned at the time of conception.

4. Survival Time of 18-Trisomics

The mean survival time for the 153 E+ subjects was about 71 days (Table 6-3). Conen and Erkman (1966a) have found a mean survival time for their 17 patients of 189.9 days. They have also shown both for their own series and for 62 additional patients from the literature that the mean survival time for males and females differed significantly: 22 males survived for a mean period of 96.3 days while 57 females survived for a mean period of 294 days.

Some mixoploids showed a much increased survival time, three 46,XX or XY/47,XX or XY, 18+ mixoploids had survived for 53, 52, and 103 months, respectively, at the time of study (Weiss *et al.*, 1962; Kulakowski *et al.*, 1966; Warkany *et al.*, 1964) while two other patients had survived for 11 and 13 months, respectively (Koulischer *et al.*, 1963; Hook and Yunis, 1965). The converse was seen among seven double trisomics who showed a mean survival time of 22.3 days and a range from 8 hr to 2 months (Table 6-3).

Over all, therefore, there is a similar pattern of clinical severity to be seen in 18-trisomy as in G-trisomy; the full primary trisomic, translocation trisomics, and double trisomics being severely and uniformly affected, the mixoploids have variable clinical features and are usually less severely affected.

5. Gestation and Birth Weight

The majority of E-trisomics are postmature: 153 patients with 18-trisomy have a mean gestational age of 42.2 ± 0.8 weeks (Table 6-3, Taylor, 1968a, 1970). A proportion of E-trisomics abort, usually prior to the twelfth week of gestation; the majority of these have 16-trisomy (Carr, 1965). Loss of 18-trisomics later in gestation has not been reported, but clearly some postconceptional loss of affected males must occur unless the primary sex ratio is abnormal (see above and also Chapter 9). Double trisomics are also postmature; on the other hand, mixoploid and translocation trisomics are usually born at term (Table 6-3).

Although the majority of 18-trisomic subjects were postmature, the mean birth weight was low (2242 gm) (Table 6-3) (Taylor, 1968a, 1970). This indicated developmental retardation which is so characteristic of the trisomic syndromes in man. The retardation of growth and development was a characteristic of this condition even after birth and two cases reported to be surviving to the ages of 10 and 15 years weighed only 20 and 35 lb, respectively; the 10-year-old girl had a bone age of only 3½ years (Weber *et al.*, 1964; Hook *et al.*, 1965). A comparison of the duplication and deletion syndromes showed that the subjects with a duplication of E group material had a uniformly low birth weight (2298 gm) compared with subjects with a deletion in which the birth weight was considerably higher (2981 gm) (Table 6-3). This, combined with a lower survival time and more extensive congenital malformations, is further evidence for the severe effects of chromosome trisomy in man.

II. Other Numerical and Structural Alterations in the E Group Autosomes

A. *16-Trisomy*

No live-born 16-trisomics have been reported, and the evidence suggested that duplication of material from this chromosome was usually lethal. Carr (1965) reported that six out of the seven abortuses with trisomy of an E group chromosome were trisomic for chromosome No.

16 while only one was trisomic for a chromosome in the 17-18 group (Chapter 9).

F. J. W. Lewis *et al.* (1963b) reported a woman age 59 with apparent 16-trisomy. However, they gave very little data, and the brief clinical description indicated extremely mild congenital malformations. Furthermore, they did not exclude the possibility that the additional chromosome could be an Xpi, and this may be more likely. A boy 12½ years old with gross developmental retardation and metaphyseal dysostosis was reported to have 46,XY/47,XY,16+ mixoploidy (Schmidt *et al.*, 1963). In this patient the normal cell line predominated. More recently, Backus and Darien (1968) reported a girl with Sprengel's deformity, costal chronditis (Tietze's syndrome), absence of the right breast and right ovary, minimal webbing of the neck on the right side and other skeletal anomalies, who had 45,XX,?16−/46,XX/47,XX,?16+ mixoploidy. Examination of the karyotypes was not entirely convincing, and the identification of the additional chromosome was doubtful. It is interesting that in two cases with a ?16+ cell line, skeletal anomalies have been reported. However, the identification of the additional chromosome was not certain in either case so that neither provided conclusive evidence for the viability of 16-trisomy.

One family is known [t(D;E)1] (see Volume I, Table 8-3 and this volume, Table 8-8) in which the mother had had 10 consecutive spontaneous abortions all between the eighth and twelfth week of gestation. Chromosome studies revealed that she was a mosaic [46,XX/46,XX, t(Dp+;16q−)]. The eleventh abortus had 47 chromosomes, 47,XY, t(16q−mat)+ (Fig. 6-8). In this case, therefore, triplication of even the short arm of No. 16 had proved lethal.

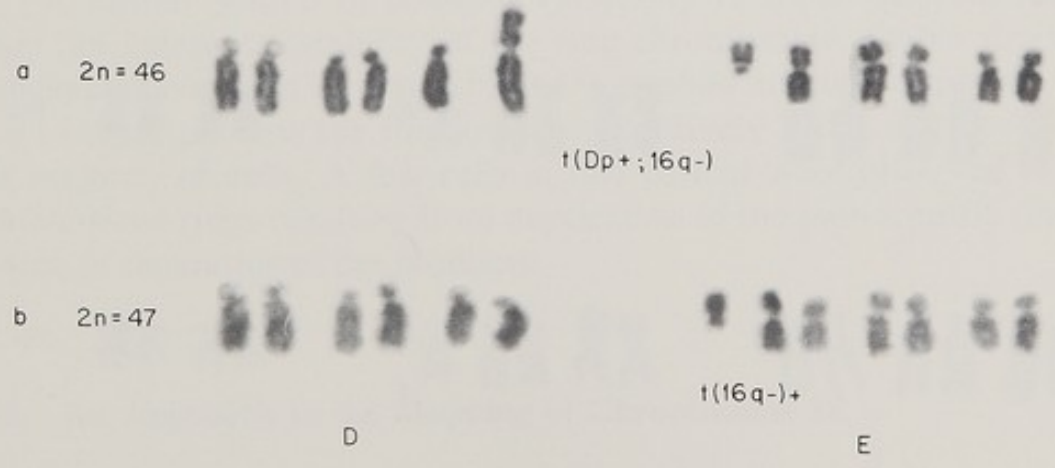


FIG. 6-8. (a) Partial karyotype to show the t(Dp+;16q−) in a mother and (b) triplication of the short arm of 16 which she had transmitted to her eleventh abortus: [Family t(D;E)1, Tables 8-3, Volume I, and 8-8, Volume II.]

B. *Structural Alterations of Chromosomes of the 16-18 Group*

1. Short Arm Deletion—No. 18 (46,XX or XY,18p—)

This chromosome constitution (Fig. 6-9) has now been reported in 18 different subjects and resulted in rather variable clinical features (Table 6-5). These are characterized by developmental and often mental retardation, abnormal facies, sometimes webbing of the neck, short stature, epicanthic folds, and ptosis. The pupils were sometimes abnormal. Some of the features were suggestive of Status Bonnevie Ullrich (Fig. 6-10) or Turner's syndrome. The latter was, however, excluded since there was no evidence of any gonadal anomaly. Other data are summarized in Table 6-3; the expectation of life in subjects with an 18p— was found to be reasonably good, the age of the oldest being 33 years. Birth was usually at term and the reduction in the mean birth weight for eight subjects was slight (2946 gm). Both maternal and paternal ages were slightly raised, but this was probably not significant.

It is interesting that the sex ratio was disturbed and that out of 17 subjects, 12 were females (70.6%) (cf. 18-trisomy). In this group of patients this might result from selection since several were originally ascertained as possibly having Turner's syndrome.

2. Long Arm Deletion—No. 18 (46,XX or XY,18q—)

Sixteen patients with a long arm deletion (Fig. 6-9) have been re-

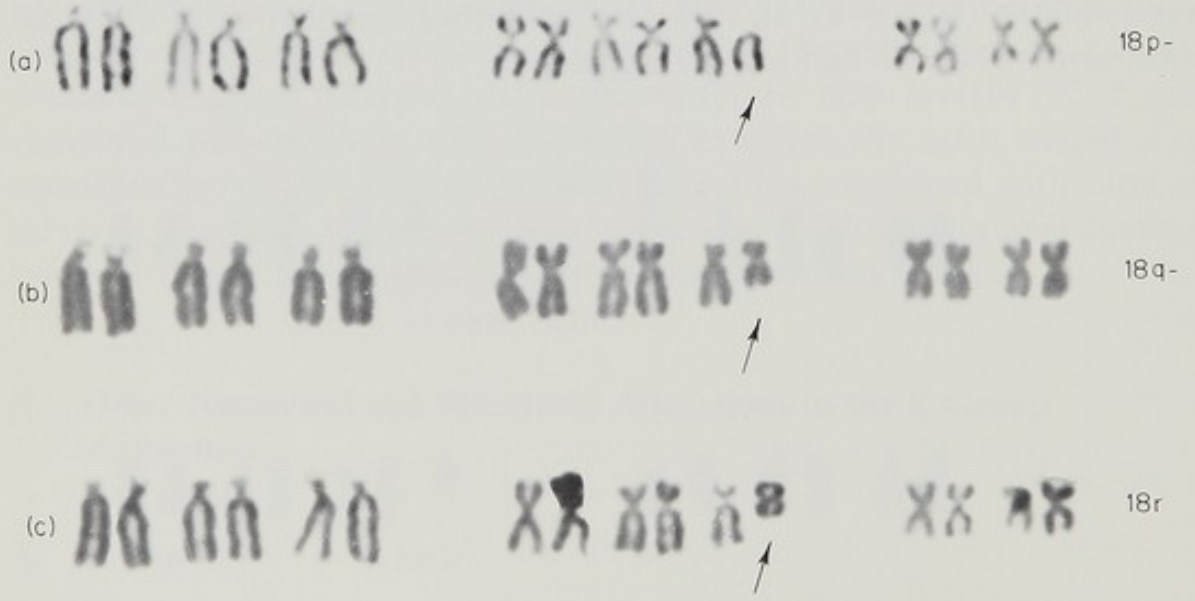


Fig. 6-9. Partial karyotypes of groups D, E, and F to show the various structural aberrations which have been reported (a) 18p—, (b) 18q—, (c) 18r. (Reproduced by courtesy of Dr. J. De Grouchy.)

ported, and these all have a similar phenotype (Fig. 6-11) which consisted usually of mental retardation, microcephaly, abnormal facies, and midface dystrophia. Developmental retardation and short stature were also reported, and the middle ear and eyes are often abnormal; the dermatoglyphic patterns show a high frequency of whorls on the digits (Table 6-6). Birth weight was often low although gestation was usually at term, and there was no evidence of an increase in either maternal or paternal age (Table 6-3). The prognosis for survival was good, and at least one subject has survived to the age of 15 years. There was no evidence of any abnormality of sex ratio.

3. Ring Chromosomes (46,XX or XY,18r+)

Eight children with ring chromosomes (Fig. 6-9) which replaced one chromosome in the 17-18 group have been reported (Table 6-7). All of them had generalized mental and developmental retardation and a variety of congenital malformations which overlap the phenotype of both 18p− and 18q− patients (Fig. 6-12). This is not unexpected since the formation of a ring chromosome must have involved a deletion of both terminal segments of the chromosome involved. A single subject with 45,XY,16−/46,XY,16r mosaicism has also been reported, and the clinical details have been summarized (Table 6-7). The major clinical features of these patients included abnormal facies, malformed and low-set ears, and atresia of the middle ear. The parental ages do not differ significantly from the general population although a slight lowering of maternal age occurred while paternal age has remained relatively constant (Table 6-3).

A further source of possible variability in these subjects resulted from the inherent instability of the ring chromosome. Stable ring chromosomes have been reported from *Drosophila* and other species. In all five of these patients the ring appeared relatively stable and occurred in the majority of cells. A few cells in one patient were observed to have double-sized rings resulting from duplication of the monocentric ring and failure of separation of the products.

III. An Approach to the Mapping of Chromosome 18

An attempt has been made to use the phenotypic data from 18-trisomic and deletion syndromes to determine the effect of duplication or deletion of different regions of chromsome 18 on particular phenotypic

TABLE 6-5

Clinical Features of 18 Patients Having a Deletion of the Short Arm of Chromosome No. 18 (18p−)

Case No.	Age[a] (years)	Parental ages[b] Mother	Father	Birth wt. (gm)	Gestation age (weeks)	Sex	Developmental retardation	Mental retardation[c]	Neck	Stature
1	16	30	32	3118	..	F	+	+	Webbed	Short
2	Birth	30	34	..	..	..	..	..	..	..
3	33	41	..	..	..	M	+	+	..	Short
4	1	32	31	1700	38	M	+	..	Short	..
5	4-10/12	21	26	3515	..	F	+	+	Webbed	Short
6	3	40	40	..	..	F	+	+	Normal	..
7	22	31	35	3629	40	F	+	..	Webbed	Short
8	13	22	27	3515	..	F	+	+	Webbed	Short
9	6	41	42	..	..	M	+	+	..	..
10	..	30	34	2650	8 months	M	+	..	Webbed	..
11	1-1/12	29	34	3250	..	F	+	..	Normal	Normal
12	..	39	39	2730	37	F	+	..	Normal	Normal
13[e]	31	46	47	..	..	F	+	+	Normal	Short
14	14/12	29	40	..	..	M	+	+	Normal	Short
15	Birth	28	40	..	..	F	..	..	..	..
16	1-9/12	28	31	..	..	F	+	+	..	..
17	4	35	37	..	..	F	+	+	Webbed	..
18	2-6/12	31	31	2410	8	F	+	..	Short	..

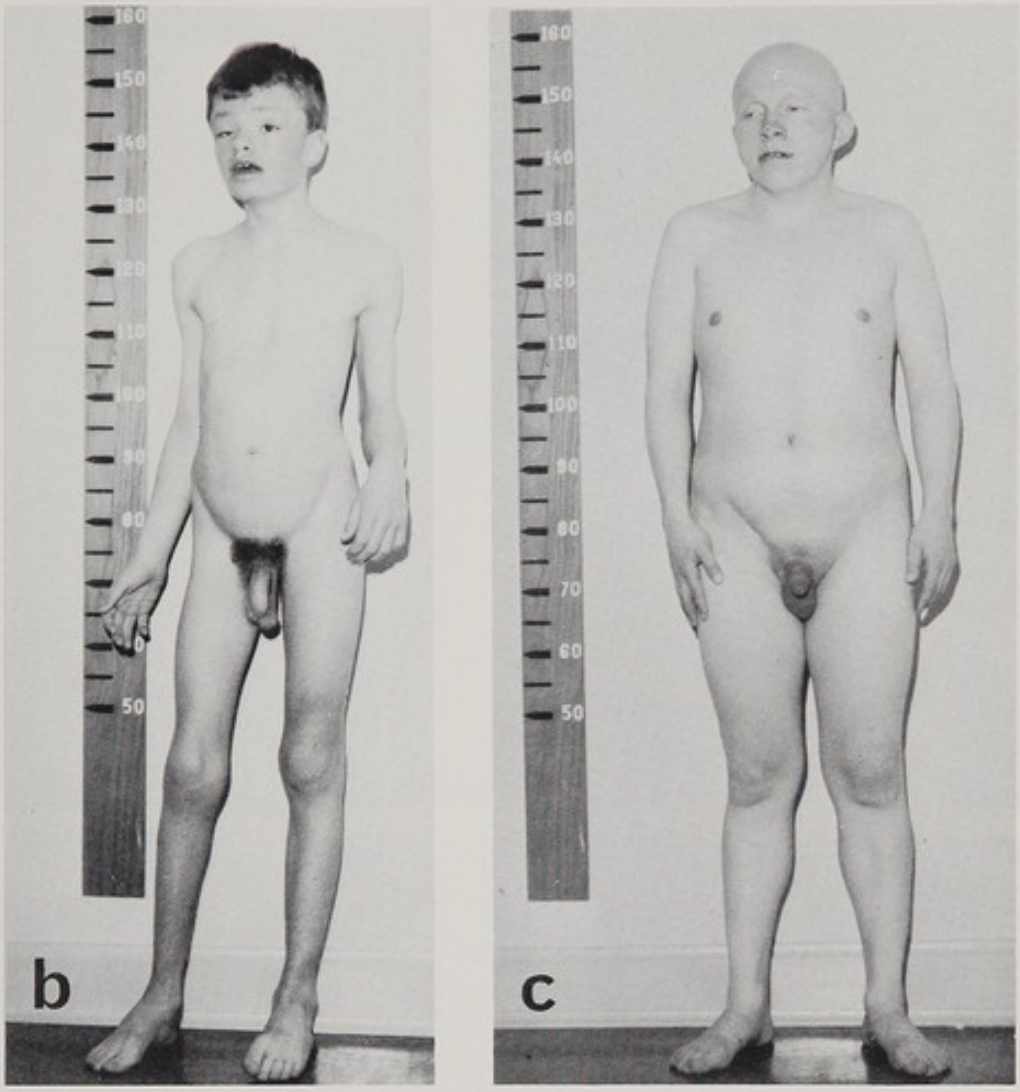
[a] Age at examination.
[b] Ages at birth of patient.
[c] Here .. means unrecorded; + means present; − absent.
[d] Here, ASD stands for a trial septal defect.
[e] Case 13 is 46,XX/46,XX,18p−, mother of Case Nos. 14 and 15.

Eyes	Ears	Jaw	Brain and CNS	Skeleton	Reference
..	..	..	..	..	Van Dyke *et al.*, 1964
One only	..	..	Cyclops	..	Faint and Lewis, 1964
Abnormal	Low set	Micrognathos	..	..	F. J. W. Lewis *et al.*, 1963c
Epicanthic folds	Low set	Slight micrognathos	..	Congenital dislocation of hip	Migeon, 1966
Eccentric pupils	Prominent, normal position	Micrognathos	..	Congenital dislocation of hip Shield chest	Summitt, 1964
Epicanthus (Patient is hypothyroid)	..	..	..	..	Bühler *et al.*, 1964
..	..	..	..	..	PRU 2509/WS301142
(Patient has congenital heart disease ?ASD[d])					
Hypertelorism; epicanthus	Low set	..	..	Cubitus valgus	PRU 806/CC10547
..	..	..	..	Abnormal hands and feet	De Grouchy *et al.*, 1963b
(Patient is described as having the "dysmorphic syndrome)					
Hypertelorism; ptosis	Low set	Micrognathos	Microcephalic	Abnormal hands and feet; hypotonic	Lejeune *et al.*, 1966b
Normal; ptosis	(Patient is described as having dysmorphic syndrome)			normal heart	De Grouchy *et al.*, 1966a
Normal	Normal	Cleft lip and palate	..	Broad flat nose. Absent nasal bone.	Pfeiffer, 1966b
..	..	..	..	..	Uchida *et al.*, 1965
(Alopecia congenita and dental caries)					
Epicanthus; ptosis	Large (Patient has dental caries)	Micrognathos	..	..	Uchida *et al.*, 1965
Hypertelorism	..	..	Cebocephaly	..	Uchida *et al.*, 1965
Hypertelorism	..	..	Brachycephaly Anterior capsular defect	Congenital dislocation of hip	Dill and Miller, quoted by Uchida *et al.*, 1965
Hypertelorism	..	..	..	..	Hickox, quoted by Uchida *et al.*, 1965
	(Dental caries)				
Normal	..	Micrognathos	..	..	De Grouchy *et al.*, 1967



FIG. 6-10. Clinical features of three patients heterozygous for a presumptive deletion of the short arm of chromosome 18 (18p−). (a) ♀ age 2½ months, (b) ♂ age 14½ years, and (c) ♂ age 22 years. [(a) From De Grouchy *et al.*, 1967d; (b) and (c) from Jacobsen and Mikkelsen, 1968b).]

characters and then to use this data to map the chromosome (De Grouchy, 1965b). This approach, however, is an oversimplification and is of little value in locating and mapping specific gene loci. Attempts have been made to locate specific blood group loci and other markers on specific regions of chromosome 18. Lejeune *et al.* (1966a) contrasted the 18q− subjects with the trisomic subjects and considered that partial



monosomy should give phenotypic features which were the antithesis of the trisomic phenotype.

There are several reasons why "deletion mapping" of human chromosomes is likely to be of little value in respect of generalized features; these can be summarized as follows:

Identification of chromosome No. 18. Although most authors considered that No. 18 was the chromosome involved in both the "trisomic" and the "deletion" syndromes, and this has been accepted in the present chapter, the unequivocal identification of the chromosome involved has not always been possible, even after detailed autoradiographic and morphological studies. Without a clear chromosome identification deletion mapping is of little value.

The type of structural change. Morphological examination of a deleted chromosome in somatic cells does not give any real indication

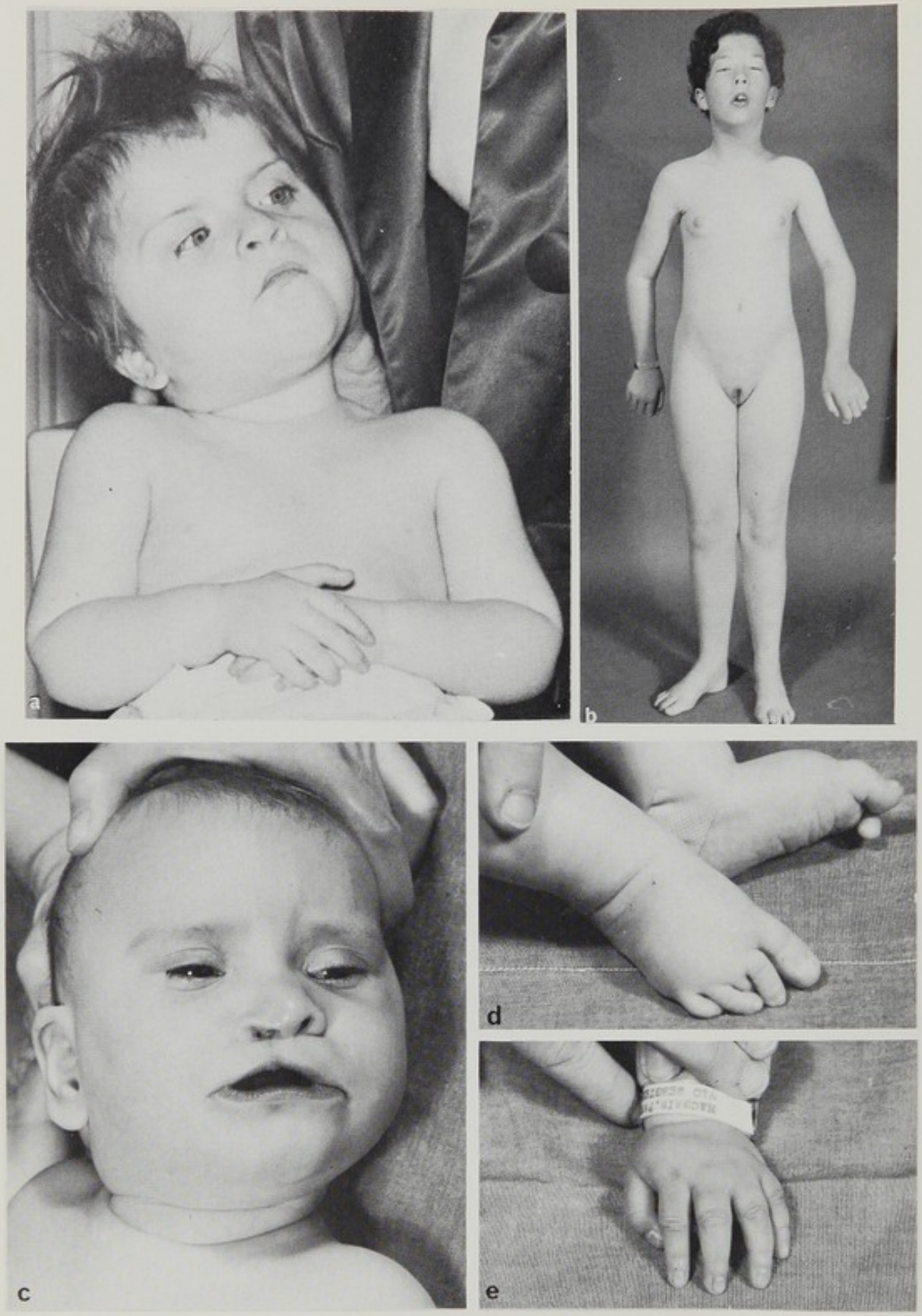


FIG. 6-11. Clinical features of three patients with an 18q− chromosome (46,XX,18q−). (a) Female, aged 1 year, (b) female, aged 10 years, and (c), (d), and (e) from female, aged 10 months. Note abnormal facies with some features resembling Turner's syndrome. In (c) note repaired cleft lip, (d) edema of feet, and abnormal toes, (e) long thin fingers. [(a) From De Grouchy *et al.*, 1964b; (b), (c), (d), and (e) from Destine *et al.*, 1967).]



FIG. 6-12. Clinical features of a male, age 13½ years, with a 46,XY,18r chromosome complement. Note short stature, microcephaly, and abnormal facies. (From De Grouchy *et al.*, 1968b.)

TABLE 6-6

Clinical Features of 16 Patients with a Deletion of the Long Arm of Chromosome No. 18 (18q−)

Case No.	Age[a] years	Parental ages[b] Mother	Father	Gestation age (months)	Birth wt (gm.)	Sex	Mental or developmental retardation[c]	Eyes	Ears	Skull	Face, jaw, and palate	Genitourinary	Dermatoglyphics	Hands, feet, and skeleton
1[d]	1	27	40	8	2300	F	+	Hypotrophia and other abnormalities	Atresia of middle ear	Microcephalic	High arched palate	Abnormal kidneys	Abnormally high frequency of whorls	
2[e]	3-6/12	22	25	8	2750	M		Hypotrophia	Marked anti-helix and pro-nounced helix	Microcephalic	Receding chin, re-traction of mid-part of face, sub-acromial dimples	..	Abnormally high frequency of whorls	Spindle-shaped fingers
3[e]	..	33	31	9	2350	F	+	Hypotrophia	Similar to Case No. 2	Microcephalic	Similar to Case No. 2	..	Abnormally high frequency of whorls	Spindle-shaped fingers
4[f]	..	..	..	Premature	..	M	..	Slight epi-canthus, micro-cornea	..	..	Abnormal facies	..	..	Abnormally long thumbs
5[f]	..	..	..	..	..	F	..	Similar anomalies to Case No. 4 but less severe.						
6[g]	4	..	..	..	..	..	Mentally retarded, microcephalic patients with midface dystrophia, short stature, congenital heart disease, hypertonia, nystagmus, fundus abnormalities.						Abnormally high frequency of whorls	
7[g]	9/12	..	..	..	..	..								
8[g]	1/12	..	..	..	..	..								
9[g]	4	..	..	..	..	..								
10[h]	26/12	32	40	Term	3500	M	+	Normal	Normal hearing	Microcephalic	Normal facies High arched palate	Umbilical hernia	..	Mild spasticity Immobile hips Bilateral club-feet. Normal heart

11	2	33	26	..	2720	M	+ Sucking reflex poor	..	..	Microcephalic	Carp-shaped mouth	Umbilical hernia External genitalia small. Crypto-orchidism. Hypospadias.	..	Abnormal fingers and nails. Talipes calcaneo valgus. (Neck webbed, wide spaced nipples)
12	15	29	29	10	4000	M	+ Sucking reflex poor	Hypotrophic fundus normal	..	Dolicocephalic. Prominent occiput.	Abnormal facies Micro-gnathos. Low hair-line. Irregular teeth.	Cryptor-chidism small exter-nal genitalia	Abnormal	Short neck. Kyphoscoliosis. Cubitus valgus. Rudimentary digit. Syndactyly
13	10	40	45	..	..	F	..	Optic atrophy, epicanthic folds. Hyper-telorism.	Low set abnormal antihelix, antitragus.	..	Irregular teeth	..	..	Abnormal toes
14	3/12	32	37	8	2600	F	+	Ocular abnormalities Mongoloid slant, epicanthus.	Low set antihelix, antitragus.	Microcephalic	High arched palate	..	Whorls on 10 digits	Flection deformities fingers and toes
15[l]	8	31	41	Term	3250	F	+	Hypotrophia, ocular anomalies, hypertelorism, epicanthus.	Normal	Microcephalic	Abnormal mouth and teeth (Congenital heart disease)	..	Ulnar loops	Abnormal fingers
16[m]	4-5/12	25	27	41	3330	F	+	Hypertrophia, ocular anomalies, nystagmus, epicanthus.	Small, low set	Microcephalic	Wide nasal bridge, carp mouth	..	..	Long tapered fingers

[a] Age at examination.
[b] Ages at birth of patient.
[c] Here .. means unrecorded, + means present, – means absent.
[d] De Grouchy *et al.* (1964b).
[e] Lejeune *et al.*(1966a).
[f] Law and Masterson (1966).
[g] Wertelecki *et al.* (1966).
[h] Briebart *et al.* (1964).
[i] Day *et al.* (1964).
[j] Van Kempen (1967).
[k] Destine *et al.* (1967)
[l] U. Wolf *et al.* (1967).
[m] Nance *et al.* (1968).

TABLE 6-7
Clinical Features of Eight Patients with a Ring Chromosome Replacing One of the E Group Chromosomes (Er)

Case No.	Age[a] (years)	Parental ages[b] Mother	Father	Gestation age (months)	Birth wt (gm)	Sex	Mental and/or developmental retardation	Eyes	Ears
1[c]	..	23	..	..	..	..	..	Hypertelorism, bilateral epicanthus.	Atresia of mid ear, Deaf
2[d]	3	31	31	Term	..	F	Slight	Hypertelorism, bilateral epicanthus	Atresia of mid ear. Small EAM[k]
3[e]	1	25	24	Term	..	F	+	..	..
4[f]	5	27	37	8	2300	F	+	Slight hypertelorism and epicanthus.	..
5[g]	Birth	26	27	Term	3230		+	Normal	Low set auricles, normal.
	..	26	..	40 weeks	1996	M	..	Hypertelorism	Low set, atresia mid ear
7[i]	10	26	29	..	3970	M	+	Hypertelorism. No epicanthus. Anti mongoloid slant. Strabismus.	Low set
8[j]	13-6/12	25	29	Term hydramnios	3600	M	+	No hypertelorism. Epicanthus. No strabismus.	Low set, Normal hearing.

[a] Age at examination.
[b] Age at birth of patient
[c] Wang *et al.*, (1962)
[d] Genest *et al.* (1963).
[e] Lucas *et al.* (1963). ?45,XX,E−/46,XX/47,XX(Er)+.
[f] De Grouchy *et al.* (1964c).
[g] Gropp *et al.* (1964).
[h] Pergament *et al.* (1965). 45,XY,16−/46,XY,16r.
[i] Palmer *et al.* (1967).
[j] De Grouchy *et al.* (1968b).
[k] Here EAM stands for external auditory meatus.

Skull	Face, jaw, and palate	Genitourinary	Dermatoglyphics	Hands, feet, and skeleton
..	..	..	..	Bilateral syndactyly second and third toes
..	..	..	..	"Rocker bottom" feet Abnormal flection of toes.
Slight microcephaly	Slight micrognathos, Cleft palate.	..	..	Congenital dislocation of hip
Microcephalic (Low hairline, wide-spaced nipples, generalized hypotonia)	..	..	10 digits with whorls	Short fingers, incurved little fingers.
Dolicocephaly	Micrognathos. High-arched palate	Renal anomalies (Ventricular-septal defect)	..	Short blunt hands "Rocker bottom" feet.
..	Micrognathia, high arched palate, abnormal face, beak nose, and wide bridge	Small penis, scrotum cryptorchid.	..	..
Microcephalic (Congenital heart and speech defect)	Normal	..	Abnormal	Short fingers, low thumb implantation. Valgus feet. Abnormal toes
Microcephalic	Abnormal face. Palpebral fissure. normal high-arched palate.	..	9/10 whorls	Short fingers. Normal thumb implantation.

about the type of structural rearrangement which has occurred, and meiotic studies are necessary to determine this. For instance, an apparent deletion of the terminal region of a chromosome could result from at least four different mechanisms, all of which would result in a chromosome of identical morphology but differing genetic content (Fig. 6-13).

1. A terminal chromosome deletion with healing of the broken ends to produce new telomeres and loss of acentric fragments.

2. An interstitial deletion. This is a two-break rearrangement with loss of an interstitial segment and rejoining of the proximal centric and distal acentric fragments. This results in a deleted chromosome which does not require the formation of new telomeres; it is however a two-break event while 1 above requires only a single break.

3. Some of the 18p− chromosomes appear almost telocentric, and

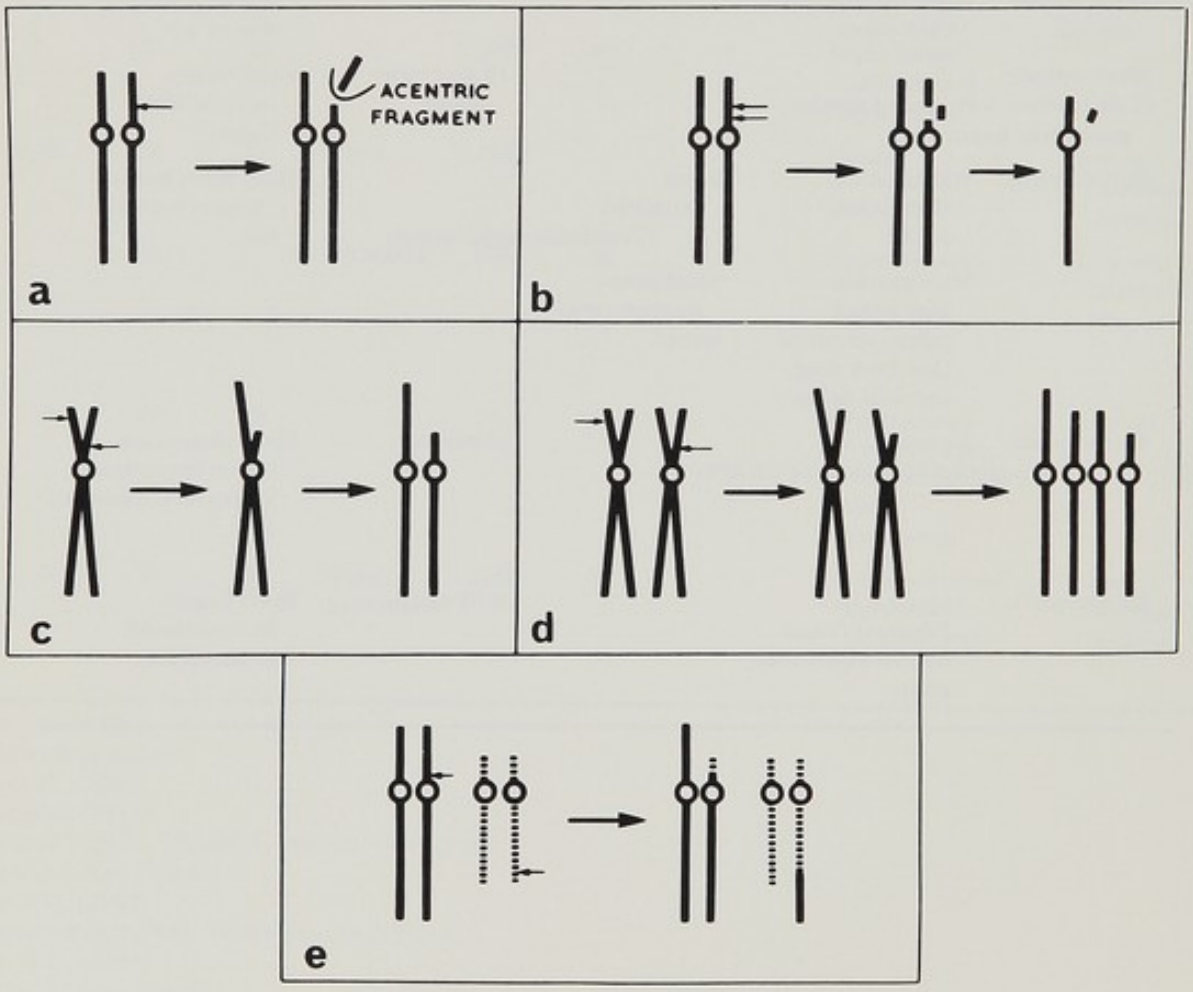


FIG. 6-13. Schematic diagram to illustrate the various types of chromosome rearrangement which may result in an identical karyotype, each of which has a different genome: (a) terminal deletion, (b) interstitial deletion, (c) unequal intrachromatid exchange, (d) unequal interchromatid exchange, and (e) reciprocal translocation. (From Hamerton, 1969.)

these may be the result of transverse breakage at the centromere resulting in a truly telocentric chromosome which in some instances may be stable while in other instances may produce an isochromosome (see Volume I, Chapter 8, J. Q. Miller *et al.*, 1965). Each of these mechanisms involved only a single chromosome break and resulted in a deficiency of chromosome material and no duplication. Examination of Fig. 6-13, however, clearly illustrates how difficult it is to decide which mechanism is responsible by a study of the somatic chromosomes.

4. The fourth type of rearrangement which might have the same morphological effect is a reciprocal translocation and four families with deleted 18's resulting from this mechanism have been reported (Lejeune *et al.*, 1966b; Law and Masterson, 1966; E. J. Day *et al.*, 1967; Nance *et al.*, 1968). The family reported by Lejeune and his colleagues was well documented, and it is clear that examination of the karyotype of the propositus alone would not have indicated the origin of the deleted 18; it was only the fact that the mother was heterozygous for a t(17p+;18p−) which indicated the origin of this chromosome abnormality. This type of rearrangement usually results in a duplication/deficiency situation. In the case reported by Lejeune *et al.* there was a presumptive deficiency of the short arm of 18, and a duplication of the short arm of 17. Other deleted eighteens may also have resulted from a similar mechanism, the only difference being a failure to locate a balanced karyotype in one of the parents which is necessary to establish the presence of a reciprocal translocation. Finally, both inter- and intrachromatid rearrangements could result in a similar somatic chromosome picture.

A ring chromosome originates from a double terminal deletion of both the long and short arms of a chromosome with subsequent fusion of the two broken ends to form a monocentric ring (see Fig. 8-2, Volume I). It is impossible to state where the breaks occurred or how much chromosome material was lost, and it is therefore difficult to predict phenotypic features. It is, however, clear from an examination of the tables that the phenotype of subjects carrying a ring chromosome tends to overlap both the 18p− and 18q− phenotypes. A further source of phenotypic variability in subjects with a ring chromosome may be instability of the ring at mitosis. A ring chromosome may be completely lost from one cell line, or may form double-sized rings, with resulting duplication of genetic material. These may be stable or unstable; in any case the result may be one or the other type of mixoploid and an increase in phenotypic variability.

The generalized nature of the phenotypic features. Examination of Tables 6-1, 6-5, 6-6, and 6-7 shows that many of the clinical features

associated with both the trisomic state as well as with the various presumptive deletions are generalized and must normally be controlled by a number of genetic factors and not a single gene locus. Developmental retardation, which is shown in De Grouchy's map to be the result of a deletion of a specific region of chromosome 18, also results from duplication, and in fact is the most usual result of chromosome imbalance. It occurs not only in subjects with a duplication or deletion of chromosome 18 but also in Down's syndrome and in the various other trisomic states; it is also a result of chromosome imbalance resulting from the segregation of rearranged chromosomes. This argument may also be applied to many other features. Loss or gain of a chromosome segment leads to loss or gain of many gene loci, some of which may be structural genes and others regulating genes. It may thus affect many facets of cellular development and lead to the production of a whole range of congenital malformations and developmental retardation. Such generalized features are therefore of little use in chromosome mapping. However, if a specific locus, such as that for a blood group, serum protein, or enzyme in which the gene product can be directly demonstrated, can be shown to be segregating in a compatible manner with the deletion or other chromosome marker, the location of this locus can be established with some degree of reliability (see, e.g., Donahue *et al.*, 1968). Eventually no doubt a useful genetic map of the human autosomes will be constructed by conventional linkage studies. Meanwhile, the construction of generalized maps on the basis of gross chromosome "deletions" have little value and may even be misleading.

IV. Concluding Remarks

Sufficient data have been presented in the present chapter to show that an E group chromosome when present in triplicate leads to a severe and invariably lethal combination of clinical signs which has been termed *Edwards' syndrome*. The evidence that this chromosome is No. 18 (Denver Conference) is becoming strong and is based both on chromosome morphology as well as labeling studies. The suggestion that either chromosome No. 17 or 18 might cause the same condition is not supported in the absence of evidence of chromosome homology. The grossly aberrant sex ratio is not at present readily explicable but might be accounted for on the basis of either very early or very late (stillbirth) loss of male 18-trisomic fetuses or by selective fertilization. 16-Trisomy

is unknown among live births but accounts for a relatively high proportion of E-trisomic abortuses, and it is suggested that unbalance of material of chromosome No. 16 is highly lethal.

An approach to the mapping of chromosome No. 18 on the basis of the clinical effects of deletions and ring chromosomes has been considered and is not felt to be especially useful at present.

Chapter 7

ABNORMALITIES OF THE AUTOSOMES—GROUP D (13-15 GROUP—DENVER CONFERENCE)

I. Introduction

The numerical and structural anomalies which affect the D group result in either gross phenotypic malformations or have no apparent effect on the phenotype and appear as normal variants in the human chromosome set (see Volume I, Chapter 4). D-Trisomy is an example of the first situation, while variation in satellite size and structure or in the length of the short arms is an example of the second. The reason for this phenotypic variation is probably dependent both on the amount of chromosome material involved and its genetic content. For instance, the short arms of a D group chromosome can be deleted or duplicated without any obvious effect. "Robertsonian fusion" can take place between the long arms of two acrocentric chromosomes with loss of one centromere and short arms, resulting in normal and usually fertile heterozygotes who have no obvious loss of fitness and may have some selective advantage (see also Volume I, Chapter 8).

Two autosomal trisomy syndromes have been described as associated with chromosomes of this group. The first, Patau's syndrome, (47,XX or XY,13+) is well established; the second is much more doubtful and is thought in some instances to be associated with congenital analgesia.

II. Numerical Aberrations

A. *Primary D-Trisomy (Patau's Syndrome) (46,XX or XY,D+ or ?13+)*

Patau *et al.* (1960) first described a clinical syndrome in a female infant who had cerebral, ocular, and cardiac defects; harelip; cleft palate; polydactyly; and multiple capillary hemangiomata. She was found to have 47 chromosomes with an additional chromosome in the D group and was considered to be a primary D-trisomic (47,XX,D+).

Between 50 and 100 children with this syndrome have been described since 1960, and the majority have been shown to have a 47,XX or XY,D+ chromosome complement (Fig. 7-1) (Taylor, 1967, 1968a, 1969).

Several attempts have been made to identify and define the D chromosome involved in D-trisomy using morphological and autoradiographic criteria (Yunis *et al.*, 1964d; Giannelli, 1965; Büchner *et al.*, 1965; Giannelli and Howlett, 1966; Yunis and Hook, 1966). The six D group chromosomes can be divided into three pairs based on labeling pattern and grain count at the end of the S period (Giannelli, 1965). The first pair showed a pattern of dense labeling along the distal part of the long arm, while the proximal part of the long arm and the centromere were unlabeled; the second was marked by a diffuse labeling which was often denser over the proximal part of the long arm and the centromere; and the third was unlabeled or had less than five autoradiographic grains per chromosome. Yunis *et al.* (1964d) and Büchner *et al.* (1965) have both studied the labeling patterns in subjects with D-trisomy and have shown that the seventh D chromosome present in these subjects had a labeling pattern which corresponded to the first pattern described by Giannelli (1965). This author studied a patient with D-trisomy but with only 46 chromosomes and an additional chromosome resembling No. 3 (46,XX,D−,t(DqDq)+ or Dqi+). He showed that both arms of this chromosome labeled symmetrically with a pattern similar to the D chromosome which was labeled densely at the termination of the S period and quite distinct from the morphologically similar pair No. 3; he concluded that the additional chromosome was either an isochromosome or a translocation between two homologous D chromosomes. Giannelli and Howlett (1966) analyzed the labeling patterns, grain counts and chromosome measurements in a female balanced heterozygote for a t(DqDq) interchange in which the two D chromosomes involved must be nonhomologous, as well as in a subject with primary D-trisomy. They showed that the D group could be divided into three pairs on the basis of

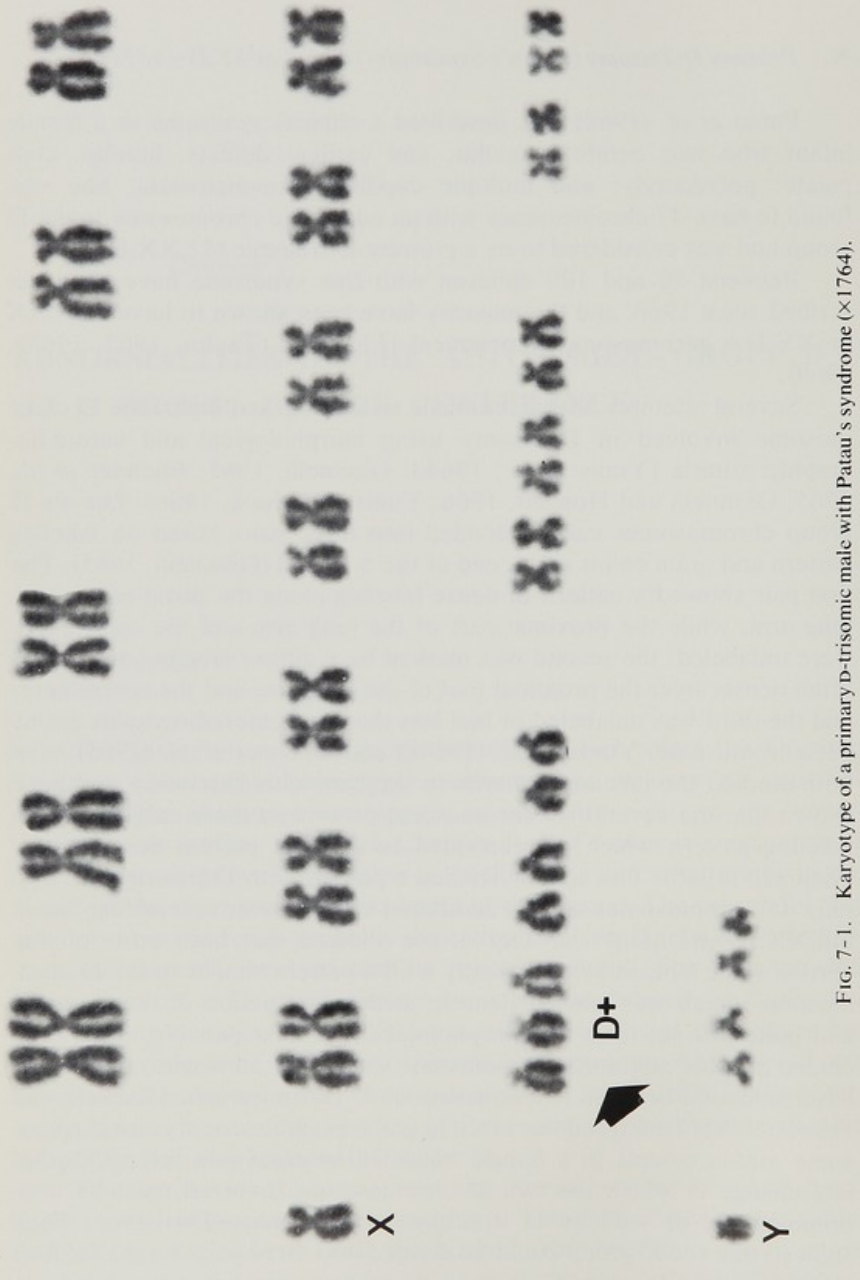


FIG. 7-1. Karyotype of a primary D-trisomic male with Patau's syndrome (×1764).

length and that the longest chromosome was also the late replicator; the chromosome pair of intermediate length showed a more diffuse labeling pattern in the proximal region, while the third and shortest pair was the early replicator. The first and longest pair was termed *No. 13*, the second and intermediate pair *No. 14*, while the third and shortest early replicating homologues were termed *No. 15*. They concluded that the t(DqDq) involved chromosome numbers 13 and 14 and that the trisomic chromosome was number 13. The translocation discussed by Giannelli (1965) was either at (13q13q) or at 13qi. These autoradiographic and measurement studies therefore show that the D group can now be defined into its three homologous pairs Nos. 13, 14, and 15 (Denver Conference), and it seems most likely on the basis of these studies that pair No. 13 is responsible for D-trisomy (Patau's syndrome).

B. *D_1-Mixoploidy and Double Trisomy*

Twelve mixoploid subjects have been reported (Table 7-1): 10 out of the 12 mixoploids had a normal and a trisomic cell line while one also

TABLE 7-1

Some Chromosome Complements Which Have Been Reported in Incomplete D-Trisomy

Chromosome complement	No. of subjects	References
46,XY/47,XY,D+	9	Taylor and Polani, 1964; Warkany *et al.*, 1962b; Stone *et al.*, 1966; Bain *et al.*, 1965; Conen and Erkman, 1963b; Tsoneva-Maneva *et al.*, 1965; Engel *et al.*, 1967.
46,XX/47,XX,D+	1	Forteza *et al.*, 1964
46,XX/47,XX,D+/48,XX,D+,D+	1	Taylor, 1968a;
46,XX,Dp−/46,XX,Dqi	1	Therman *et al.*, 1963
46,XX,Dp+	2	Taylor, 1968a; Zellweger *et al.*, 1962.
46,XX,Dq−	1	Taylor, 1968a
47,XY,(?Dq−)+	1	Ishmael and Laurence, 1965
47,XX(?Dq−)+	2	Zellweger *et al.*, 1962; Krüger *et al.*, 1968

had a tetrasomic line. The twelfth (Therman *et al.*, 1963) was a mixoploid with two cell lines both with 46 chromosomes, one having an apparent telocentric Dp− while the other had Dqi (46,XX,Dp−/46, XX,Dqi). The child had a milder manifestation of the trisomic syndrome, but many of the clinical features were present (see below). The frequency of the two cell lines in different tissues and at different times is given in Table 7-2. No significant difference was detectable between the blood culture and the bone marrow ($P = 0.06$) or between the blood and skin culture in 1960. By 1962, however, the Dqi cell line was completely lost after 3 months *in vitro* culture. The most likely origin for these two cell lines is misdivision of the centromere of a D chromosome in an early cleavage division resulting in a telocentric chromosome. Stabilization of this chromosome in one cell line and formation of an isochromosome in the other would give the mixoploidy observed. Alternatively, the abnormal telocentric chromosome could have been formed during gametogenesis and become stabilized as a Dqi in one cell line only in the zygote (see Polani, 1962; see also Volume I, Chapter 8, Section II,C). The proportions of the two cell lines present in different tissues and in normal/D+ mixoploids is extremely variable, and the available data are summarized in Table 7-3. Two of these subjects perhaps require some additional comment. The first is the child reported by Taylor and Polani (1964) who showed only minimal features of Patau's

TABLE 7-2

The Frequency of the Two Cell Lines in a 46,XX,Dp−/46,XX,Dqi Patient[a]

Tissue	Date	46,XX,Dp−	46,XX,Dqi	Total	Proportion Dp−
Bone marrow	1960	14	8	22	0.64
Blood	1961	10	16	26	0.38
Blood	1962	30	38	68	0.44
Total blood		40	54	94	0.43
Skin	1960	8	13	21	0.38
Skin	1962	5	2	7	0.71
After 3 months *(in vitro)*	1962	58	0	58	1.00

Comparison blood and bone marrow:

$P_1 - P_2$	SE	P
0.22	0.014	0.06

[a]Reported by Therman *et al.* (1963).

TABLE 7-3

Proportion of Normal Cells in D-Trisomic Mixoploids

Blood			Other tissues				
46,XX or XY	47,XX or XY,D+	Proportion normal	Tissue	46,XX or XY	47,XX or XY,D+	Proportion normal	Reference
147	2	0.99	Skin	121	4	0.97	Taylor and Polani, 1964
22	70	0.24	Skin	35	59	0.37	Warkany *et al.*, 1962b
10	14	0.42	Bone marrow	34	15	0.69	Forteza *et al.*, 1964
–	–	–	Thymus	28	8	0.78	Bain *et al.*, 1965
–	–	–	Spleen	12	21	0.36	Bain *et al.*, 1965
36	14	0.72		–	–	–	Bain *et al.*, 1965
78	14	0.85		–	–	–	Stone *et al.*, 1966
10	53	0.16		–	–	–	Engel *et al.*, 1967 (Case No. 2)

syndrome and who was 13 months of age at time of examination and has now survived to be about 6½ years old. When first seen he had about 2% 47,XY,D+ cells, but in subsequent cultures the D+ cell line had completely disappeared. In this case the minimal features of Patau's syndrome together with the longer period of survival correlates well with the low frequency of abnormal cells. The second subject, a child of 6½ years at the time of examination (Warkany *et al.*, 1964), also showed only very minimal features of Patau's syndrome and extremely minor congenital malformations. He had about 76% 47,XY,(Dp−)+ cells in blood culture and 63% in skin culture. The additional chromosome is not typical of the D group, lacks short arms in every cell, and could therefore represent the product of a structural rearrangement rather than a true trisomic. Either way, however, there is considerable duplication of chromosome material, and if this is autosomal then the mild phenotypic malformations are surprising. The possibility that this chromosome might be a second X with deleted short arms does not seem to have been considered and sex chromatin and autoradiographic studies would be required to test this hypothesis. At present, however, the available evidence that this boy is a 46,XY/47,XY,(Dp−)+ is questionable both on phenotypic and cytological grounds.

Two subjects, one female and one male, with 48 chromosomes and presumptive D- and G-trisomy (48,XX,D+, G+; 48,XY,D+G+, respectively) have been reported (Gustavson *et al.*, 1962b; K. L. Becker *et al.*, 1963). The first of these children had many of the features of D-trisomy and few, if any, of the features of Down's syndrome, while the second child had many of the features of Down's syndrome and few of the features of Patau's syndrome. Evidence from various double trisomics suggests that the phenotype usually resembles that of the primary trisomic which results in the severest malformations; for instance, XXX,21+ and XXY,21+ subjects usually have the typical features of Down's syndrome while XXY,18+ and XXX,18+ subjects have Edwards' syndrome. The rarer 18+,21+ subject usually has a few features of Down's syndrome, although these are usually masked by the more severe features of Edwards' syndrome. It was not therefore surprising to find a grossly malformed child with both D- and G-trisomy who had the typical features of Patau's syndrome and few of the features of Down's syndrome. On the other hand, the converse, a child with both D- and G-trisomy who only had features of Down's syndrome, was much more unlikely; this suggested that the additional long acrocentric chromosome did not belong to the D group despite its superficial resemblance to that group. The child was reported as having 22% normal-sized single sex

chromatin masses and 5% drumsticks. However, as with the boy described by Warkany *et al.* (1964) (see above), if the additional chromosome was an autosome, the mild phenotype is surprising; perhaps the most likely hypothesis is a deletion of the third X chromosome (48,XX,?X p or q−,21+).

C. *D-Trisomy and Mixoploid D-Trisomy Not Associated with Patau's Syndrome*

Beçak *et al.* (1963b, 1964) studied five subjects with congenital analgesia belonging to three unrelated families. Four of these patients as well as the father of two of them were mixoploids with two cell lines (46,XX or XY/47,XX or XY,D+). In one patient all the cells were trisomic and no evidence of mixoploidy could be found, while in one subject 14% of the cells were apparently tetrasomic (48,XX or XY,D+D+). No features of Patau's syndrome could be found in any of these patients. Beçak *et al.* (1964) argued that these subjects were normal D+ mixoploids involving a different D group chromosome from the one which causes Patau's syndrome and further that these subjects represented a group of mixoploids in which the full primary trisomic state was lethal. Blau and Mutton (1967) studied a further eight patients with a congenital indifference to pain, but they were unable to confirm these observations and found a normal chromosome complement in each case.

The absence of any phenotypic abnormalities except analgesia was surprising, particularly in two individuals who had a high frequency of trisomic cells. Furthermore, the lack of information about any other tissues apart from blood is regrettable since the possibility that this chromosome abnormality is confined to the hemopoietic tissues cannot be excluded. Finally, Blau and Mutton's (1967) failure to confirm these observations on a series of carefully selected patients throws considerable doubt on the validity, not on the observations of Beçak *et al.* but on their conclusions, and much additional data are needed before a second D-trisomic syndrome causing analgesia can be established. A further series of 10 mosaic patients with otosclerosis and four normal relatives were studied by Tato *et al.* (1963); all 14 including the normal relatives showed normal/D+/D+,D+ mixoploidy in skin in three subjects, blood in 10 subjects, and blood and skin in one subject. As yet these observations have not been confirmed, and until they are it is not reasonable to postulate any relationship between the observed mixoploidy and the finding of otosclerosis, particularly when the findings of Francois *et al.*

(1966) are considered. They studied a series of 50 patients clinically affected with otosclerosis, which had been surgically confirmed, and found a completely normal karyotype in each subject. The finding by Tato *et al.* (1963) of mosaicism in normal relatives of these patients with otosclerosis suggests that in fact no relationship exists between the chromosome abnormality and the clinical condition. The authors, however, argued that since only about 16% of subjects with histological otosclerosis showed any clinical manifestation, all these subjects with mosaicism, including the apparently normal relatives, had histological otosclerosis but unaffected hearing. In conclusion, at the present time only one clinical syndrome associated with D-trisomy has been established and this is D_1- or 13- trisomy (Patau's syndrome). The association of congenital analgesia and otosclerosis with D-trisomic and tetrasomic mixoploidy has not been proved.

III. Structural Alterations in the D Group Resulting in Features of Patau's Syndrome

A. *Alteration in the Short Arms (46,XX or XY,Dp+, or Dp−)*

Variation in the length and structure of the short arms of the D group chromosomes has already been discussed (see Volume I, Chapter 4) and does not generally result in any obvious clinical effect and occurs in about 2% of the normal subjects. It is, therefore, extremely difficult to correlate this type of abnormality with an abnormal phenotype.

Taylor (1968a) reported a female infant with the full clinical picture of Patau's syndrome, except that the neutrophil projections were normal, who had a 46,XX,Dp+ chromosome complement (Fig. 7-2). It is tempting to postulate a connection here between the phenotype and the chromosome anomaly, and it is of course possible that this particular chromosome anomaly could have resulted from the translocation of a piece of the long arm of one homologous D chromosome onto the short arms of another, resulting in a duplication of Dq material in the proband. This interpretation would be proved valid if a balanced karyotype were to be found in the parents who were not available for study. A child with a very similar karyotype (see Fig. 7-2) but showing much milder phenotypic malformations consisting of low birth weight, mental retardation, microphthalmia and coloboma, cleft palate, harelip, and esophageal artesia was reported by Zellweger *et al.* (1962). Again the phenotype may be the result of chromosome duplication, but evidence for this is unfortunately lacking. Therefore, in the absence of evidence to the contrary, it seems most likely that both of these patients may be examples of chance

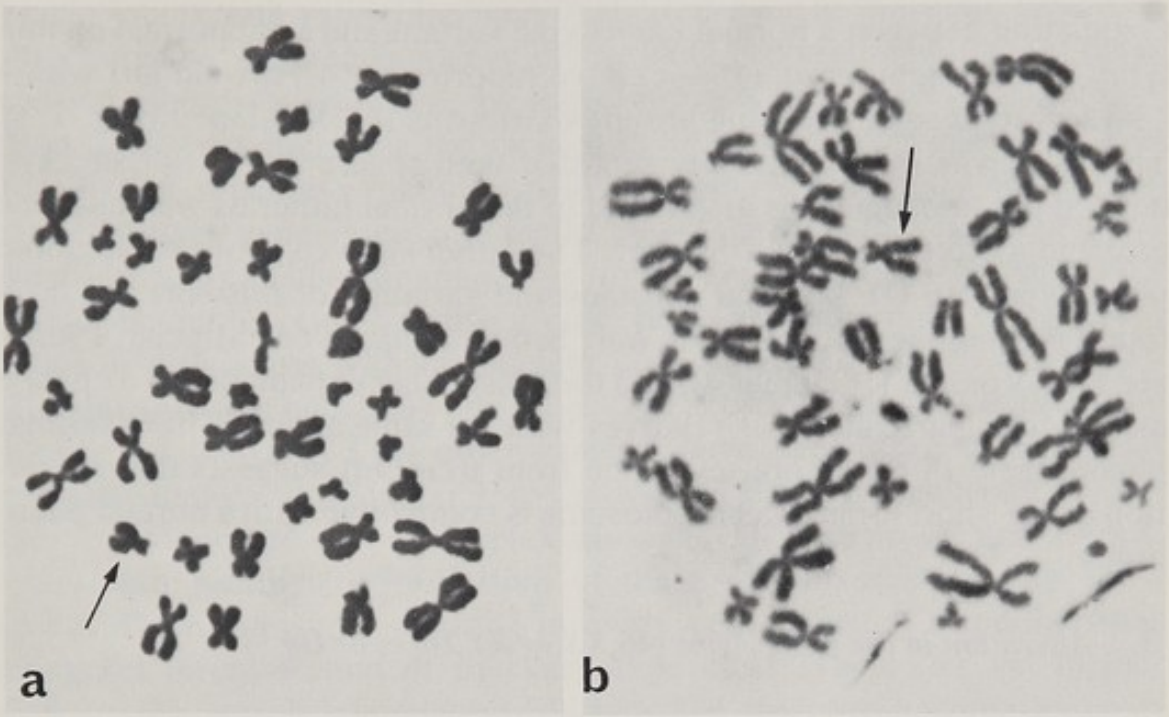


FIG. 7-2. Metaphase plate from two patients with Patau's syndrome and a D chromosome with enlarged short arms: (a) from Zellweger *et al.*, 1962 and (b) from Taylor, 1968a.

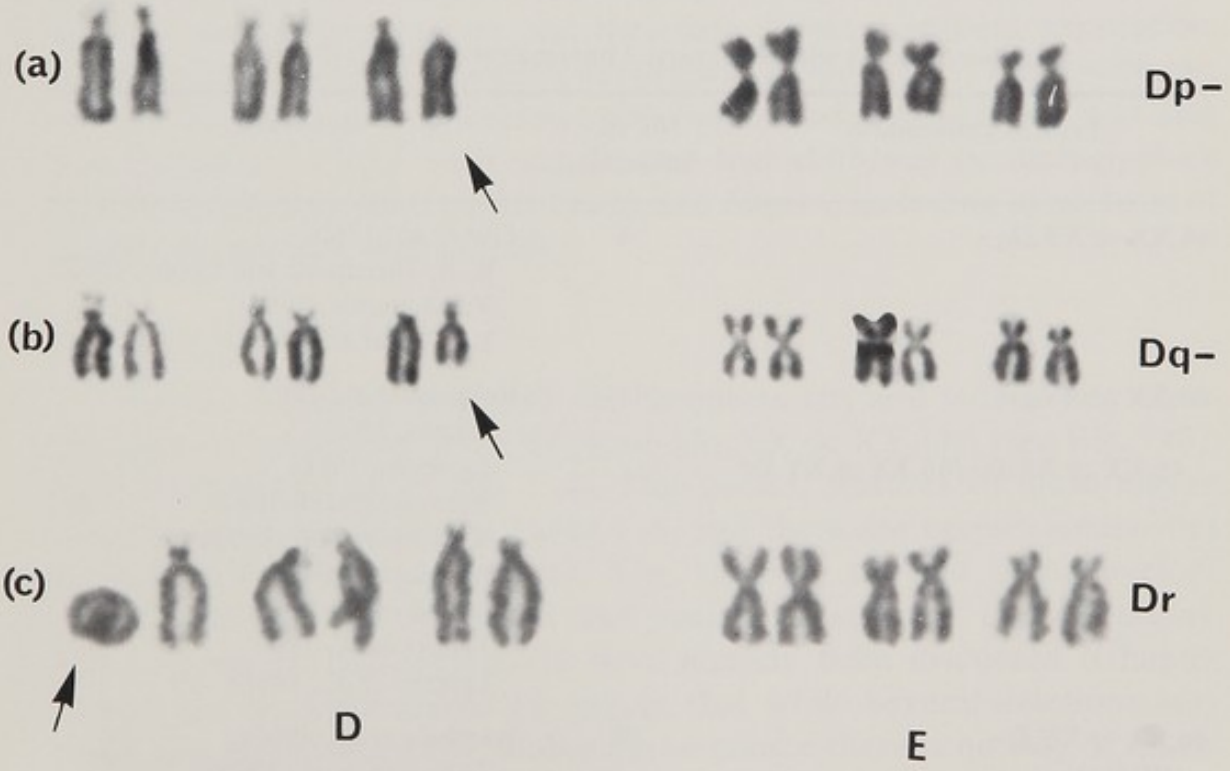


FIG. 7-3. Structural alterations in the D group. Partial karyotypes (a) Dp−, (b) Dq−, and (c) Dr. (a) From De Grouchy *et al.* (1966c), (b) Laurent *et al.* (1967), and (c) Lejeune *et al.* (1968b). (See text for further details.)

association between a normal karyotypic variant and an abnormal phenotype. De Grouchy *et al.* (1966c) have reported a 14-year-old girl with a 13-15 chromosome showing absent short arms (46,XX,Dp−) (Fig. 7-3). The child was mildly mentally retarded with severe hypertelorism. The deleted chromosome was also found in the normal father as well as in the proband's brother and half-brother. The father showed a rare haptoglobin phenotype (Hp-O). Familial chromosome variation of this sort has been found in a number of families (Court Brown *et al.*, 1966; Migeon, 1965b; see also Volume I, Chapter 4), and the most likely explanation is a chance association, particularly as relatives with the same anomaly have normal phenotypes. Furthermore, evidence from t(DqDq) suggests that a deletion of the short arms of a chromosome is compatible with a normal phenotype.

B. *Alteration in the Long Arms (46,XX or XY,Dq+, or Dq−)*

1. Deletion

Four patients have been reported (Table 7-4) with 46,XX or XY,Dq− (see Fig. 7-3). Lele *et al.* (1963) reported a slightly retarded

TABLE 7-4

Some Patients with Structural Abnormalities of the D Group

Type of abnormality	No. of subjects	Reference
46,XX or XY,Dq−	4	Lele *et al.*, 1963; R. B. Thompson and Lyons, 1965; Van Kempen, 1966; Laurent *et al.*, 1967
46,XX or XY,Dr or 45,XX or XY,D−/46,XX or XY,Dr	11	Reisman *et al.*, 1965; Adams, 1965; Jacobsen, 1966; Bain and Gauld, 1963; MacIntyre *et al.*, 1963; Wang *et al.*, 1962; Gerald *et al.*, 1967; Teplitz *et al.*, 1967; Lejeune *et al.*, 1968b (3)
46,XX or XY,D− t(DqDq)+ (sporadic)	10	Bumbalo *et al.*, 1967; Tolksdorf *et al.*, 1965b; Jongbloet *et al.*, 1964; Conen and Erkman, 1966b; Taylor, 1968a.

female infant with retinoblastoma in the left eye; at the same time, five other subjects with the same eye defect were reported who had no chromosome abnormality. Three of these subjects had familial retinoblastoma while two, including the child with an abnormal chromosome, had no affected relatives. Bilateral retinoblastoma is generally thought to have a single gene dominant mode of inheritance (S. M. Smith and Sorsby, 1958). This dominance is irregular, and some of Macklin's (1959) pedigrees can be interpreted both as recessives (McKusick, 1966) or dominants with incomplete penetrance. Unilateral cases may often be sporadic and Falls and Neel (1951) estimated the mutation rate to be 2.3×10^{-5}. Two other subjects have been studied. Both had retinoblastoma and a similar Dq− as well as other chromosome anomalies and appeared to be complex mosaics (H. Thompson and Lyons, 1965; Van Kempen, 1966). Both of these patients appeared to show loss of D chromosome material in every cell, although in neither was the exact interpretation of the karyotype clear. These are yet further instances in which the relationship between the chromosome anomaly and the specific phenotypic defect is extremely doubtful. It may be that in these cases there is some connection, and one possibility is that these subjects are heterozygotes in which the mutant would normally show incomplete penetrance or be completely masked; in which case the deletion must include the normal allele so that each of these subjects is effectively a mutant hemizygote and therefore shows complete expression. A fourth child has been recently reported (Laurent *et al.*, 1967) with eye defects including microphthalmia, coloboma, and cataract. She was also microcephalic, of low birth weight, and had abnormal dermatoglyphics as well as abnormalities of the hands and fingers, including synostosis of the fourth and fifth metacarpals.

2. Ring Chromosomes

Eleven subjects, each with 46 chromosomes and with a ring chromosome replacing one of the D group (46,XX or XY,Dr) (see Fig. 7-3), have been described (Table 7-4). The clinical features of these eleven patients are summarized in Table 7-6, and there are certain similarities between Dr and Dq− patients. The majority showed both developmental and mental retardation and variable congenital malformations. The reasons for this variability have already been discussed (Chapter 6) and can be summarized by saying that while several deletions may result in a morphologically similar chromosome there is no way of establishing the identity of genetic material. Lejeune *et al.* (1968b), from a study of three cases, suggested that a definite syndrome could be established consisting of microcephaly, hypertelorism and prominent naso-

frontal bones eliminating the bulge of the nose. The ocular abnormalities range from heterochromia to microphthalmia. The external ears are large with deep helices and well-developed lobules and the upper incisors are abnormally placed. Most of these features are, however, by no means confined to subjects with this particular chromosome abnormality but are found in many subjects with different abnormalities. At least ring chromosomes are formed as a result of double terminal deletions (see Volume I, Chapter 8), whereas chromosomes showing an apparently simple deletion may have arisen by one of several mechanisms and may have duplicated as well as deleted segments. Finally, it cannot be stated with certainty, except by extensive autoradiographic studies, that any two cases involve the same D chromosome.

The Dr chromosomes seem to be relatively stable and were found in all the cells in six of the patients, while no cytological data were given in the seventh case (Table 7-5). The remaining four subjects were all mixoploids with the major cell line carrying the ring. Generally, the rings appear to be of one size and usually monocentric. The stability of the ring chromosomes which have been recorded in man is interesting, and these D rings appear to have a greater stability than the 17-18 rings discussed in the previous chapter. Gripenberg (1967) has studied the stability of a 17-18 ring and found about 19% of monosomic cells with both the ring and the normal 17-18 chromosome missing and about 9% of the cells with an enlarged and apparently dicentric ring. Two mechanisms for the loss of the ring are suggested, lagging and an unstable structure, and some degenerating ring chromosomes were reported. Shaw and Krooth (1966) studied the stability of a C ring in five parallel fibroblast lines over about 70 cell generations. They found that the proportion of cells carrying ring chromosomes dropped with time and that they disappeared completely in two cell lines. They also found a high proportion of monosomic cells and cells containing rings of variable structure. Stable ring chromosomes have been reported in other species including *Drosophila* and maize. In man, the apparent stability of the rings in somatic cells probably depends on the chromosomes involved, for instance, a ring-X is likely to appear relatively unstable in culture because cells can survive X-monosomy; autosomal monosomy may, however, act as a cell lethal, so that an autosomal ring might appear to be stable because its loss results in cell death.

3. Translocations Resulting in Patau's Syndrome

In this section only translocations which resulted in complete or nearly complete duplication of the long arms of a D chromosome, and

TABLE 7-5

Chromosome Counts in Subjects with Ring Chromosomes in the D Group

Reference	Cells counted	45	46	47	Analysis	Karyotype
Wang *et al.*, 1962	>100	–	–	–	Ring present in all cells. Usually small monocentric, occasional large rings.	46,XY,Dr
Jacobsen, 1966; (Four blood cultures)		2	73	1	All cells showed a ring. Monocentric size relatively constant.	46,XY,Dr
Bain and Gauld, 1963		4	56	–	Small ring. Five D group chromosomes.	46,XX,?Dr
MacIntyre *et al.*, 1963		–	100	–	Ring in all cells	46,XY,Dr
Reisman *et al.*, 1965.	No. of cells not recorded.				Ring present in all cells	46,XY,Dr
Gerald *et al.*, 1967 (Three blood cultures)		10	68	2(end)	All 78 cells have ring. 10 cells with <46 show random loss.	46,XX,Dr
Teplitz *et al.*, 1967 (bone marrow)		13	49	3	93% cells with 46 Dr. A few cells (5%) were C+.	46,XY,Dr/46,XY,?C+
First blood culture		3	25	–	Total cells 344– 263 46,XY,Dr;	?C+ interpreted as an
Second blood culture		–	277	–	14 46,XY,?C+, 67 including cells with 2 rings and no ring	open ring
Lejeune *et al.*, 1968b						
Case 1. Blood		22	232	2	D–/Dr mixoploid	45,XY,D–/46,XY,Dr/47,XY,Dr,Dr
Bone marrow		–	84	3		46,XY,Dr/47,XY,Dr,Dr
Skin		44	32	–		45,XY,D–/46,XY,Dr
Case 2. Blood		5	105	1	D–/Dr mixoploid	
Skin		4	14	–		45,XY,D–/46,XY,Dr
Case 3. Blood		7	117	–	D–/Dr mixoploid	
Skin		62	22	–		45,XY,D–/46,XY,Dr

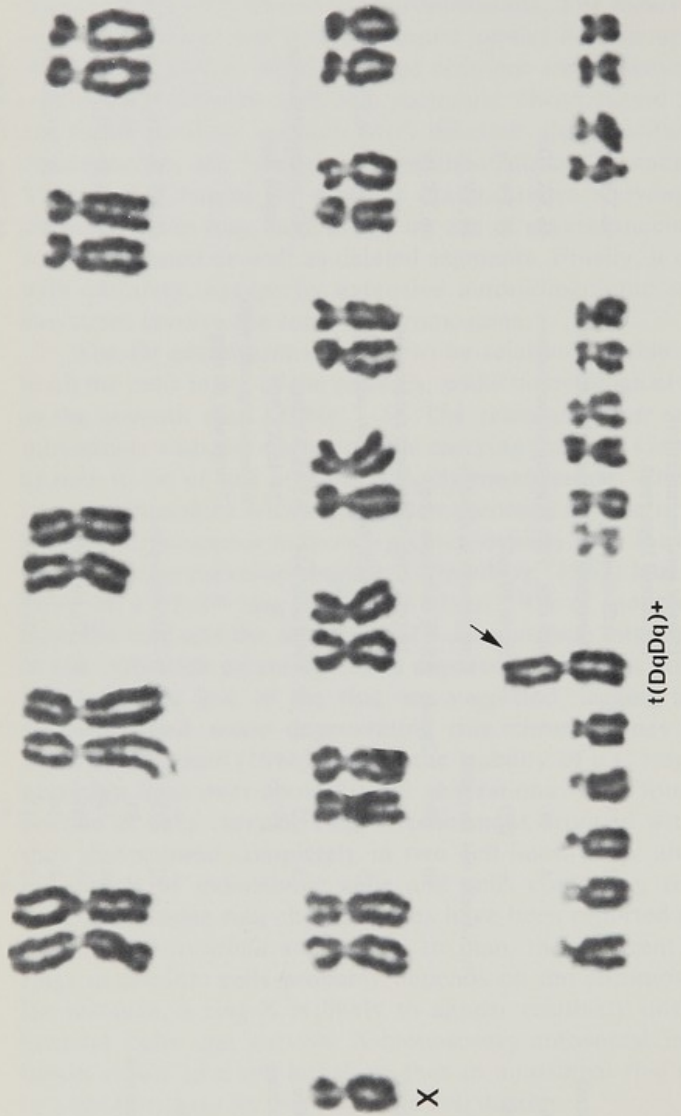


FIG. 7-4. Karyotype of patient with Patau's syndrome and a t(DqDq) [46,XY,D−,t(DqDq)+] (×1169).

which were ascertained because of Patau's syndrome, will be considered.

t(DqDq). These translocations between the long arms of two D chromosomes have been discussed in detail in Chapter 8 (Volume I). Patau's syndrome is rare in families in which there is a segregating t(DqDq), and the reasons for this have already been discussed. In the 24 kinships with a t(DqDq) segregating there were five children with Patau's syndrome of whom four were probands out of a total of about 170 children, a frequency of just over 2%, which, if corrected for the probands, drops to 0.67% (see also Volume I, Chapter 8). Apart from the five infants referred to above in which Patau's syndrome is the result of a familial t(DqDq), 10 children with the typical features of Patau's syndrome, 46 chromosomes, one D chromosome missing, and an additional long metacentric chromosome are known. These are all thought to carry either a sporadic Dqi or t(DqDq) [46,XX or XY,D−,Dqi+ or 46,XX or XY,D−,t(DqDq)+] (Fig. 7-4) (Jongbloet *et al.*, 1964; Taylor, 1967; Huehns *et al.*, 1964; Conen *et al.*, 1966; Giannelli, 1965; Tolksdorf *et al.*, 1965b; Erkman *et al.*, 1965). In addition to these 10 children, a single stillborn child with the clinical features of D-trisomy and a t(DqDq) translocation was reported by Montero *et al.* (1964). Atkins and Keenan (1965) reported a child with the typical features of Patau's syndrome (see Table 7-6) with only 46 chromosomes, six chromosomes in the D group, and a morphologically abnormal long chromosome with elongated arms replacing one No. 3 (Fig. 7-5) (46,XY,3?+). The chromosomes of both parents were studied and found to be normal. In view of the phenotype the authors interpreted the abnormal chromosome as being the result of translocation between a seventh D chromosome and a No. 3 [t(3;D)], and this was confirmed by autoradiography.

A number of other reciprocal translocations involving group D are known. These will be discussed along with other reciprocal translocations in Chapter 8, Section III.

IV. Clinical Features of D_1-Trisomy

A. *Description of the Phenotype*

The phenotype associated with 13-trisomy (D_1-trisomy) (46,XX or XY,13+) was first described in 1960 in a female infant, and subsequently in greater detail in 1961 and 1963 (Patau *et al.*, 1960, 1961b; D. W. Smith *et al.*, 1963; Taylor and Polani, 1964). Recently, Taylor (1967,

TABLE 7-6

Clinical Features of Patients with Abnormalities in the D Group

Condition	Patau's syndrome[a]	Patau's syndrome[b]	Mixoploid D-trisomy[c]	Dr[c]	Dq−[c]
Number of subjects	55	29	10	11	4
Major clinical features[d]					
Developmental/mental retardation	100	100	75	7/7	4/4
Hypertonia	35	28	25	–	–
Hypotonia	20	48	40	–	–
Jitteriness and apnoea	93	63	20	–	–
Seizures	63	28	43	–	–
Presumptive deafness	95	53	0	–	–
Odd facies	–	–	–	6/6	3/4
Microcephaly	83	59	25	8/8	2/2
Hypertelorism	–	93	–	4/4	1/4
Epicanthus	–	52	–	4/5	1/4
Ptosis	–	–	–	2/5	–
Harelip	67	55	38	2/5	–
Cleft palate	81	65	60	2/5	2/4
Micrognathia	–	86	33	3/3	–
Microphthalmos	74	78	22	3/4	2/2
Coloboma	64	35	33	5/5	2/2
Large ears	–	–	–	7/8	–
Malformed ears	91	81	56	2/6	1/4
Short neck	–	–	81	–	–
Capillary hemangioma	74	73	25	–	–
Polydactyly	76	78	11	–	–
Flexion deformity of fingers	59	70	56	3/5	–
Retroflexible thumbs	46	27	17	–	–
Long hyperconvex nails	81	71	43	3/3	–
Single palmar crease	92	64	25	–	–
Distal axial triradius	93	77	66	–	–
Prominent calcaneus	65	33	25	–	–
Fibular S-shaped hallucal arch	78	–	50	–	–
Abnormal feet	–	56	–	6/6	–
Undescended testes (♂)	100	93	–	3/7	1/2
Hypospadias (♂)	–	–	–	3/7	–
Cerebral holosphere	10	–	–	–	–
Absent olfactory bulbs	56	71	–	–	–
Superficially normal brain	17	25	Not recorded	–	–
Congenital heart disease unspecified	–	–	67	–	–
Ventricular septal defect	61	52	33	–	–
Major atrial septal defect	44	87	–	–	–
Patent ductus arteriosis	48	67	–	–	–
Dextraposed heart	65	17	–	–	–
Normal heart	12	22	–	–	–
Polycystic renal cortex	53	30	–	–	–
Hydronephrosis/ureter	35	17	–	–	–
Normal renal tract	18	44	–	–	–
Biseptate uterus (♀)	70	43	–	–	–

[a] Series from Taylor (1967); 55 cases mainly from literature.
[b] Taylor (1969); 29 cases, Pediatric Research Unit data.
[c] See Table 7-1 for references.
[d] Frequencies expressed as percentages except in Dr and Dq⁻ columns.



FIG. 7-5. Metaphase from a patient with Patau's syndrome and a presumptive t(3;D). Six D chromosomes can be seen. One No. 3 is replaced by an abnormal long submetacentric chromosome which is presumed to be the product of a translocation between the long arm of the seventh D and the other No. 3. (From Atkins and Keenan 1965.)

1968a, 1969) reviewed the clinical and epidemiological features of 74 trisomic subjects.

The infant originally described by Patau *et al.* (1960) had the following major congenital defects: severe developmental retardation, apparent anophthalmia, harelip, cleft palate, and polydactyly of the left foot. She was not microcephalic and had a normal jaw. The external genitalia were normal. There were also external ear deformities and flexion deformities of the thumbs. A large number of capillary hemangiomata were seen on the face, neck, and back. The neurological examination was relatively normal, although it is possible that the child was deaf. She suffered from brief grand mal seizures from 8 months, and although she had a normal cranial circumference at birth she was microcephalic by 1 year. She died at the age of 22 months. At autopsy she was found to

have a congenital heart defect with partial dextraposition and an interventricular septal defect. The brain showed no abnormality except for hypoplasia of the optic nerves and chiasma. Subsequently, between 50 and 100 13-trisomics have been reported in the literature and the clinical features of 55 of these are summarized in Table 7-6. These trisomic subjects all had severe developmental retardation combined with a number of characteristic clinical features (Fig. 7-6). The majority were microcephalic and microphthalmic. Malformations of the ears, lips, and palate were common and many of the children were deaf. Coloboma was frequent and numerous capillary hemangiomata were typical. There were frequently abnormalities of the fingers and toes including polydactyly, syndactyly, and flexion deformities. The fingernails were often long and hyperconflex. The dermatoglyphics were abnormal (Penrose, 1963; Uchida *et al.*, 1962b), and there was usually only a single palmar crease and a distal axial triradius with a high atd angle (Fig. 7-7).

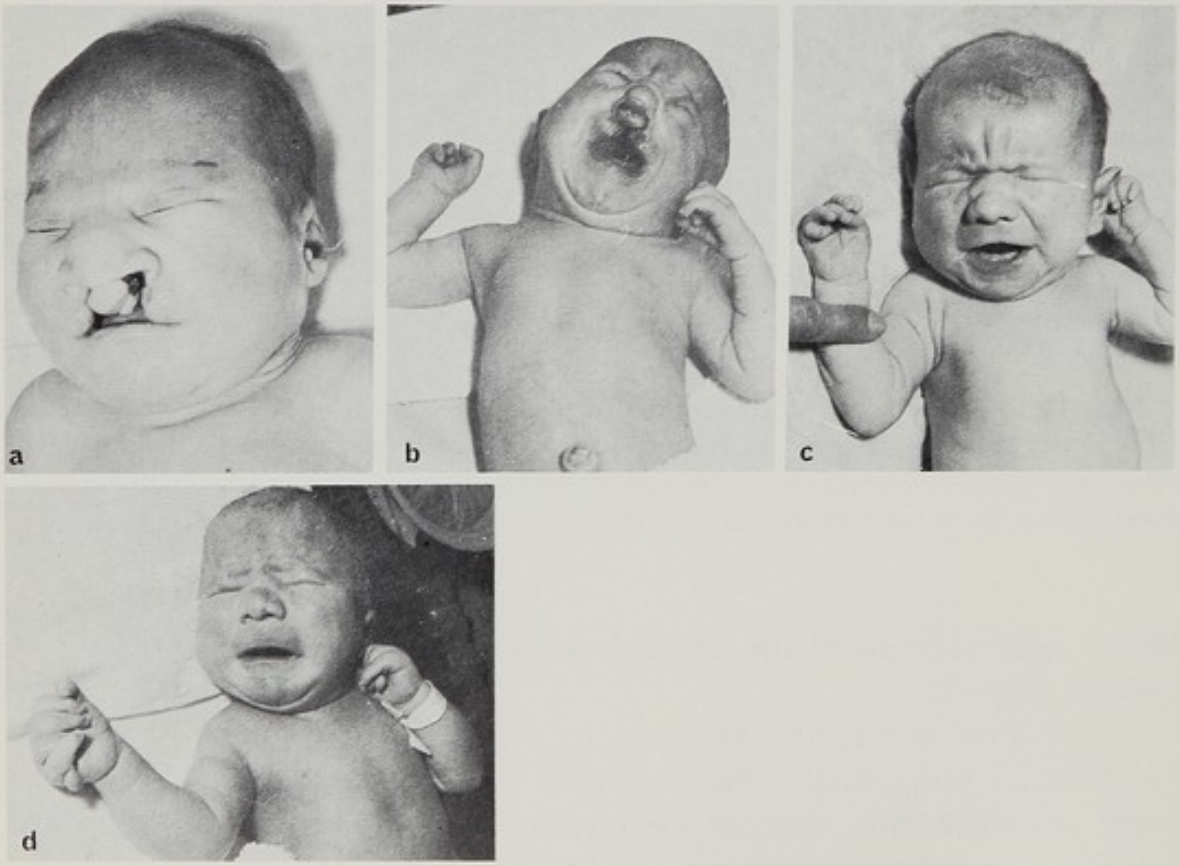


FIG. 7-6. Photographs of infants with D-trisomy at birth showing (a) microcephaly, severe defects of lip and palate, mongoloid slant to eyes, and malformed pinnae of left ear; (b) microcephaly, severe defects of lip and palate and umbilical hernia; (c) long thin mouth, low-set primitive ears, and polydactyly; (d) trapezium-shaped face, triangular nose, long thin mouth, long tapering fingers, and polydactyly. (Reproduced by courtesy of Dr. A. I. Taylor.)

At autopsy brain defects were common, only 17% of subjects having a superficially normal brain. Ten per cent of the subjects had a single cerebral holosphere, while about 56% had absent olfactory bulbs, and there have been a number of reports of the specific association of arrhinencephaly and 13-trisomy (Bühler *et al.*, 1962; J. Q. Miller *et al.*, 1963; Laurence, 1964; Laurence and Ishmael, 1969). This association is not, however, absolute, arrhinencephaly frequently occurring without any visible chromosome anomaly (DeMyer *et al.*, 1963; DeMyer, 1964). Norman (1966) has examined five brains from 13-15-trisomics and found arrinencephaly in four of them. It therefore seems likely that while arrhinencephalic brains may occur without the associated chromosome anomaly, the brains of 13-trisomics are frequently arrhinencephalic.

Optic defects were common and included gross microphthalmia or anophthalmia, coloboma of the iris, retinal dysplasia, and cataract (M. Miller *et al.*, 1963; Yanoff *et al.*, 1963; Cogan and Kuwabara, 1964). Roch *et al.* (1965) considered that the main effect of the abnormal karyotype on the development of the eye appeared to be on the growth and differentiation of tissues derived from the anterior margin of the inner wall of the optic cup and affected the eye at not later than the sixth week of gestation. Mottet and Jensen (1965) described in detail the pathology of three D-trisomics and concluded that the associated anomalies seem to be manifestations of developmental retardation occurring in embryos of 5-6 weeks gestation and that the mesodermal derivatives appeared to be principally affected. The major clinical features of 11 46,XX or XY/47,XX, or XY,13+ mixoploids are summarized and compared with the primary trisomics in Table 7-6. Clearly, the frequency of major congenital malformations is less in the mixoploids than in the full primary trisomic subjects. Finally, consideration of the clinical features of the t(DqDq) translocation trisomics suggests that these closely resemble the primary trisomics. No specific clinical features are associated with a deletion of the short arms of one D chromosome which must have occurred during the formation of the structural rearrangement.

A further characteristic feature in D-trisomy is the finding of a high frequency of aberrant projections on the neutrophil leukocytes (Fig. 7-8) which are quite unlike those observed in any other condition (Walzer *et al.*, 1966b; Lutzner and Hecht, 1966; A. E. Becker, 1965; Powars *et al.*, 1964). It has been suggested that these changes reflect an alteration of enzyme content. There is, however, little evidence for this hypothesis. Several authors have reported abnormal levels of fetal hemoglobins (Hb-F) surviving into the neonatal period in these and other trisomic infants (Powars *et al.*, 1964; Huehns *et al.*, 1964). Elevated levels of

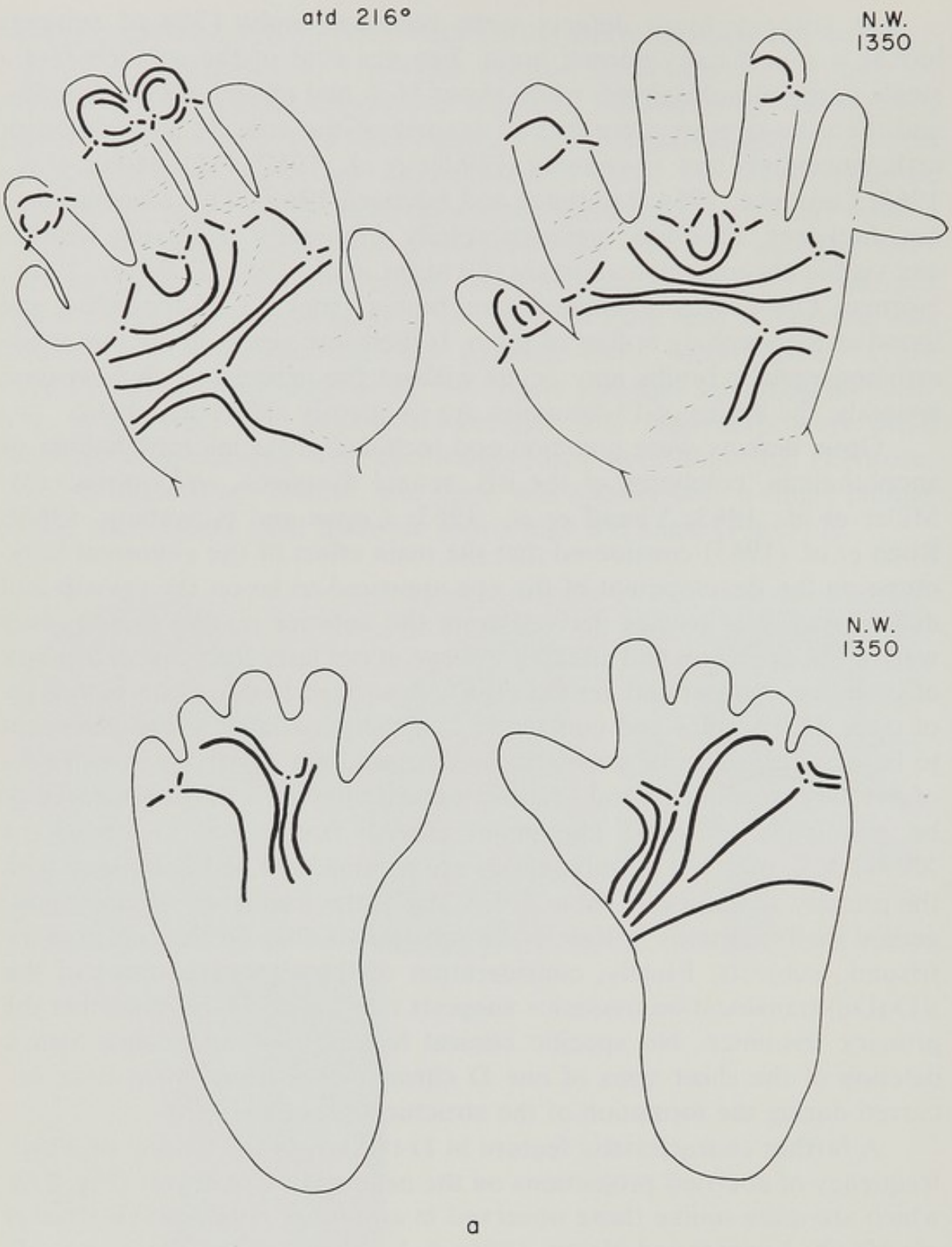
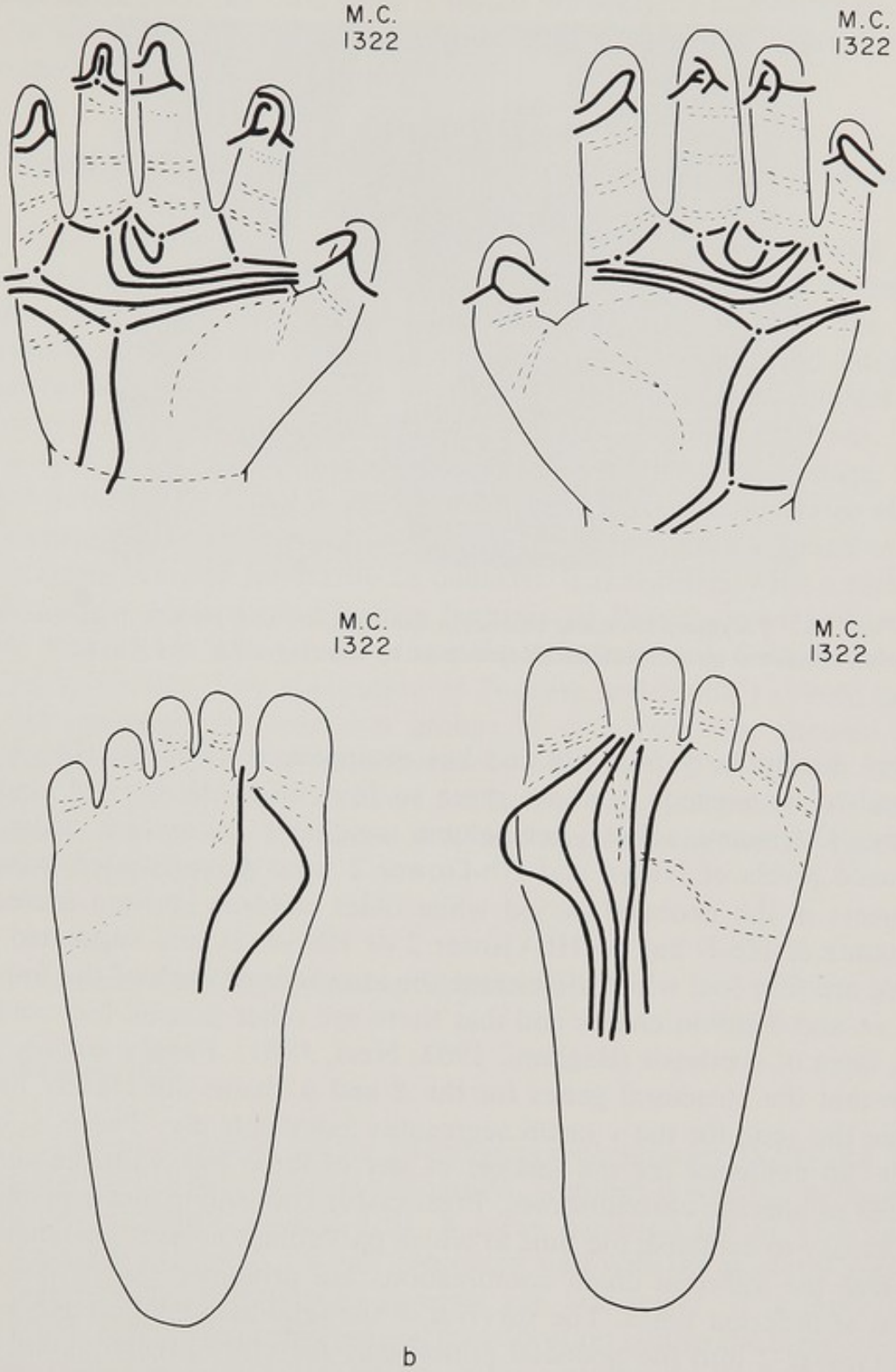


FIG. 7-7. Dermatoglyphic patterns seen on the palms and soles of two infants with D-trisomy. (a) Case 8. Note t''' position of palmar triradius and high atd angle, a high frequency of loops, and supernumary digits on the hands. Note unusual patterns on the soles. (b) Case 7. t''' position of palmar triradius and large tibial loop in the hallowed area of soles. (From Taylor and Polani, 1964.)



b

Hb-F were also found in three older children with D-trisomy. Two other abnormal hemoglobins were also found in seven D-trisomics at birth. These were Hb-Gower 2 and Hb-γ4. Hb-Gower 2 is normally

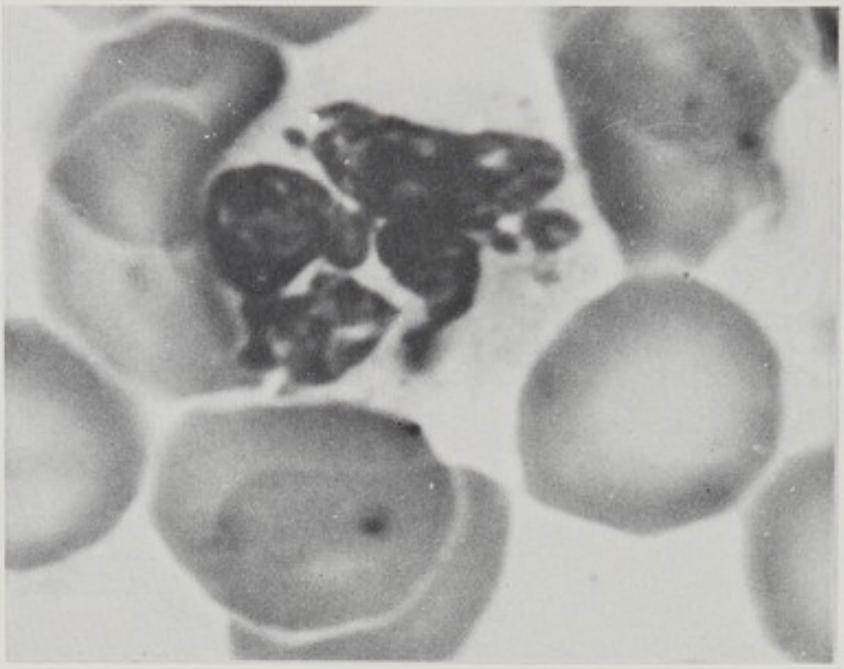


FIG. 7-8. Polymorphonuclear leukocyte from patient with Patau's syndrome. Note abnormal lobulation and projections. (Reproduced by courtesy of Dr. A. I. Taylor.)

found during early fetal life and has disappeared by birth. Hb-γ4 was found to be present in about three to four times the normal amount. Thus, D-trisomy affects hemoglobin synthesis in several ways. Increased levels of Hb-γ4 and Hb-Gower 2 were demonstrated in seven subjects in the neonatal period while older children showed increased amounts of Hb-F but no Hb-Gower 2 or Hb-γ4. It was suggested that there are four loci which determine the structure of each of the four α-, β-, γ-, and δ-globin chains and that there are other genetic loci controlling rates of synthesis (Baglioni, 1963; Neel, 1961). Family studies indicate that the structural genes for the β and δ chains are closely linked while the gene for the γ chain segregates independently. There is, however, no evidence for the linkage of any of these loci with the centromeres of specific chromosomes. Presumably controlling mechanisms are necessary to establish the time at which particular loci are "switched on" so that the different chain combinations are produced during development at different times. The survival of the fetal hemoglobins Hb-F and Hb-Gower 2 into the neonatal period may therefore involve a defect at any one of three places, the structural locus, the rate controlling locus, or, finally, the switching mechanism. The most likely hypothesis is that the trisomy has caused a defect in the switching mechanism which has become delayed so that the production of these fetal hemoglobins con-

tinues far beyond the time when it would normally be discontinued. This fits in well with the general hypothesis of developmental retardation associated with autosomal trisomy.

B. *Phenotypic Discrimination between Edwards' and Patau's Syndromes*

It is clear from the clinical features that Patau's and Edwards' syndromes show considerable overlap. Taylor (1968a) attempted to demonstrate which were the main discriminating features for the two syndromes out of the 46 which she scored during life and 24 postmortem findings. Out of these 70 characteristics only two clinical features and six postmortem findings do not occur in both conditions. Taylor's method of discrimination was to calculate the percentage with which a feature is found in both conditions and to take the ratio of the percentage found in Edwards' syndrome to the percentage found in Patau's syndrome and arbitrarily to consider that features with a ratio of <0.5 are the main discriminatory features of Patau's syndrome while those with ratios 1.5 and above are the discriminatory features of Edwards' syndrome. The application of Penrose and Smith's (1966) index of discrimination to these two groups of characteristics showed that none of them had a high discriminatory efficiency. The highest values (Tables 7-7 and 7-8) are obtained for harelip and cleft palate in Patau's syndrome (PS) and an elongated skull and simple arches on all digits for Edwards' syndrome (ES).

V. Anamnestic and Epidemiological Data

A. *Parental Age*

The mean maternal age for 74 subjects with primary D-trisomy was higher than that of the general population, although it was not as high as in Down's syndrome (Table 7-9). A mean maternal age of 31.6 years and a paternal age of 31.9 years compared well with the parental ages of the 18-trisomics, although the paternal age was lower. It is, however, noticeable that in the mixoploid and translocation groups the mean parental ages are much lower and do not differ significantly from the general population. Subjects with other structural D group abnormalities do not appear to show any consistent alteration in parental age distribution. In four subjects with Dq−, the maternal age was slightly lower (27.8) while

TABLE 7-7

Clinical Features Which Discriminate for Patau's Syndrome[a]

Feature	Frequency		Probability score in favor of PS		Index of efficiency
	PS p	ES e	Presence (+) $\log \exp^{p/e}$	Absence (−) $\log \exp[(1\text{-}p)/(1\text{-}e)]$	$(p\text{-}e)\ \log \exp[p(1\text{-}e)/e(1\text{-}p)]$
Microcephaly	0.64	0.08	+2.08	−1.11	1.67
Eye defects	0.88	0.29	+1.11	−2.41	1.79
Microphthalmos	0.76	0.29	+0.96	−1.77	0.96
Iris coloboma	0.33	0.00	–	–	–
Low set normal ears	0.12	0.04	+3.00	−0.17	0.009
Harelip	0.58	0.04	+2.67	−0.92	1.79
Cleft palate	0.69	0.11	+1.84	−1.27	2.45
Capillary hemangioma	0.72	0.19	+1.33	−1.47	2.45
Polydactyly	0.76	0.08	+2.25	−1.51	2.43
Long hyperconvex finger nails	0.68	0.16	+1.45	−1.31	1.78
Talipes equinovarus	0.17	0.08	+0.70	−0.27	0.09
Fibular S-shaped hallucal arch	0.39	0.05	+2.05	−0.54	0.85
			Postmortem Findings		
Pyelon duplex	0.14	0.00	–	–	–
Polycystic renal cortex	0.33	0.15	+0.79	−0.56	0.18
Biseptate uterus(♀)	0.42	0.00	–	–	–
Absent olfactory bulbs	0.70	0.00	–	–	–

[a] After Taylor (1968a).

TABLE 7-8

Clinical Features Which Discriminate for Edwards' Syndrome[a]

Feature	Frequency		Probability score in favor of ES		Index of efficiency
	ES e	PS p	Presence (+) $\log \exp^{e/p}$	Absence (−) $\log \exp[(1-e)/(1-p)]$	$(e-p) \log \exp[e(1-p)/p(1-e)]$
Hypertonia	0.50	0.26	+0.65	−0.99	0.25
Elongated skull	0.93	0.16	+1.76	−0.53	3.35
Webbed neck	0.31	0.00	–	–	–
Partial syndactyly	0.32	0.12	+0.98	−0.51	0.70
Distally implanted thumb	0.52	0.12	+1.46	−0.87	0.88
Retroflexible thumb	0.50	0.25	+0.69	−0.98	0.27
Nail hypoplasia	0.63	0.37	+0.53	−1.47	0.27
Short dorsiflexed big toes	0.75	0.24	+1.13	−1.66	1.15
Talipes calcaneo valgus	0.52	0.09	+1.75	−0.82	1.06
Prominent calcaneus	0.77	0.28	+1.01	−1.80	1.09
Limited hip abduction	0.68	0.19	+1.28	−1.35	1.09
Abnormal shoulder abduction	0.13	0.05	+0.96	−0.19	0.09
Short sternum or shield chest	0.68	0.13	+1.65	−1.28	1.46
High-pitched catlike cry	0.33	0.04	+2.11	−0.44	0.69
Simple arches on fingers	0.96	0.33	+1.07	−3.51	2.62
			Postmortem Findings		
Horseshoe kidney	0.23	0.00	–	–	–
Hydronephrosis	0.23	0.10	+0.83	−0.37	0.12
Thin diaphragm	0.40	0.00	–	–	–
Meckels diverticulum	0.40	0.11	+1.29	−0.53	0.49
Superficially normal brain	0.92	0.27	+1.23	−2.84	2.28
Meningomyelocoele	0.12	0.00	–	–	–
Pyloric stenosis	0.25	0.05	+1.61	−0.34	0.48

[a] After Taylor (1968a).

TABLE 7-9

Birth and Survival Data in Patients with a Chromosome Abnormality in the D Group

	47,XX or XY,13+	46,XX or XY/ 47,XX or XY,13+	46,XX or XY, D−,t(DqDq)+	46,XX or XY,Dq−	46,XX or XY,Dr
Mean maternal age at birth (years)	31.6	28.2	25.5	27.8	24.8
Mean paternal age at birth (years)	31.9	29.6	27.4	35.0	28.0
Gestational age (weeks)	39.0	40.9	Term[c]	38.0	Term
Birth weight (gm)	2609	3522	2674	2337	2245
Survival	89.2 days ($\sigma > \bar{x}$)	44 hr–9 years	½ hr–9 months	Stillborn–3.5 months	Stillborn–15.5 years
Sex ratio[a]	0.47	0.18	0.50	0.75	0.18
No. of subjects	74	11[b]	10[c]	4[c]	11[c]

[a] Sex ratio = (No. of females)/(total).
[b] See Table 7-1.
[c] See Table 7-4.

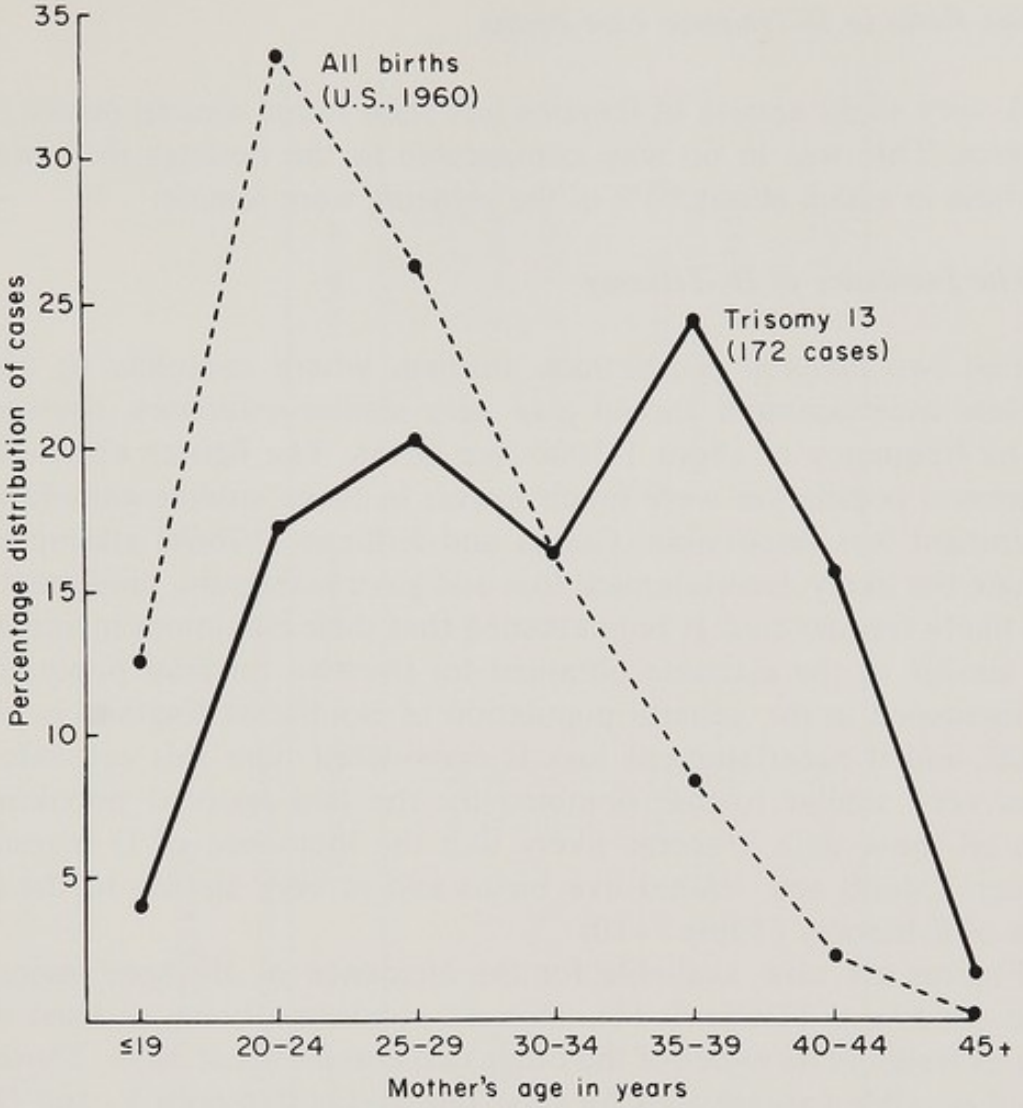


FIG. 7-9. Maternal age distribution curve for 172 cases of D-trisomy compared to the maternal age distribution for the general population (United States). (Modified from Magnenis *et al.*, 1968.)

the paternal age was higher (35.0 years), a difference of 7.2 years. In 11 subjects carrying a Dr or D−/Dr cell line both the mean maternal and paternal ages were lower (24.8 and 28.0 years respectively), a difference of 3.2 years.

Taylor (1967, 1968a) and Magnenis *et al.* (1968) pointed out that the maternal age distribution curve in the primary D-trisomics was bimodal (Fig. 7-9). This compared well with both G- and E-trisomy and suggested that, as in Down's syndrome, there was a small group of patients who were maternal age independent. Inclusion of the mixoploids and patients with sporadic translocations would increase the size of this maternal age independent group which includes all these subjects as well as a proportion of subjects with primary D-trisomy.

B. *Sex Ratio in D-Trisomic Live Births*

A very slight excess of females has been found among primary 13-trisomics. This was in no way comparable to the findings in Edwards' syndrome in which about 80% of the subjects were female.

C. *The Incidence of D_1-Trisomy*

The two hospital populations studied, where complete or almost complete ascertainment should give very similar estimates, showed an over-all frequency of about 1:5000 live births. The figures obtained for the general population were much lower; in these studies complete ascertainment was impossible. Conen and Erkman (1966b) attempted to estimate the likely ascertainment loss and gave maximum, minimum, and most likely frequencies. It is interesting that their maximum incidence is very similar to the estimate obtained for the two hospital populations. The incidence in the general population of Southeast England is about 1:8000, and if ascertainment loss is considered here this estimate becomes very similar to that obtained for the two hospital populations. From all these data it seems likely that the incidence of D-trisomy is between 1:4000 and 1:8000 live births and is very similar to the incidence of E-trisomy (Table 7-10).

Figures are now available for the incidence of all three major trisomic conditions (Table 7-11), Down's syndrome being at least eight times as frequent as either of the other two conditions at birth. There are several possible explanations for this. The first is that both E- and D-trisomics suffer a higher rate of prenatal loss than do G-trisomic fetuses. This, however, is not supported by the data, since all three trisomics occur with approximately the same frequency among spontaneous abortions (see Chapter 9). If we assume, however, that there are initially more G-trisomic conceptuses than either D- or E-trisomics then the relative prenatal loss of G-trisomics must be greater. It seems, therefore, that we can conclude that the higher incidence of G-trisomy may reflect an increased frequency of nondisjunction in the G group as compared with either the D or the E groups (see also Chapter 9 for further discussion).

D. *Survival of D_1-Trisomics*

Taylor (1968a) gave a mean survival time of 89.2 days for 74 subjects (Table 7-9). Conen and Erkman (1966b) gave a mean figure of 132 days for 36 subjects: 16 male trisomics survived for 129.6 days and 20 females for 133.5 days. There was, therefore, no difference between

TABLE 7-10

Incidence of Patau's Syndrome in Different Populations

Reference	Country	Total births	D-trisomy	Incidence
(a) Hospital populations				
D. W. Smith, 1964	United States	10,345	2	1 : 5,173
Taylor and Moores, 1967	London, England	9,688	2	1 : 4,844
Total		20,033	4	1 : 5,008
(b) General population				
Conen and Erkman, 1966b	Canada	134,325	5	Max, 1 : 4,761; min, 1 : 47,610; most likely, 1 : 14,705
Taylor and Fraser Roberts (quoted by Taylor, 1968a)	Southeast England	94,000	11	1 : 8,455
Total		228,325	16	1 : 14,270

TABLE 7-11

The Incidence of Three Trisomic States in Man

Condition	Frequency	
	Range	Best estimate
Down's syndrome (G+)	1 : 400–1 : 700	1.6 : 1000
Edwards' syndrome (18+)	6.5×10^{-4}–7.9×10^{-5}	0.22 : 1000
Patau's syndrome (13+)	2.1×10^{-4}–2.1×10^{-5}	0.20 : 1000

the mean survival of males and females in D-trisomy (cf. E-trisomy). This correlates with the relatively normal sex ratio in this condition. The survival of the nine mixoploids was much more variable, ranging from 44 hr to survival at 9 years of age (Table 7-9). The translocation subjects showed a similar pattern of survival to the primary trisomics and in nine cases the survival time ranged from half an hour to 216 days. The survival of Dq− and Dr subjects was also variable, ranging from stillborn to 15.5 years, and may reflect the variable degree of chromosome imbalance in these subjects resulting from differing amounts of deleted or duplicated material.

E. *Gestation and Birth Weight*

Gestation was relatively normal (Table 7-9) in all four groups and occurred around or just after term; despite this and with the exception of the mixoploid group, birth weights were low and in the range of prematurity. This implies considerable developmental retardation *in utero* and fits in with the observation of Mottet and Jensen (1965) that developmental retardation and abnormalities of organogenesis began at between 4 and 6 weeks gestation.

VI. Genes on Chromosome 13 or Other D Chromosomes

There is no satisfactory evidence for the location of any specific gene loci on chromosome 13 or on any other chromosome in the D group. The presence of abnormal amounts of Hb-F, Hb-Gower 2, and Hb-γ4 in D_1-trisomics (see Section IV, A) does not necessarily indicate that the structural genes coding for the specific globin chains are located on this chromosome. It may simply indicate a degree of developmental retardation which results in abnormal switching from the production of

the polypeptide chains in the fetal hemoglobins to the chains required for the adult hemoglobins. Equally, but perhaps less likely, this abnormal production of fetal hemoglobins could result from the effect of additional gene dosage which could either be at the level of the structural gene or a regulatory gene. Our knowledge of the effect of such additional gene dosage is fragmentary, and it is therefore not possible to speculate on the result if the alleles for globin production were present on chromosome No. 13. Finally, it is possible to speculate that one or more of the regulating loci are present on this chromosome, in which case this could cause the abnormalities of globin production which are observed.

D group structural changes have yielded little information on the genetic content of the group. The association of retinoblastoma with, in a few cases, a deletion of the long arm of a D chromosome could indicate the unmasking of a recessive gene, or "haplo-insufficiency," which implies that the presence of an allele at only one locus as the result of a deletion is insufficient for normal gene function. It is thus possible that the gene for normal retinal formation is present on this chromosome.

Finally, Gerald *et al.* (1967) have shown that a child with a ring D did not carry her putative father's haptoglobin locus but only the allele which she inherited from her mother. They suggested that since the formation of a ring chromosome involved two terminal deletions, one in the long arm and one in the short arm, the father's Hp locus may have been deleted during ring formation and may therefore have been located either on the long or on the short arm of the deleted D chromosome. If this were so, it would have resulted in the child's expressing only the maternal Hp. Other explanations are possible, including the presence of a silent Hp allele in which case the father would have an Hp^{2}/Hp^{-} genotype and the propositus an Hp^{1F}/Hp^{-} genotype. This would result in the Hp^{1F} electrophoretic pattern observed. However, the genotype Hp^{2}/Hp^{-} would also be expected to be "weak" and this was not observed; besides, variant Hp alleles are very rare in Caucasian populations, and since the father had a normal strength $Hp^{2\text{-}2}$ phenotype, a silent Hp^{-} allele was not thought to account for the anomalous inheritance pattern. De Grouchy *et al.* (1966c) have also reported a Dp− subject with an Hp-O phenotype suggesting again the possibility that the locus is situated on the short arm of one D chromosome. Unfortunately, autoradiographic studies in order to identify the D chromosome were not reported.

Bloom *et al.* (1967) have presented autoradiographic evidence that the D chromosome forming the ring in two families (Reisman *et al.*, 1965; Gerald *et al.*, 1967) involved the D chromosome which had a distinct late labeling distal region (D_1 or No. 13). Studies by the same authors on a t(B;D) patient who appeared to have a Dq deficiency sug-

gested to them that the Hp locus was on the distal portion of the short arm. Bias and Migeon (1967), however, studied a family with a segregating 13p− chromosome and concluded that the Hp locus was *not* on the deleted segment. Hustinx *et al.* (1965) have also suggested that the Hp locus is on the short arm of a D chromosome. This was based on the calculation of a 14% crossover frequency in t(DqDq) and t(DqGq) heterozygotes which they maintained was too low a frequency for the distance between the centromere and the distal region of the long arm. Several of these translocation heterozygotes were $Hp^{2\text{-}1}$ so that either the Hp locus was not on the short arm or it was very close to the centromere. These translocations involved loss of almost the entire short arms so that it seemed likely that a 14% crossover frequency might be too high for the very short chromosome region remaining.

If a deletion is the correct explanation for the anomalous inheritance of Hp in these families reported by Gerald *et al.* (1967), then the most likely position for the locus seems to be the distal terminal segment of the long arm of one D chromosome, perhaps No. 13, rather than the distal segment of the short arm, which is heterochromatic and frequently deleted and therefore *per se* less likely to carry major gene loci. Ring chromosomes involve two terminal deletions, one in the long arm and one in the short arm. There are a number of structural rearrangements

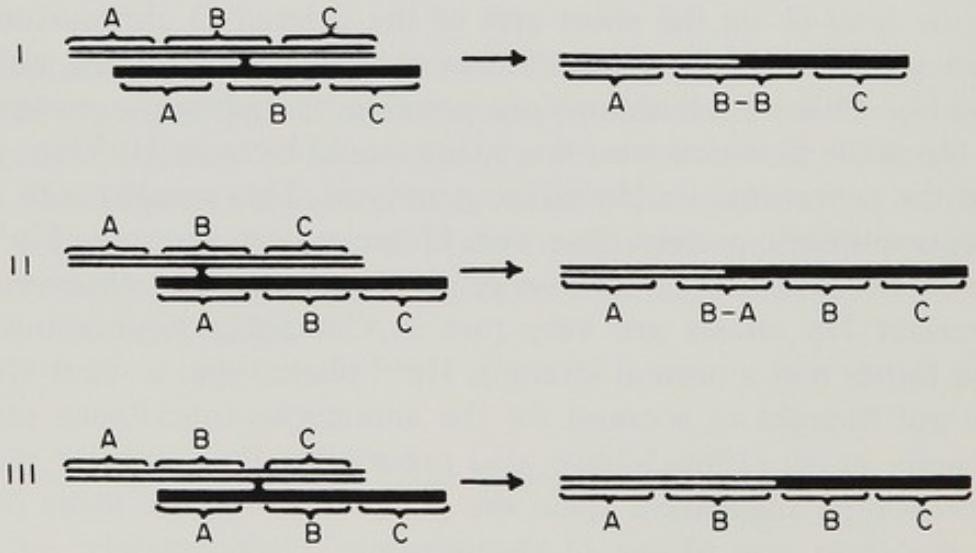


FIG. 7-10. Diagrammatic representation of the possible formation (by nonhomologous crossing over) and the consequences of duplications of several types. The brackets indicate DNA coded for polypeptide sequences: (I) An intragenic duplication of the type suggested as involved in the evolution of Hp^1 from Hp^{1F} and Hp^{1S}; (II) a duplication involving parts of two genes leading to the formation of a new gene B-A without loss of the preexisting genes A and B; (III) a duplication of the same extent as (II), but formed by crossing-over between genes. The result is classic gene duplication such as may have been involved in the evolution of the hemoglobin polypeptide chains. (From Smithies *et al.*, 1962.)

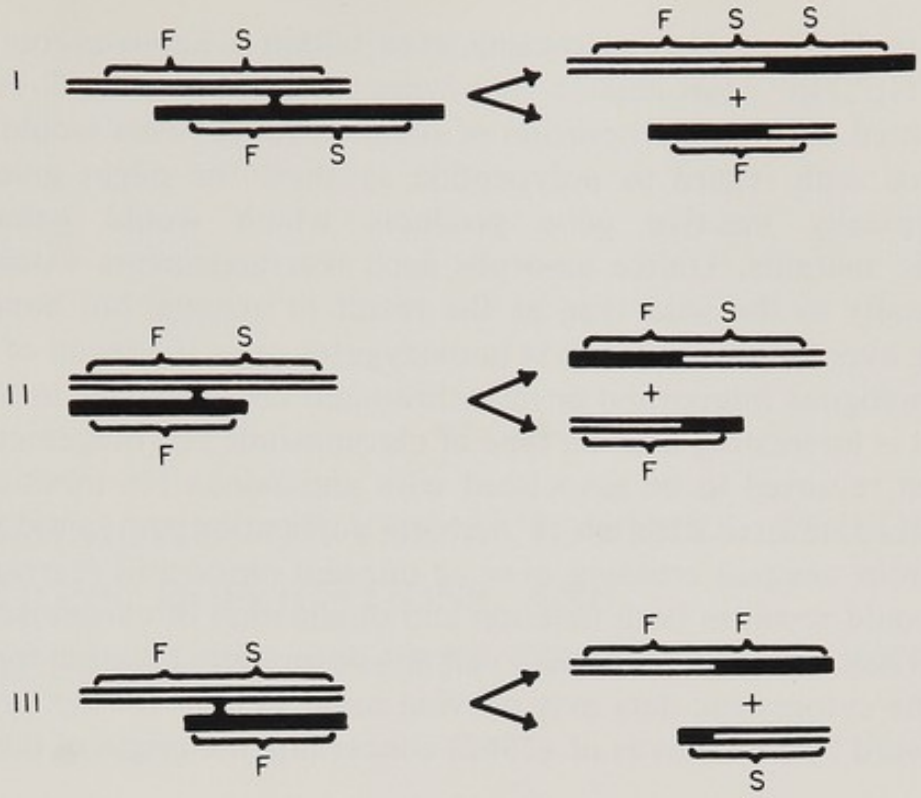


FIG. 7-11. Diagrammatic representation of the consequences of: (I) Unequal but homologous crossing over occurring during displaced synapsis in a Hp^2/Hp^2 homozygote, leading to the possible evolution of a haptoglobin triplication or to reversion of Hp^2 to Hp^{1F} or Hp^{1S}; (II) and (III) crossing over within the locus in a heterozygous individual (Hp^2/Hp^{1F}) during the two possible synaptic configurations. This crossing over will always be unequal and can lead to the production of four types of Hp^2 gene and to the formation of a gamete containing the gene Hp^{1S} in an individual of genotype Hp^2/Hp^{1F}. (From Smithies *et al.*, 1962.)

which involve loss of the short arms of one D chromosome including translocations and normal karyotype variants. For this reason, if the Hp locus were to be found on the short arm, anomalous inheritance of this locus should already have been detected. Other deletions of the long arm of a D chromosome which have been reported may result from some other type of rearrangement such as an interstitial deletion or translocation; thus, they do not involve the Hp locus if it is located in the distal segment of the long arm. The evidence given above is conflicting and until more data become available, both as to the identity of the chromosomes involved and the type of rearrangement, it is not possible to be more definite about the location of the Hp locus and the mechanism by which the different α chains (Hp^{1F}, Hp^{1S} and Hp^2) have evolved (Smithies *et al.*, 1962). Smithies *et al.* have suggested that evolution has occurred not only by point mutation but also by chromosome rearrangement involving nonintegral numbers of genes (Fig. 7-10). Such rearrangements include unequal but homologous crossing over which can lead to the possible triplication of the Hp locus as well as reversion

of Hp^2 to Hp^{1F} or Hp^{1S}. Crossing over within a heterozygote, for instance, Hp^2/Hp^{1F}, can lead to four types of gametes (Fig. 7-11). They also pointed out that a proportion of such rearrangements would be nonfunctional with regard to polypeptide synthesis or might give rise to phenotypically inactive gene products which would behave like amorphic mutants. Unlike amorphs such rearrangements would revert occasionally to the wild type as the result of unequal but homologous crossing over within the locus in homozygotes or as the result of unequal but homologous interstrand or intrachromatid crossing over in heterozygotes. It is interesting that the type of chromosome rearrangement which has been reported to be associated with anomalous Hp inheritance involves chromosome deletion or perhaps duplication and could have resulted from unequal crossing over or unequal chromatid rearrangement which could result in both deletion and duplication of chromosome segments. Thus, although there may still not be any firm location for the Hp locus, the cytogenetic data may provide some support for the hypothesis put forward by Smithies *et al.* (1962) concerning the origin of the three α chains.

VII. Concluding Remarks

The phenotype of Patau's syndrome is distinctive and shows gross congenital malformations of the majority of organ systems which result from abnormal organogenesis starting between 5 and 6 weeks gestation. Autoradiographic and measurement studies have established chromosome No. 13 as most probably responsible for Patau's syndrome. Other trisomics for a D chromosome have not been satisfactorily established. The possibility of the location of the Hp locus in the distal part of the long arm of one D chromosome has been discussed. Other syndromes resulting from structural rearrangements of a D chromosome have been considered, and neither the phenotypic nor cytogenetic evidence is considered to be satisfactory to distinguish any of these conditions by the term *syndrome*.

Chapter 8

ABNORMALITIES OF THE AUTOSOMES: TRISOMICS, DELETIONS, DUPLICATIONS, AND TRANSLOCATIONS (EXCEPT GROUPS D, E, AND G)

I. Chromosome Rearrangements and Phenotypic Malformations

The three major human autosomal trisomies as well as other abnormalities of groups D, E, and G have been described (Chapters 5, 6, and 7); the present chapter will be concerned with other autosomal abnormalities resulting from structural change and with the remaining autosomal trisomics which have been reported among live births.

The types of chromosome imbalance which usually lead to a phenotypic change are either a duplication or a deficiency of chromosome material. There is now considerable evidence from other species as well as man that alteration of a chromosome segment from one position in the chromosome set to another (position effect) does not usually result in a phenotypic change unless it is also associated with either a duplication or a deletion of genetic material. It is therefore essential that great care should be taken in establishing a causal relationship between a structural rearrangement and a given phenotype (see Volume I, Chapter 8, Section II). The causal association of a particular unbalanced karyotype with an abnormal phenotype is usually justified if several similar cases are reported and the chromosomes can be clearly identified. This applies to the trisomic states as well as to such conditions as the *Cri du chat* where the same chromosome abnormality is associated with the

same phenotype in many subjects. Even in as clear an association, the origin of the abnormal chromosome may be very different from subject to subject, the deletion resulting in some patients from a reciprocal translocation transmitted by one parent or from a simple terminal or interstitial deletion (see Fig. 6-13). The relationship between a chromosome abnormality and the phenotype can therefore be simply stated as "no phenotypic abnormality without chromosome imbalance."

The concept of *aneusomie de recombinaision* (see also Chapter 8, Section II) was originally introduced by Lejeune and Berger (1965) to account for the association of the same apparently balanced karyotype in a mother and her malformed daughter, and Lejeune and Berger postulated a highly complex rearrangement to account for a presumptive unbalanced karyotype in the daughter, which morphologically was identical to the mother's. De Grouchy *et al.* (1966b) have indicated two situations. The first they termed *the general case,* when the karyotypes of the balanced and unbalanced situations differ from each other but apparently cannot be derived, one from the other. The second they termed the *particular case*, when the balanced and "unbalanced" karyotypes are morphologically identical. The general case may therefore require a more complex explanation than the simple segregation of rearranged chromosomes from a multivalent formed during meiosis; there is, however, no necessity for a new term. The particular case, on the other hand, provides no evidence, apart from an abnormal phenotype, that any chromosome imbalance exists.

II. Autosomal Structural Rearrangements

A. *Introduction*

Most of our knowledge about human chromosome rearrangements is based on the morphological appearance of the human somatic chromosomes and the conclusions which can be drawn from such observations. These are necessarily limited and may therefore eventually be found to be erroneous and require alteration when we know more of the actual mechanisms involved in a particular structural rearrangement. For similar reasons it is logical at present to consider the phenotypic effects of morphological changes in each group of chromosomes without considering too deeply the mechanisms involved in any given chromosome rearrangement unless there is evidence available from family or meiotic studies.

A good example of this is the deleted B group chromosome resulting in the *cri du chat*. This could arise by at least four different mechanisms (see Fig. 6-12) which are terminal deletion, interstitial deletion, translocation, and unequal chromatid intrachange, and there are at least eight families in which the mechanism has been shown to be a reciprocal translocation [see Table 8-8; t(B;C) Nos. 5 and 6; t(B;D) Nos. 2, 5, and 7; t(B;G) No. 2; and t(B;?) Nos. 1 and 2]. In these cases although the major result appears to be a deficiency of short arm material of a B group chromosome (No. 5 ?), there may also be a duplication of chromosome material belonging to the other chromosome involved. Nevertheless, the cause of the phenotypic abnormality is not clear cut and this may be one reason for the phenotypic variability which exists and which makes a phenotypic classification of chromosome abnormalities so complex.

B. *Deletions, Duplications, and Inversions*

1. Group A (1-3)

a. Chromosome No. 1. Gordon and Cooke (1964) and Cooke and Gordon (1965) reported a microcephalic dwarf with mental and developmental retardation with a 46,XX,1r chromosome complement. The ring chromosome is present in 87.3% of the cells (Fig. 8-1). In the remaining 12.7% metaphases only one No. 1 was present and the ring was absent, but an additional chromosome was observed in the X + 6-12 group. The origin of this chromosome is not clear but presumably results from breakage of the ring. Recently, C. B. Wolf *et al.* (1967) reported a similar microcephalic dwarf with an "elfin" face, large low-set ears, and mental retardation with an apparently identical karyotype (46,XX,1r). In this subject the ring chromosome was present in all the cells examined. Some clinical and other data on these two patients are given in Table 8-1, and it is clear that the dwarfism is extreme with all the measurements falling below the third percentile for age.

Lele *et al.* (1965) have observed two individuals with coloboma of the iris who are heterozygous for a presumptive pericentric inversion of chromosome 1. They studied three other phenotypically similar subjects all of whom had normal karyotypes. Both patients with coloboma and a chromosome anomaly also had other congenital abnormalities. The interpretation that the structural change is an inversion is based purely on chromosome morphology, although in one family the phenotypically normal mother also carried the same chromosome. If the chromosome



FIG. 8-1. Metaphase from a patient with a 1r chromosome (arrow). (From Gordon and Cooke, 1964.)

abnormality can be related to the phenotype then it is necessary to assume a balanced complement in the mother and an unbalanced complement in the son. This could result from crossing over within the inverted segment to give a morphologically similar but genetically unbalanced chromosome complement. In the second family it is unlikely that a simple pericentric inversion will result in genetic imbalance, so that one must either postulate a position effect or a different type of chromosome rearrangement such as a translocation, in which the other chromosome is not detectable. The finding of two subjects with chromosome abnormalities in a group of patients selected because of eye anomalies suggests a relationship which may perhaps be indirect and further studies

TABLE 8-1

Some Clinical Data on Two Subjects with a 46,XX,1r Chromosome Complement

	Gordon and Cooke, 1964	C. B. Wolf, *et al.*, 1967	
Maternal age	–	26	
Paternal age	–	–	
Gestation age (weeks)	40	39	
Birth weight (gm)	1644	1080	
Age at examination (years)	5	2-2/12	2-11/12
Weight (kg)	11.6	3.7	5.3
Height (cm)	91.4	67.0	72.4
Head circumference (cm)	38.1	37.5	–
Mental retardation	Yes	Yes	
Other malformations	Nil	"Elfin" face, large low-set ears. Bone age 9-12 months; dental age 22 months.	

are needed. Coloboma may be inherited as a dominant characteristic but more frequently is sporadic (McKusick, 1966); it also occurs in subjects with other developmental defects, for instance, mental retardation (Penrose, 1938), 13-15-trisomy (D. W. Smith *et al.*, 1963; Chapter 7) and developmental errors of the brain and heart (Angelman, 1961). There have been suggestions of chromosome anomalies in other cases of coloboma and related defects, but nothing specific has been reported (Cottom, 1961; M. V. Richards, 1961; Edwards *et al.*, 1961; Angelman, 1961). The possibility remains that some cases may result from a chromosome rearrangement possibly involving a deletion which may not always be detectable by morphological examination.

There are a number of reports of subjects with dimorphic No. 1 chromosomes. These usually result from an elongation of the region proximal to the centromere and may involve a coiling alteration of the secondary constriction (see Section III below). This type of variability has been found in association with ocular abnormalities (Koulischer and Zanen, 1964), Apert's syndrome (acrocephalo-syndactyly) (Genest *et al.*, 1966), and with primary amenorrhea (Philip *et al.*, 1965). Several subjects with Apert's syndrome have also been reported without any chromosome abnormality, and it seems most likely that this chromosome anomaly is a fairly rare normal polymorphic variant and is not associated with alteration of the phenotype.

b. CHROMOSOME NO. 2. De Grouchy *et al.* (1966b) reported a family with a presumptive pericentric inversion (Fig. 8-2) of chromosome No. 2 (2p+q−) carried by both phenotypically normal subjects as well as the abnormal proband (III-2, Fig. 8-2), who showed developmental retardation, microcephaly, and congenital heart disease. The mother of the proband (II-3) had a congenital heart defect as well as being mentally retarded. The maternal grandmother (I-2) was of normal intelligence but had two spontaneous abortions and a pair of stillborn twins (Fig. 8-2). The proband, her mother, grandmother, and a cousin of the mother's (II-7) were all presumptive inversion heterozygotes (Fig. 8-3). The most likely cause of chromosome imbalance in this family would be crossing over within the inversion which could result in a morphologically similar chromosome carrying a duplication deficiency (see Volume I, Chapter 8). This could account for the phenotype of the proband; which is, however, sufficiently nonspecific to be associated

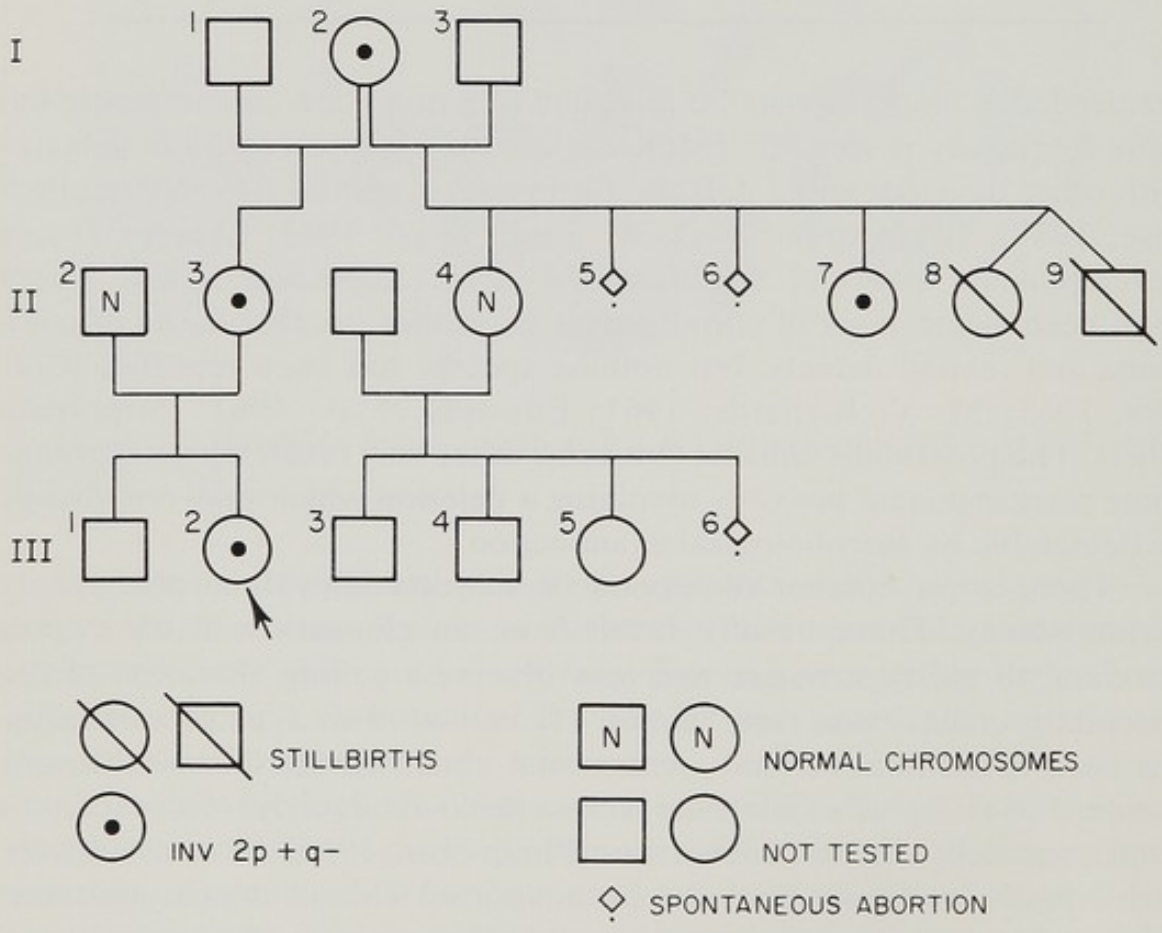


FIG. 8-2. Family reported by De Grouchy *et al.* (1966b) showing transmission of a No. 2 chromosome carrying a pericentric inversion (2p+q−).

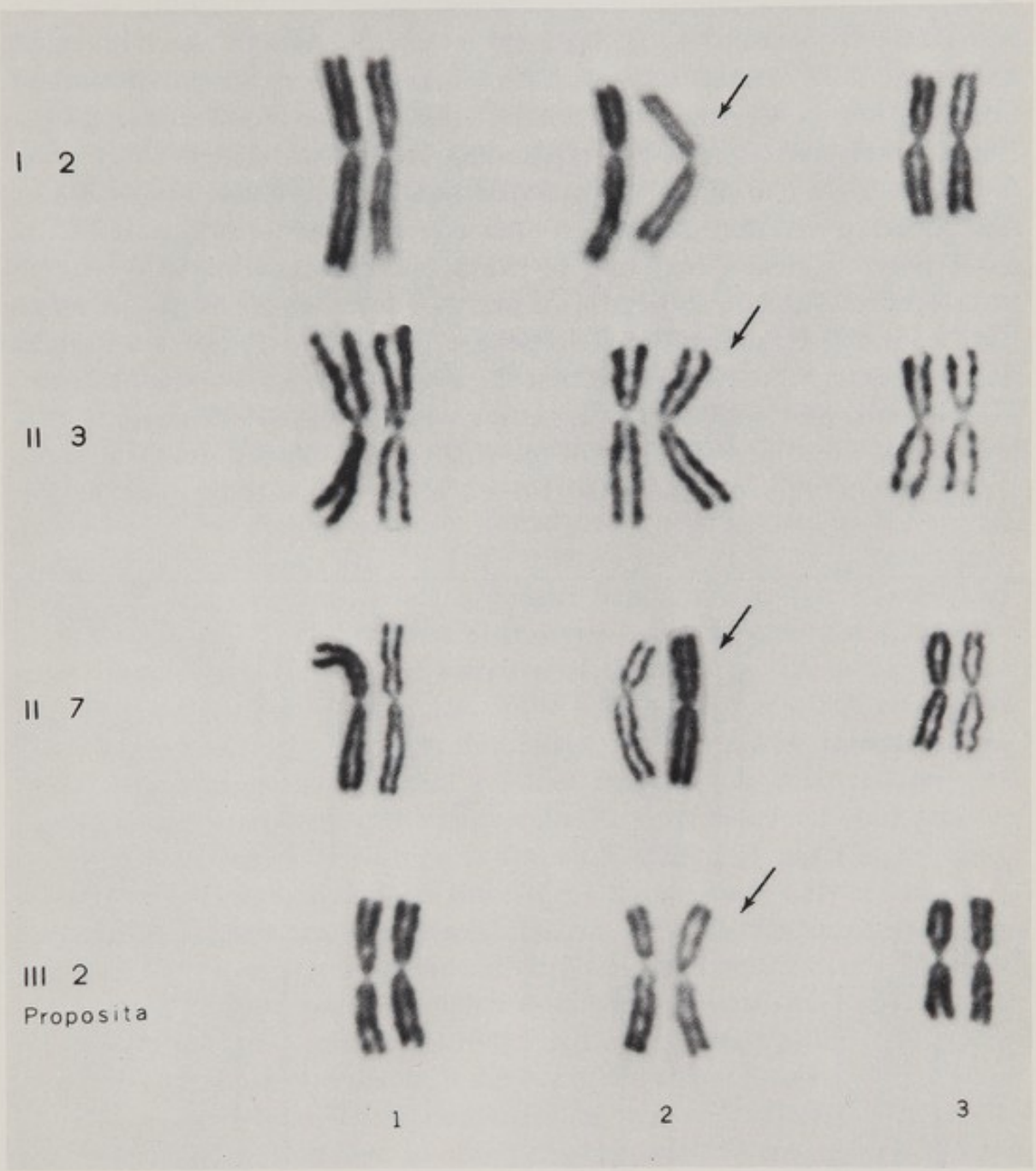


FIG. 8-3. Partial karyotype of the A group in 2inv heterozygotes from the family reported by De Grouchy *et al.* (1966b) (see Fig. 8-2).

with the chromosome anomaly purely by chance as the result of ascertainment. The unfortunate reproductive history of I-2 may well result from chromosome imbalance because of inversion heterozygosity.

c. CHROMOSOME NO. 3. Mukerjee and Burdette (1966) reported a child who was heterozygous for a ring 3 (3r), and an associated t(3;X) who had been ascertained because of congenital abnormalities.

The patient was a female, microcephalic dwarf; at 8 months she had congenital dislocation of the hips, and an examination at age 2 revealed epicanthic folds, a short neck with prominent webbing, hirsutism, and an umbilical hernia. Chromosome findings showed one No. 3 replaced by a ring chromosome, and a late-replicating X with elongated short arms (46,XXp+,3r). The authors postulated that a double deletion of No. 3 had occurred and that the broken ends had rejoined to form a ring (Fig. 8-4); they suggested that one of the acentric fragments had become translocated onto the short arm of one X chromosome while the other had been lost. Examination of dividing cells in culture revealed bridges and fragments which indicated that the ring chromosome was unstable. Despite this, only cells containing a ring were observed in culture so that it might be presumed that loss of the ring resulted in cell death. It is interesting that this patient also had an abnormal chromosome in the

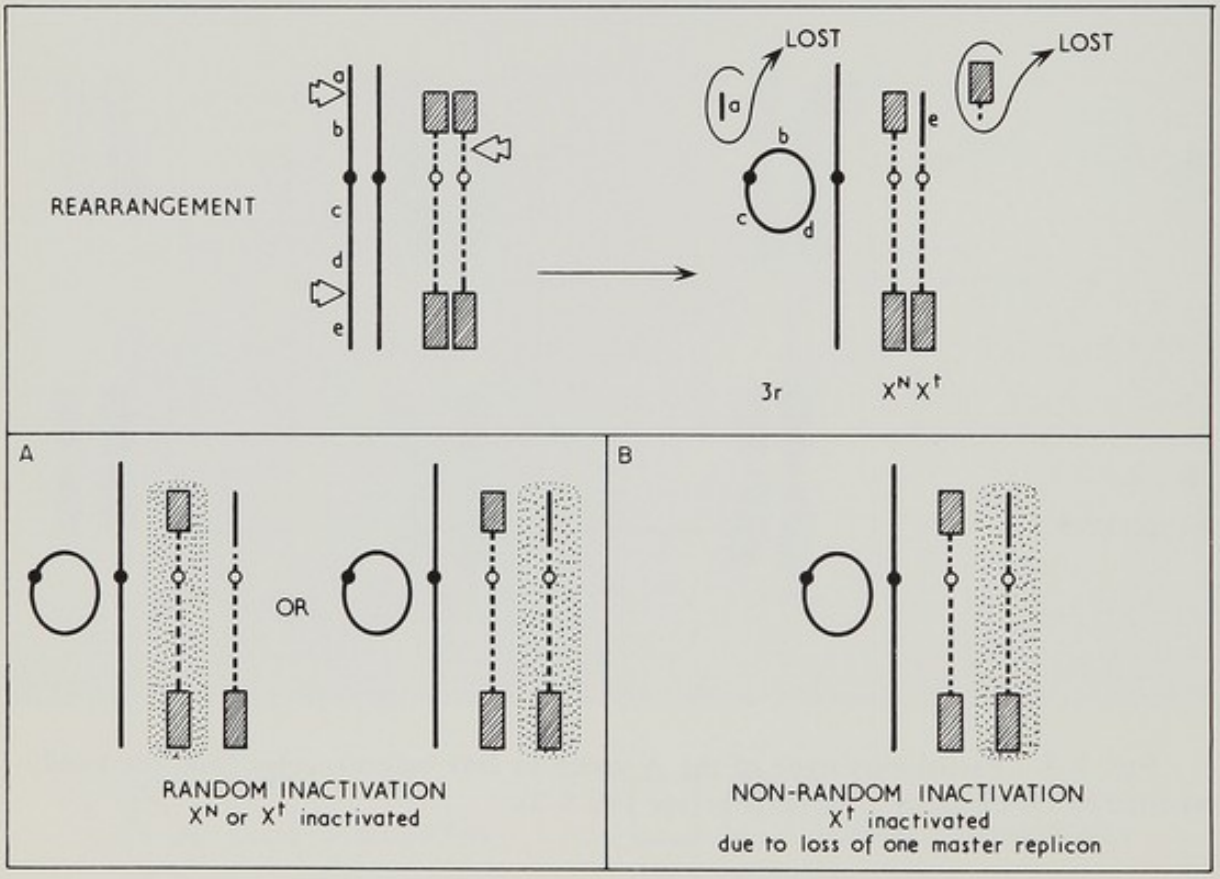


FIG. 8-4. Schematic diagram to show the possible origin of a 3r and t(3;X) reported by Mukerjee and Burdette (1966). In this case the t(3;X) was always late replicating as in (B), and it is suggested that this may result from the possible loss of one of the X master replicons in the translocation. The theoretical situation for random inactivation is shown in (A). (Hatched blocks indicate postulated terminal master replicons).

X+6-12 group, which was presumed to be the X chromosome because of its autoradiographic behavior. This chromosome was considered to be the product of a 3;X translocation and always appeared to be late replicating, indicating a disturbance of random inactivation. This is the first A;X translocation reported in man, and some rather more precise data on the behavior and labeling patterns of the abnormal X would have been of value. A number of X;A translocation stocks are available in mice (Volume I, Chapter 6, Section VI). Nine of these stocks (Russell, 1961; Cattanach, 1961) showed a variegated type position effect of autosomal coat color loci, which suggested a random inactivation of the autosomal material translocated onto the X although this interpretation has been questioned (Russell, 1963, 1964; Grüneberg, 1967). One stock of mice carrying Searle's translocation (T16H) showed only inactivation of the normal X while the translocated X was active in all cells. The reasons for this variation in activity of the two types of X have already been discussed (Volume I, Chapter 6, Section V, 7). If heteropycnosis and late labeling indicate genetic inactivation, the translocated X;A is inactive. The abnormal phenotype could therefore result either from chromosome imbalance because of deletion or the unmasking of recessive genes. The small region of the translocated X which must have been deleted strongly suggests that inactivation must be an active process. If it was passive so that random inactivation occurred but cell selection operated against the cells with the least balanced chromosome complement, then cells with an active translocated X might be expected to have a selective advantage since these would have only a small portion of the X chromosome deleted and an even smaller autosomal deletion and therefore a more balanced chromosome complement (Fig. 8-4). Thus if the chromosomes of higher organisms consist of a large number of replicons (Plaut and Nash, 1964; Plaut *et al.*, 1966), which function in an ordered fashion and result in the observed sequence of DNA replication, then any deletion of replicating units or more particularly of a controlling replicon could lead to allocyclic behavior. In the mouse, if these "master" replicons are close to the centromere, then in the T16H translocation only the normal X carrying the "X-master replicon" becomes inactive. In Cattanach's translocation which is an insertion (Ohno and Cattanach, 1962; Ford, 1969) both X chromosomes have retained their master replicons and therefore inactivation was not disturbed. In man, there is evidence that the two chromosome arms replicate independently of each other and that translocation does not affect replication patterns. It is therefore possible that the master replicons on the X chromosome are terminal in position and that deletion of one of them leads to that X

becoming late replicating and inactive. This would not only account for the replication behavior in the 3;X translocation discussed above but also for nonrandom inactivation of a wide variety of abnormal X chromosomes (see Volume I, Chapter 6 and Chapter 10, this volume).

2. Group B (4-5)

The B group can be separated into two homologous chromosome pairs by means of autoradiographic and measurement studies (German *et al.*, 1964; D. A. Miller *et al.*, 1966; Warburton *et al.*, 1967). The distinctive features which separate these two very similar chromosomes are the replication pattern and grain count and the length of the long and short arms. Chromosome No. 4 terminates DNA replication later than chromosome No. 5 and has both longer short and long arms.

Deletions of the short arms of both the early- and late-replicating pair have been reported, and evidence suggests that the *cri du chat* syndrome originally described by Lejeune *et al.* (1963) results from a substantial deficiency of genetic material in the short arms of the shorter early-replicating chromosome pair (No. 5). Recently, several examples of presumptive deletions of the short arm of chromosome No. 4 have been reported; these differ in some of their clinical features from the *cri du chat* subjects, although there is some phenotypic overlap. A further complication exists because the voice defect, which is so characteristic of the *cri du chat* in early infancy, disappears so that it can no longer be used as a diagnostic characteristic later in life.

Sixty-five subjects with a presumptive deficiency of chromosome 4 or 5 have been reported, and the results of the chromosome analysis on these patients are given in Table 8-2. Fifty-eight of these have presumptive deletions of No. 5, in two the chromosome involved is in doubt, while in the remaining five autoradiographic and clinical data suggest that No. 4 is involved (Fig. 8-5).

a. Deficiencies. i. *Chromosome No. 5* Clinical data from 57 subjects with a presumptive deficiency for the short arm of chromosome No. 5 (5p−) are summarized in Table 8-3. In general these infants were born at or around term to parents whose mean ages were normal. They were often of low birth weight and the pregnancies were normal. The majority were female (31/45) and all were microcephalic; they all had a high-pitched mewing cry in infancy ("cat cry"), and it is this characteristic feature which gave the syndrome its name—the *cri du chat*. Other characteristic features included failure to thrive and developmental and/or mental retardation; those subjects who were ascer-

TABLE 8-2

Summary of Chromosome Findings in Some Patients Heterozygous for a Bp− Chromosome

Type	Origin	No. of subjects	Phenotype
5p−[a]	Uncertain	45	*Cri du chat*
4p−[b]	Uncertain	5	Congenital malformations "midline syndrome"
4p− or 5p−[c]	Uncertain	2	–
5r(p−q−)[d]	Terminal deletion	2	*Cri du chat*
t(5p−)[e]	Reciprocal translocation	11	*Cri du chat*

[a] From Taylor (1967; review 17 cases, refs. 88-100); O. J. Miller *et al.*(1966); Breg (1968); Bergman *et al.* (1965); Ricci *et al.* (1966); Urano *et al.* (1965); Milunsky and Chitham (1966); Kajii *et al.* (1966); Hustinx and Wijffels (1965); Hobolth and Mikkelsen (1965); Pfeiffer and Simon (1965); Neuhäuser and Lother (1966); Engel *et al.* (1966); Zellweger (1966); Bettecken *et al.* (1965); Gordon and Cooke (1968); Schlegel *et al.* (1967); Silber *et al.* (1966).

[b] From Leao *et al.* (1966); Taylor (1968a); Hirschhorn *et al.* (1965); U. Wolf *et al.* (1965a,c); O. J. Miller *et al.* (1966).

[c] From Berg *et al.* (1965); Giorgi *et al.* (1965).

[d] From Rohde and Tomkins (1965); Steele *et al.* (1966).

[e] From Laurent and Robert (1966a); O. J. Miller *et al.* (1966); Koulischer and Quersin (1965); MacIntyre (1969); Lejeune *et al.* (1965); De Grouchy and Gabilan (1965); Reinwein and Wolf (1965); De Capoa *et al.* (1967); (for further details of these translocations see Volume I, Table 8-3, and this volume, Table 8-8).



FIG. 8-5. Partial karyotypes of groups A and B to show the appearance of 4p− and 5p− chromosomes. These can only be clearly separated on the basis of measurement and autoradiography (×1800).

TABLE 8-3

Summary of Clinical Features of Patients with a Bp– Deficiency[b]

Feature[a]	Chromosome complement[c]				
	5p–[c]	5r	t(5p–)	4p–[c]	
Maternal age	28.1	23.5	30.1	26.8	
Paternal age	32.4	25.0	33.8	30.5	
Gestational age (weeks)	Full term	Full term	Full term	Full term	
Birth weight (gm)	2650	2070	2560	1898	
Female sex	31/45	2/2	6/10	2/5	
No. of subjects	45	2	10	5	
Failure to thrive[d]	10/42	2/2	6/8	5/5	
Mental retardation	45/45	2/2	9/9	3/4	
Abnormal cry	39/45 (3?)	2/2	10/10	2/4	
Hypertelorism	30/41	2/2	5/5	4/5	
Epicanthus	29/39	2/2	6/6	2/4	
Microcephaly	41/43	2/2	9/9	–	
Micrognathia	28/40	2/2	2/6	4/5	
Oblique palpebral fissures	11/21	1/2	4/4 (downward mainly)	0/2	
Abnormally shaped ears	13/18	2/2	4/4	–	
Hypotonia	23/38	2/2	1/1	4/4	
Transverse palmar crease	28/34	2/2	8/8	0/4	
Congenital heart disease	6/34	? 1/2	0/6	3/4	
Strabismus	12/17	0/1	6/7	4/4	
Short stature	10/12	–	–	–	
Face abnormal	12/17	–	5/5 (moon face)	1/4	
Genitalia	Usually normal	–	–	3/3	Hypospadias cryptorchidism
Skeletal abnormalities	8/10	–	–	4/4	
Inguinal herniae	2/10	–	–	–	
Coloboma	–	–	–	3/3	
Harelip, cleft palate	–	–	–	4/5	
EEG anomalies	–	–	–	4/4	
Abnormal nose	2/12	–	–	4/4	

[a] Feature only scored when given as actually present or absent.

[b] For references see Table 8-2.

[c] Not always confirmed by autoradiography.

[d] Not easy to assess among adult cases.

tained in later life have all been located in institutions for the mentally retarded. They usually have ocular hypertelorism, epicanthic folds, and frequently have muscle hypotonia. The majority have a round "moon-like" face, low-set and sometimes malformed ears, strabismus, and oblique palpebral fissures (Fig. 8-6). These features all add up to a fairly nonspecific syndrome of mild congenital malformation combined with mental retardation. The distinctive feature in infancy is the *cri du chat* which disappears later in life; thereafter detection is usually based on facial appearance and mental retardation (Breg *et al.*, quoted by O. J. Miller *et al.*, 1966).



FIG. 8-6. Faces of children with deleted short arms of a B group chromosome: (a) and (b) Front and side view of a female patient age 32 months with the *cri du chat* (De Grouchy *et al.*, 1964d); (c) 9-month-old boy with the *cri du chat*. Both patients had a 5p−; (d) newborn male with a 4p−. Note the more extensive facial malformations including cleft lip and very marked ocular hypertelorism [(c) and (d) reproduced by courtesy of Dr. A. I. Taylor)].

The chromosome abnormality carried by each of these subjects is essentially a deficiency of the greater part of the short arm of chromosome No. 5. In 10 subjects this has resulted from a reciprocal translocation in one or the other parent. Two of the remaining 42 patients had ring chromosomes (Rohde and Tompkins, 1965; Steele *et al.*, 1966), and so presumably had deletions of both the long and short arms; their phenotypes however showed no significant differences from the other subjects with this condition. One of these two children was a mosaic with 98% of cells having the ring and 2% having a normal female complement (46,XX/46,XX,Br) (Steele *et al.*, 1966). In both children the ring chromosome seemed to be relatively stable. In the remaining 40 subjects there is no evidence about the origin of the abnormality for which there are several possible mechanisms, including *de novo* translocation, terminal or interstitial deletion, or unequal chromatid interchange or intrachange; each of these could result in a morphologically identical chromosome having a different genetic content (see Fig. 6-13). For these reasons a variable phenotype is to be expected. The most characteristic feature of the *cri du chat* is the abnormal cry which results from a laryngeal malformation; other commonly found features included microcephaly, mental retardation, and an abnormal facial appearance.

ii. *Chromosome No. 4.* There are five patients who have been reported to have presumptive deletions of the short arm of chromosome No. 4 (4p−) (U. Wolf *et al.*, 1965a,c; U. Wolf and Reinwein, 1967; Giorgi *et al.*, 1965; Hirschhorn *et al.*, 1965; Leao *et al.*, 1966; Taylor, 1968a; O. J. Miller *et al.*, 1966; Breg, 1968). Two of these have been shown to have a deficiency in the longer, later replicating chromosome, while in the other three, although autoradiographic studies have not been carried out, the chromosome does appear to belong to the longer pair. The phenotype (Table 8-3) differed in a number of features from the *cri du chat* phenotype. None of these five children had the characteristic cry, and they were much more grossly malformed than the 5p− subjects. The mean birth weight was nearly 1 kg less than in the *cri du chat*, although birth was usually at term. The syndrome was sometimes difficult to distinguish from 13-trisomy (Taylor, 1968a) and frequently included abnormalities of the eyes, ears, and mouth. The children were microcephalic and failed to thrive. They invariably had EEG anomalies, asymmetry of the face, and an abnormal nose. The male infants had hypospadias.

4p− subjects appear to be far less common than patients with a 5p−. The reason for this may be the ease with which 5p− children can be ascertained since they have a most distinctive cry during the neonatal period. Children with a 4p− are likely to be ascertained as possible 13-

trisomics (Taylor, 1968a). An alternative explanation might be that chromosome No. 5 is more liable to breakage and rearrangement than chromosome No. 4 or that a deletion of No. 4 might be more lethal during fetal life, although there is no evidence for this from studies on spontaneous abortions (Chapter 9).

Recently, Ockey *et al.* (1967) reported a child with a 4q− deletion (Fig. 8-7). The child was listless and had an enlarged heart with both atrial and ventricular septal defects. There was absence of the left radius, carpal and majority of metacarpal bones; congenital dislocation of the right hip, and some syndactyly of the toes. The origin of the abnormal chromosome was not clear, but it seemed unlikely to be a simple terminal deletion. The chromosomes of both parents were normal and no other abnormality was found in the patient's karyotype. This suggested a prezygotic origin during gametogenesis, probably as the result of either a reciprocal translocation or an unequal chromatid exchange. In either case (see Volume I, Chapter 8) the abnormal chromosome would have both duplicated as well as deleted segments.

b. Duplications in the B Group Four children are reported with elongation of the long arms of one B group chromosome (Fig. 8-8)

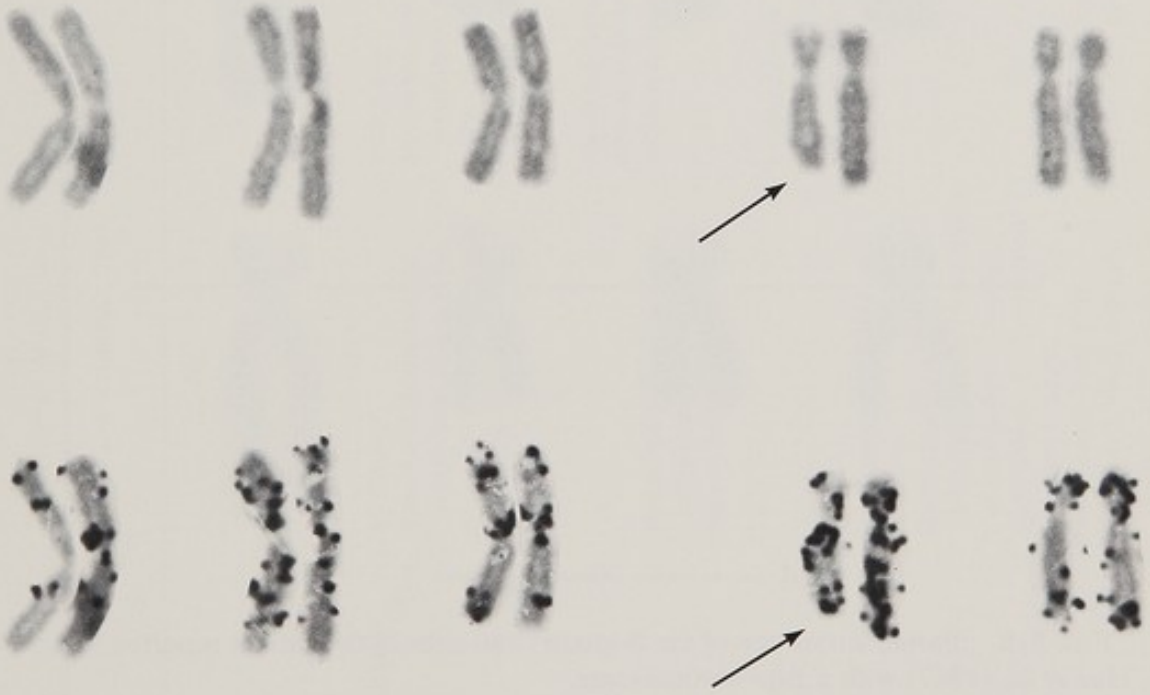


Fig. 8-7. Partial karyotype from fibroblast cultures of a child with a 4q−. The clinical features include multiple congenital malformations and congenital heart disease. Identification of the abnormal chromosome is based on autoradiographic studies (lower line). (From Ockey *et al.*, 1967.)

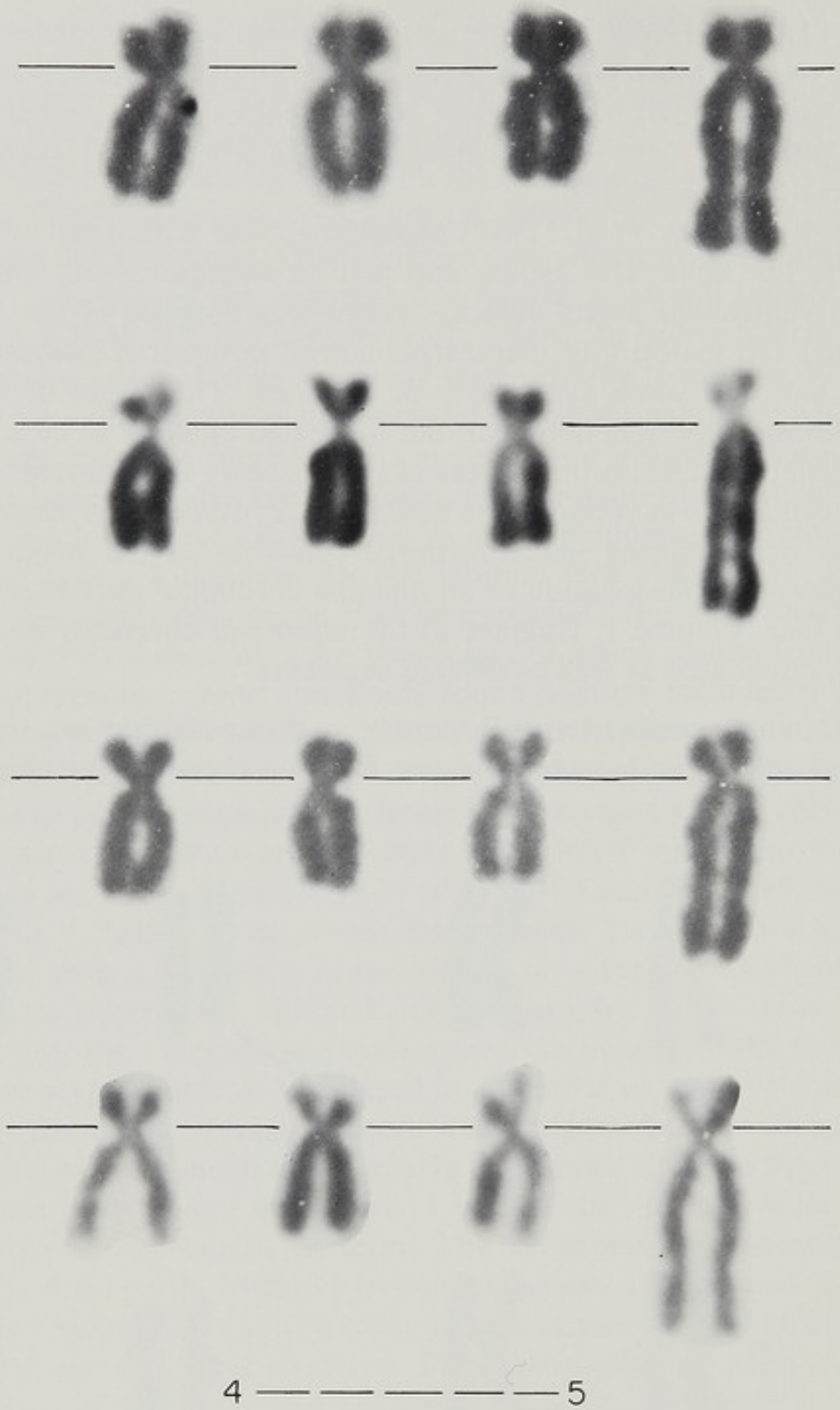


FIG. 8-8. Partial karyotype of the B group from cells of the patient reported by L. Y. F. Hsu *et al.* (1967) with a Bq+ chromosome.

(Gendel and Wasserman, 1966; L. Y. F. Hsu *et al.*, 1967; Atkins and Feingold, 1967), all of whom have some considerable degree of physical and mental retardation; in each case the chromosomes of both the parents were normal. The clinical features are summarized in Table 8-4 and

TABLE 8-4

Summary of the Clinical Features of Four Patients with a Bq+ Duplication

Feature	Gendel and Wasserman, 1966	Atkins and Feingold, 1967	L. Y. F. Hsu, *et al.*, 1967	Tischler *et al.*, 1968
Maternal age	26	23	28	27
Paternal age	36	25	29	–
Birth weight (gm)	–	1900	–	2380
Gestation	–	Full term	Full term	Full term
Sex	F	F	M	M
Age	11/12	6/52	11 years	4-6/12
Chromosome complement	46,XX,Bq+	46,XX,Bq+	46,XY/46,XY,Bq+	46,XY,Bq+
CNS	Mental and developmental retardation. EEG normal.	Mental and developmental retardation. Abnormal cry.	Mental retardation. Seizures. EEG normal.	Mental and developmental retardation. EEG normal. Seizures.
Eyes	Epicanthus	Abnormal facies	No epicanthus	Antimongoloid slant. Epicanthus. Hypertelorism. Ptosis.
Ears	–	Abnormal facies	Low set	Asymmetry. Narrow external auditory meatus
Nose	–	Abnormal facies	–	Beak-shaped
Skull	Microcephaly, wide anterior and posterior fontanelles.	Microcephaly	Normal	Microcephaly, with slight asymmetry. Plagiocephaly.
Jaw and mouth	High arched palate	–	– –	High narrow palate. Abnormal alignment of teeth.
Cardiovascular system	–	Enlarged heart. Atrial septal defect. Ventriculo-septal defect.	–	–
Gastrointestinal	Hypertrophic pyloric stenosis	–	–	–
Urinogenital	Malrotated left kidney. Umbilical hernia. Constriction at ureteropelvic junction.	–	–	Cryptorchidism
Skeleton and growth	Short stature. No ossification centers in wrists.	–	Short stature	Short stature
Hands and feet	Short hands, small fifth fingers. Transverse palmar crease.	Single transverse palmar crease	Short broad hands. Fifth digits incurved. Short metacarpals. Transverse palmar crease. Whorls on both thenar areas.	–

show little resemblance to each other. It is probable that the abnormal chromosome in the three nonmixoploid subjects resulted from duplication/deletion of chromosome material because of a reciprocal translocation or an unequal chromatid exchange. If either occurred after fertilization and was followed by nondisjunction, it could result in the mixoploid situation reported by L. Y. F. Hsu *et al.* (1967).

There are a number of other reports of subjects with a Bq+ chromosome; these are usually associated with a known donor chromosome in a reciprocal translocation (see Table 8-8).

3. Group C (6-12)

There are very few reports of either numerical or structural anomalies of the C group, and the number of reciprocal translocations reported are less than would be expected on the basis of random chromosome breakage related to the total length of the chromosomes in the group (see Volume I, Chapter 8). Several possibilities exist to account for this deficiency: the first that chromosome imbalance among the autosomes of this group is highly lethal and rapidly selected against in the form of fetal wastage early in pregnancy; the second that translocations within this group are likely to be difficult to detect unless they are extremely asymmetrical; and the third that the chromosomes within this group are less liable to breakage or more able to restitute after breakage than those in some other groups. Whatever the reason, very few abnormalities have been reported and these will now be discussed briefly.

a. C-Trisomy or C-Trisomy Mosaicism. There have been several reports of C-trisomic cell lines in blood and bone marrow associated with myeloproliferative conditions (Solari *et al.*, 1962; Nowell and Hungerford, 1962; Sandberg *et al.*, 1964a). These will be considered further in Chapter 10.

Eight patients with presumptive trisomy for a C group autosome associated with varying degrees of congenital malformation have been reported. These, however, do not have a sufficiently uniform phenotype to suggest a distinctive syndrome (Table 8-5). Seven of these 8 patients were mixoploids with a normal as well as an abnormal cell line (46,XX or XY/47,XX or XY,C+), while mixoploidy cannot be said to have been excluded in the eighth patient from whom a few cells from one blood culture only were studied (Jalbert *et al.*, 1966). Sex chromatin and limited autoradiographic studies on these subjects have always indicated that the additional chromosome was an autosome.

The variability observed in the type of congenital malformation probably results both from the presence of different chromosomes in triplicate in different subjects as well as from the frequent mixoploidy

TABLE 8-5

Summary of the Clinical Features of Eight Patients with C-Trisomy or C-Trisomy Mixoploidy

Feature	El Alfi *et al.*, 1963	Stalder *et al.*, 1963	Pfeiffer *et al.*, 1962a	Jacobs *et al.*, 1961	Jalbert *et al.*, 1966	Bargman *et al.*, 1967	D. W. Smith, 1964	U. Wolf and Reinwein, 1965
Maternal age	–	34	–	–	–	39	38	–
Paternal age	–	–	–	–	–	41	–	–
Birth weight (gm)	–	–	–	–	3450	1200	–	2350
Gestation	–	–	–	–	–	Full term	–	7 months
Sex	M	M	M	F	F	F	M	M
Age	54	2-8/12	–	19	7	7/12	4-8/12	9/364
Chromosome complement and tissue	46,XY/47,XY,?C+ Blood	46,XY/47,XY,?C+ Fascia lata	46,XY/47,XY?C+ Blood	46,XX/47,XX,?C+ Skin and omentum	47,XX,?C+ Blood (1 culture)	46,XX/47,XX,?C+ Blood	46,XY/47,XY,?C+ Skin	46,XY/47,XY,?C+ Fascia lata
Sex chromatin	Chromatin –ve	Chromatin –ve	Chromatin –ve	Chromatin +ve	Chromatin +ve	Chromatin +ve	Chromatin –ve	Chromatin –ve
CNS	Mental retardation. Slight EEG abnormality.	Mental retardation (IQ 54). EEG normal.	Mental retardation	–	Mental retardation. (IQ <50)	Mental and developmental retardation	Mental retardation	–
Eyes	High supraorbital ridges. Hypertelorism	–	–	–	Hypertelorism. Odd facies.	–	–	Hypertelorism
Ears	Normal	–	Low set-	–	Low set	Low set, malformed	Low set	Abnormal. Dysplastic pinnae.
Nose	Depressed bridge	–	–	–	–	Small short nose with skin folds over bridge	–	–
Skull	High occiput	Normocephalic	Normal	–	Normal	Brachycephalic	–	Large skull
Jaw and mouth	Prognathos	–	–	–	Retrognathos. Tooth implantation abnormal.	Micrognathos. High arched palate.	–	Micrognathos
CVS	ECG normal	–	–	–	–	–	–	Suspected congenital heart defects
G.I.	–	–	–	–	–	–	–	–
Urogenital	Hypogenitalism	Normal; scrotal testes.	Hypospadias. Cryptorchidism.	Primary amenorrhea. Streak gonads. Rudimentary fallopian tubes.	Normal female	Hypoplastic clitoris and labia minora.	Small penis, cryptorchid.	Cryptorchid
Skeleton and growth	Short stature (152 cm)	Normal height. Skeleton age advanced.	Abnormal, advanced bone age.	–	Normal stature	Short neck. Short stature.	–	–
Hands and feet	Small hands and feet. Flexion deformity of little fingers.	Plantar creases, marked flexion contractures.	–	Flexion contractures.	Flexion contracture and joint anomalies.	Flexion deformities of fingers. Dorsiflexed big toe. "Rocker bottom" feet. Abnormal dermatoglyphics.	Abnormal dermatoglyphics	–

with the possible involvement of different tissues. The additional chromosome has been placed in the 10-12 group in three subjects and in the 7-12 group in one, and in no case has the possibility been excluded that this additional chromosome is an abnormal compound chromosome resulting from a reciprocal translocation. In conclusion, no definitive C-trisomy syndrome can be established and the relative rarity of these subjects suggests that the nonmixoploid C-trisomy state is lethal (Chapter 9). It is not even conclusively established that at least some of these subjects are not triplo-X females or XXY males with aberrant sex chromatin, but available evidence points to the involvement of an autosome.

b. Ring Chromosomes in Group C. There are three reports of children with a ring chromosome replacing a chromosome in group C (46,XY,Cr) (Table 8-6) (B. Turner *et al.*, 1962; Atkins *et al.*, 1966a; Atkins *et al.*, 1966b, Case 2). These children were severely mentally retarded microcephalic boys with abnormal dermatoglyphics and, in one case, hypospadias. All were chromatin negative and in two cases the ring was shown to replicate early, which suggested that it was autosomal in origin and did not involve an X chromosome. In each case the modal cell line in blood and skin was 46,XY,Cr; there was, however, considerable variability around the mode resulting from loss or doubling of the ring. A fourth boy had a 46,XY,Bp+,Cr chromosome complement [t(Bp+;C−)] (Atkins *et al.*, 1966b, Case 1). Chromosome counts were variable because of the instability of the ring chromosome; the abnormal Bp+ chromosome was, however, a constant feature of the karyotype. A possible mechanism for the origin of this abnormal karyotype is shown in Fig. 8-9. If this is cor-

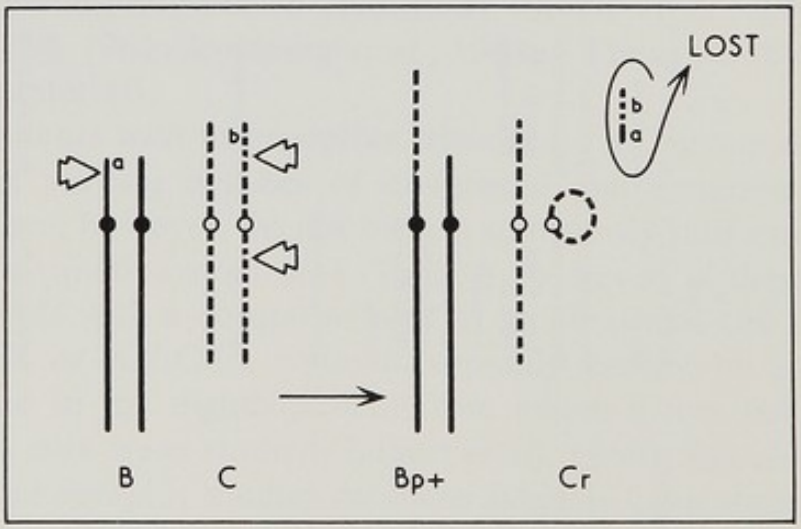


Fig. 8-9. Schematic diagram to show the possible origin of the Bp+,Cr chromosome complement reported by Atkins *et al.* (1966b).

rect then the chromosome imbalance results from a small deletion of both Bp and C material.

Biscatti (1965) reported a 3-year-old girl with mental retardation and mild congenital malformations including hypertelorism, clinodactyly, low-set ears, and simian creases, with a normal sex chromatin pattern and two presumptive X chromosomes. One C autosome was missing and was replaced by a small metacentric chromosome about the size of a chromosome in the E group. Unfortunately, the chromosomes of the parents were not studied so that the origin of the abnormal chromosome is doubtful. It could have resulted either from a long arm deletion (Cq−), a short arm isochromosome (Cpi), or a translocation. De Grouchy *et al.* (1968c) reported a ?6p− deletion in a premature baby with abnormal facies and other congenital malformations (Table 8-6). Analysis of the coagulation factors revealed no difference between the parents and the patient with the exception of factor XII (Hageman factor) which showed a coagulation rate in the patient of less than 50% of that seen in either parent, suggesting that perhaps the locus responsible for the synthesis of this factor might be on the short arm of the deleted chromosome. This, however, is by no means certain and the reduction in amount of Hageman factor may simply be further evidence of the generalized retardation which seems to result from chromosome imbalance.

4. Group F

No F group abnormalities have been established. One family has been reported (Gagnon *et al.*, 1963b) with familial hematuria and chronic nephritis but without deafness or ocular lesions which are usually associated with this condition (McKusick, 1966). Ten individuals in three generations have been studied and nonaffected subjects had normal karyotypes while affected subjects had two cell lines in both blood and fascia lata, a modal cell line with normal chromosomes (46,XX or 46,XY), and a minor F-trisomic cell line (47,XX,F+ or 47,XY,F+). The possibility that this mosaicism may be the cause of the familial disease was suggested. An alternative and perhaps more likely view is that the disease is inherited as a single gene defect and that one manifestation is nondisjunction of an F group chromosome with the F-monosomic cells being lethal.

5. Miscellaneous Chromosome Abnormalities

Four children with morphologically similar karyotypes have been reported (Frøland *et al.*, 1963b; Gustavson *et al.*, 1964c; Taft *et al.*, 1965b; Tamburro and Johnson, 1966). Each had 47 chromosomes with

TABLE 8-6

Summary of the Clinical Features of Five Patients with a Presumptive Deficiency of a C Group Chromosome

Feature	Atkins *et al.*, 1966a	Atkins *et al.*, 1966b Case 1
Maternal age	27	37
Paternal age	28	39
Birth weight (gm)	2976	3686
Gestation	–	–
Sex	F	M
Age (years unless stated)	7 days	8½
Chromosome complement and tissue	46,XX/46,XX,Cr Blood, skin.	46,XY,Bp+,Cr Blood
CNS	Developmental retardation. Apnoeic spells. Abnormal reflexes.	Hypotonia. Mental retardation (IQ 16)
Eyes	Brushfields spots. Palpebral fissures normal.	Epicanthus. No Brushfield spots. Nystagmus.
Ears	Large; low set	Low set
Face	–	–
Skull	–	Microcephalic low forehead. Prominent supraorbital ridge.
Jaw and mouth	–	High arched palate
CVS	–	–
G.I.	–	–
Urogenital and external genitalia	Normal external genitalia	–
Skeleton and growth	Abduction of hip limited	Short stature
Hands and feet	Single transverse palmar crease.	Long tapering fingers; incurving fifth toe.

an extra-small metacentric chromosome about the size of a G group autosome (Fig. 8-10). This chromosome appeared to be symmetrical and to have arms of equal length. The chromosomes of the parents were normal in each case. The abnormal chromosome was too small to represent trisomy for an F group autosome and its symmetry suggests that it might be an isochromosome, perhaps for the short arms of No. 17 or 18. A sister of the boy reported by Gustavson *et al.* (1964c) had Down's syndrome with primary G-trisomy. The four children with this abnormal chromosome showed some slight resemblance to each other (Table 8-7) and had certain features in common with Edwards' syndrome (Tamburro and Johnson, 1966); these included such general features as mental re-

Atkins *et al.*, 1966b Case 2	B. Turner *et al.*, 1962	De Grouchy *et al.*, 1968c
25	24	19
25	26	21
2268	–	1730
2 weeks postmature	–	7/9 premature
M	M	M
2½	12	3/12
46,XY,Cr Blood	45,XY,C–/46,XY,Cr Blood, bone marrow, skin	46,XY,?6p– Blood, skin.
Mental retardation	Mental retardation	Developmental retardation
Normal	Normal	No Brushfields spots. Epicanthus. Abnormal eyelids. Protruding eyes. Palpebral fissures normal.
Normal	Small, malformed	Large, low set. Preauricular tubercle.
Normal	Normal	Bulbous
Microcephaly	Microcephaly	Narrow protruding cranium
–	–	Retrognathos. General facial dysmorphia
Normal	Normal	–
Normal	Scrotal testes. Hypospadias.	Hypospadias, inguinal testes. Umbilical and inguinal hernia.
Short stature	Short stature	Short stature
Normal	Pes planus. Normal dermatoglyphics.	Abnormal dermatoglyphics. Fingers normal.

tardation, generalized hypertonicity, and ear malformations, none of which could really be said to be characteristic of any particular chromosome abnormality. Thus, neither these relatively slight phenotypic similarities nor the morphological resemblance of the abnormal chromosome to the short arms of chromosome 18 provides sufficient evidence to be able to state that the abnormal chromosome originated from the E group.

A ring chromosome additional to the normal members of the complement was reported in a female infant with apnoeic spells, abnormal ears, and hypoplastic nails. At 14 months she showed developmental and mental retardation and marked hypotonia. Four blood cultures and one skin culture revealed two cell lines (46,XX/47,XX,?r+); the ring

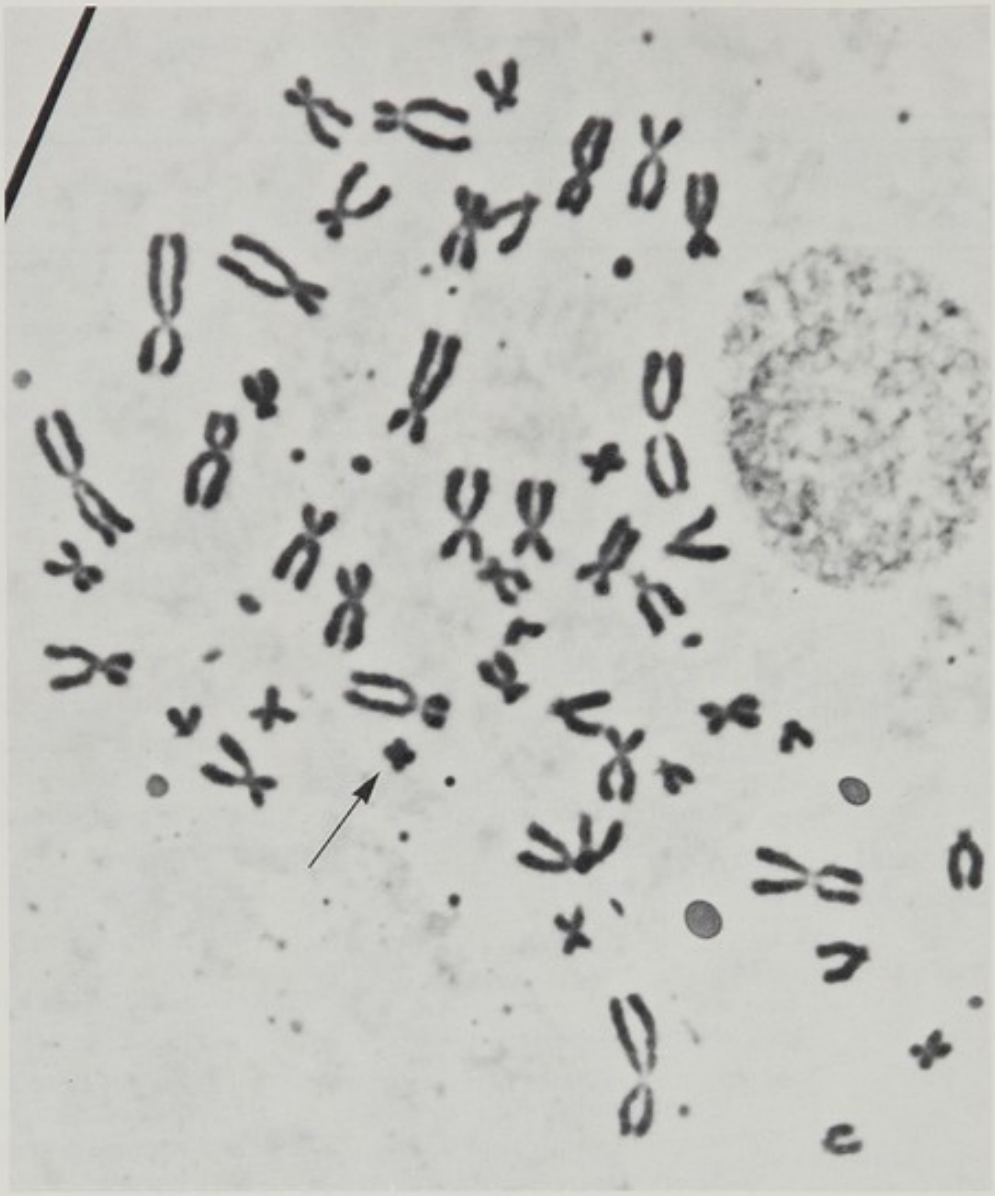


FIG. 8-10. Metaphase plate from the patient reported by Gustavson *et al.* (1964c), who had an additional small metacentric chromosome (arrow) (47,XY, mar+).

chromosome varied in size from about the size of an F or G group chromosome to that of a D chromosome. The proportion of cells with the ring fell from over 20% in the early blood cultures to 8% in the blood culture at 13 months. The frequency in the single fibroblast culture was about 10% in an early passage but dropped during later passages. These facts suggest that the abnormal cell line may be at a selective disadvantage both *in vivo* and *in vitro*. There is no evidence to suggest which chromosome formed the ring. The original zygote may have been either trisomic or normal. In either case ring formation followed by nondisjunction could result in the observed mixoploidy.

Other supernumerary chromosomes or chromosome fragments have

TABLE 8-7

Clinical Features of Some Patients with an Additional Small Metacentric Chromosome of Unknown Origin

Feature	Frøland *et al.*, 1963b	Gustavson *et al.*, 1964c	Taft *et al.*, 1965	Tamburro and Johnson, 1966
Maternal age[a]	19	28	–	36
Paternal age[a]	20	27	–	–
Gestation (weeks)	–	–	Premature	38
Birth weight (gm)	2800	3510	3006	–
Age (years)[b]	10 days and 8/12	7	16/12	2-10/12
Sex	M	M	M	F
Chromosome complement	47,XY,mar*+[c]	47,XY,mar*+[c]	47,XY,mar*+[c]	47,XX,mar*+[c]
CNS	Mental and developmental retardation. Slight hypertonicity.	Mental retardation. Slight hypertonicity. Seizures.	Mental and developmental retardation. Hypertonia.	Mental retardation. Hypertonia.
Eyes	Epicanthus, narrow palpebral fissures.	Narrow palpebral fissures. No epicanthus.	Epicanthus, bilateral retinal colobomata. Strabismus. Normal palpebral fissures.	Strabismus. No epicanthus. Palpepebral fissures, normal.
Ears	Small and low set	Normal	Small, low set	Small, low set. Left preauricular sinus.
Face and neck	Triangular mouth. Short neck with loose skin at nape.	–	Normal neck. No skin fold.	Normal
Skull	Microcephalic	Brachycephalic	Normocephalic	Normocephalic
Jaw and mouth	Small high-arched palate. Retarded dentition.	Small mouth. Micrognathos. High arched palate. Normal dentition.	Mouth normal. Normal-sized jaw. Palate normal. Retarded dentition.	Normal
CVS	Normal heart	Normal heart	Congenital heart defects	–
G.I.	–	–	–	–
Urogenital and external genitalia	Descended testes. Normal external genitalia.	Undescended at 8, descended by 15. Small testes.	Normal	Normal
Skeleton and growth	Extremities long; limited hip abduction.	Extremities long	Extremities normal	Extremities normal; limited hip abduction.
Hands and feet	Right talipes calcaneo varus. Left slight abduction. Ulnar development of hands; long fingers and toes, syndactyly. Abnormal extension of thumbs.	–	Incurved fifth fingers. Hammer toes; normal feet.	Normal

[a] Age at birth of child.
[b] Age at examination.
[c] Here "*" stands for small G-sized metacentric marker of unknown origin.

been reported in dystrophica myotonica (Fitzgerald and Caughey, 1962; Nakagome *et al.*, 1963). Chromosome abnormalities have not, however, been reported to be universally associated with this condition (Mutton and Gross, 1965). Nakagome *et al.* (1963) also reported a deleted G group chromosome in a patient with Duchenne's type muscular dystrophy, while Ruffié *et al.* (1965) reported a G group chromosome with enlarged short arms in a family in which the proband had a severe form of muscular dystrophy. The significance of these findings in relation to muscular dystrophy is not clear, but the probability is that they will be found to be chance associations between a variant chromosome and the disease. Whether such variation may predispose the disease under certain conditions or the disease predispose nondisjunction or chromosome breakage merits further study.

C. *Reciprocal Translocations*

Consideration of the Phenotype

The cytogenetic characteristics of 76 familial reciprocal translocations have been discussed in Volume I, Chapter 8 and it is clear from this discussion that the majority, at some time or other, result in chromosome imbalance and hence phenotypic malformation. The phenotype of the probands in each of these families is summarized in Table 8-8. The majority had multiple congenital malformations together with mental and developmental retardation. At present, it is not possible to relate the duplication and deletion of specific chromosome regions to a specific phenotype because there is usually far too much phenotypic overlap for this to be useful. There are exceptions. The proband in the six families ascertained through Down's syndrome all had a duplication of the long arm of a G chromosome (Gq+) which indicated that the long arm alone, when present in triplicate, was sufficient to cause this condition. Similarly, the probands in the families ascertained because of the *cri du chat* all have a Bp− chromosome. A detailed study of these phenotypes would however be useful since, eventually, sufficient families might become available to make it possible to identify specific duplicate or deleted chromosome regions and to detect phenotypic patterns related to the duplication or deficiency of specific parts of the genome. However, even where this is possible (18+, 13+, and 21+) the overlap was so great as to suggest that we are dealing with the effect of chromosome imbalance *per se* rather than the triplication of specific gene loci. For instance, the universal developmental retardation seen in the trisomic syndromes, and to a lesser or greater extent in those families with unbal-

TABLE 8-8

A Summary of the Phenotypes of 76 Probands who are Chromosomally Unbalanced as the Result of a Reciprocal Translocation[a]

No.	Translocation[b]	Chromosome imbalance in proband[c]	Related balanced heterozygotes[c]	Chromosomally unbalanced relatives[c]	Phenotype of proband
t(A;A)					
1	t(2p−;3?+)	2pdup; 3?del	M, MGF, S	S	Unslanted eyes, micrognathia, small nose, cardiac murmur, umbilical hernia, hypertonia, 8/10 simple arches on fingertips.
2	t(2p−;3?+)	2pdup;3?del	M, A, U, MGM, MGA	–	Cebocephaly, malformed ears, micrognathia, cleft palate, heart murmur, 6/10 simple arches.
3	t(1?−;2p+)	?del unspecified	M	Two S stillborn	Mental retardation and minor congenital anomalies.
t(A;B)					
1	t(2p+;Bq−)	?Balanced	F	–	Retardation, hypertonia, microcephaly, seizures, normal dermatoglyphics.
2	t(3?−;Bp+)	3?dup;Bpdel	13 confirmed heterozygotes	Several abnormal infants not studied	Harelip, cleft palate, eye defects, low-set ears, polydactyly, heart murmur, renal abnormality.
3	t(2p−;Bp+)	?Balanced	M, S	–	Normal
4	t(1?−;4q+)	Nil (16q+)	M	Two abortions?	Paranoid schizophrenia in chromatin +ve ♂. Father of proband also 16q+.
t(A;C)					
1	t(1?−;Cq+)	Balanced	F, A, PGM	–	Normal except for carcinoma
2	t(1?−;Cp+)	1?dup;Cpdel	F	–	Multiple skeletal anomalies, severe mental retardation.
3	t(1?−;Cq+)	Balanced	M, 2S	–	Syndactyly, polydactyly, asymmetry, mental retardation.
4	t(3?−;Cq+)	3?dup;Cqdel	M, S	–	Retarded growth, mental retardation, cardiac anomaly.
5	t(3?+;Cq−)	Balanced	M, A, MGF	–	Von Recklinghausen's disease Kyphoscoliosis.
6	t(2p−;?C?+)	Balanced	F, U, Co	–	Normal
7	t(2p+;Cq−)	2pdel;Cqdup	M, MA, 2Co	–	Retardation, speech defect. Spastic, long thin limbs, Cardiac anomaly. Transverse palmar crease.
t(A;G)					
1	t(3?−;Gp+)	3pdup;Gpsdel	M, 2A, 2U, S, Co	2S, Co	Deep-set eyes, pug nose, mental retardation, features of gargoylism. De Lange syndrome.
2	t(1?−;Gq+)	Balanced	M, MGM, MGA, MGGM, S	A	Down's syndrome
3	t(2q−;21q+)	21qdup	M, MGM, A, 2U, 2Co	MGU	Down's syndrome
t(B;B)					
1	t(4p+;5q−)	?4pdel;?5qdup	M, 2A, Co	–	Microcephaly, malformed ears, joint abnormalities, single kidney.

TABLE 8-8 (cont'd)

No.	Translocation[b]	Chromosome imbalance in proband[c]	Related balanced heterozygotes[c]	Chromosomally unbalanced relatives[c]	Phenotype of proband
t(B;C)					
1	t(Bq+;Cp−)	Bqdel;Cpdup	F	S	Minor somatic anomalies, mental retardation.
2	t(Bp+;Cq−)	Balanced	F, U, PGF, S	–	Minor somatic anomalies, mental retardation.
3	t(Bq+;Cq−)	Balanced	Ch	–	Normal
4	t(Bq+;Cq−)	Bqdel;Cqdup	M	–	Severe congenital malformations, growth and mental retardation.
5	t(Bp−;Cp+)	Bpdel;Cpdup	F	–	*Cri du chat* syndrome
6	t(Bp−;Cq+)	1. Bpdel;Cqdup(3) 2. Bpdup;Cqdel(1)	M	–	3 sibs with *cri du chat* synchrome; 1 sib with mental retardation.
7	t(Bq+;Cp−)	Bqdel;Cpdup	M	–	Small baby microcephalic flat head. Low-set ears. Depressed nasal bridge, abnormal dermatoglyphics.
t(B;D)					
1	t(Bq+;Dq−)	Bqdup;Dqdup	M, S.	–	Choanal atresia, cardiac anomaly. Growth and mental retardation.
2	t(Bp−;Dq+)	1. (Bpdel;Dqdup) 2. (Bpdup;Dqdel)	M, A, MGF	3S	Retarded growth, mental retardation, microphthalmia in proband and one sib. 2 sibs with *cri du chat* syndrome.
3	t(Bq−;Dq+)	Balanced	M	–	Normal
4	t(Bp−;Dp+)	Bpdup;Dpsdel	M, MGM, 3MGA, 2U, 3A, 4Co, S	–	Facial asymmetry. Eye defects. Talipes. Pyloric stenosis.
5	t(Bp−;Dp+)	Bpdel;Dpdup	F	–	*Cri du chat* syndrome
6	t(Bq−;Dq+)	Balanced	M	–	Round face. Low-set ears. Hypertelorism. Psychomotor retardation.
7	t(Bp−;Dq+)	1. 5pdel;Dqdup (Prob) 2. 5pdup;Dqdel –	M, S	2S, 1AB	Features of *cri du chat* in proband.
t(B;E)					
1	t(Bq−;Ep+)	Balanced	M, U, MGM, S	–	Coloboma, micrognathia, and dental abnormalities.
2	t(Bq−;Eq+)	Bqdup;Eqdel	F, PGF, S	–	Minor somatic anomalies, odd facies.
3	t(Bq−;Eq+)	Balanced	2S	–	Normal
4	t(4p+;18q−)	1. 4pdup;18qdel (Prob) 2. 4pdel;18qdup (Pu)	S, F, PGF, PA	PA	(Prob) Retardation, hypotonia, epicanthus, antimongoloid slant, low-set malformed ears, congenital heart defects, absent corpus callosum. P.A. Mental and physical retardation. Nonspecific congenital malformation.
t(B;G)					
1	t(Bp−;Gp+)	Bpdup;Gpdel	M	–	Omphalocoele, anal atresia, odd facies, eye defects, skeletal abnormalities, hypotonia, failure to thrive.
2	t(Bp−;Gp+) (Possibly more complex rearrangement)	?4pdel;Gpdup)	M	–	Features of *cri du chat*

t(B;?)					
1	t(5p−;?+)	5pdel;−	M?	S	Features of *cri du chat*
2	t(5p−;?+)	5pdel;−	M?S	S, 3A	Features of *cri du chat*
t(C;C;)					
1	t(Cq−;Cp+)	Cdup;Cdel	F, PGM, A, S	–	Harelip, cleft palate, microcephaly, heart and renal abnormalities.
2	t(Cq−;Cq+)	Balanced	M	Proband has had four 2/12 abortions	Normal
3	t(Cq−;Cq+)	Cqdup;Cqdel	M	–	Eye defects, skeletal anomalies, simian creases, juvenile hypothyroidism.
4	t(Cq+;Cq−) (?6 and 12)	Cqdup;Cqdel	M, Co, 2MA, MGM, MGA, MGGM	N, 5A	Retardation, microcephaly, micrognathia, abnormal facies. Short neck, small chest. Birth wt 1790 gm. 8/9. M prominent occiput.
5	t(Cq−;Cq+) (? 11 and 12)	?11qdup;?12qdel	M	3A	Microcephaly; birth wt 2500 gm at term. Abnormal cry. Similar to 18-trisomy in some respects.
t(C;D)					
1	t(Cq−;Dq+)	Cqdup;Dqdel	M, S	–	Eye defects, flat nasal bridge, low-set ears, renal anomaly, mental retardation.
2	t(Cp−;Dq+)	Balanced	M	–	Normal
3	t(Cp+;Dq−)	Cpdel;Dqdup	F, U, PGF, S	S	Retarded growth, hemangiomata of face, polydactyly,ventricular septal defect, mental retardation.
4	t(Cp+;Dq−)	Cpdup;Dpqdup	M	–	Deep-set eyes, toe syndactyly, mental retardation.
5	t(Cq−;Dq+)	Cqdup;Dqdup	M, A, MGF, MGA, Co	–	Congenital malformations, mental retardation.
6	t(Cp+;Dq−)	Balanced	F	–	Down's syndrome (due to Gqi)
7	t(Cq−s+;Dp+s−)	Cpdup;Dpdup	M	–	No details
8	t(Cp−;Dq+)	Balanced	M	–	Aplasia of corpus callosum, aortic atresia, aplasia of radius, polycystic kidneys, odd facies.
9	t(Cq−;Dp+)	Cqdup;Dpdel	F, S	–	Low birth weight. Microcephaly. Cleft lip and palate. Retrognathia. Blepharochalasis. Low-set, large ears. Hypotonia.
10	t(Cq+;Dq−)	Not known	M, S	Proband stillborn hydrocephalus, 1AB 2/12	Cyclops hydrocephalic. Clubbed hands and feet. Polydactyly. Ventricular septal defect.
t(C;E)					
1	t(Cp−;Eq+)	Cpdup;Eqdel	F	–	
2	t(Cq−;18q+)	Cqdup;18qdel	F, A, PGM, S	6 aborted and 1 malformed sib	Features resembling Edwards' syndrome
3	t(Cq−;18q+)	Cqdup;18qdel	M	1A	Optic atrophy, iris heterochromia, overriding fourth toes, hernia, cardiac murmur and mental retardation.
					Some features of Edwards' syndrome. Abnormal facies, marked epicanthus, flexion deformity overlying third finger. Fallot's tetralogy. Enlarged heart. Small brain with hypoplasia of optic nerves and corpus callosum.
t(C;F)					
1	t(Cp−;F?+)	Cpdup;F?del	M, S	–	Growth and mental retardation, skeletal abnormalities, odd facies.

TABLE 8-8 (cont'd)

No.	Translocation	Chromosome imbalance in proband [b]	Related balanced heterozygotes [b]	Chromosomally unbalanced relatives [b]	Phenotype of proband
t(C;G)					
1	t(Cq−;Gp+)	Cqdup;Gpsdel	M, S	–	Abnormal face and hands. Mental retardation. Both probands have similar facies, low-set ears, transverse palmar creases, short fifth finger. Koilonychia, pes planus, overriding fourth toes.
2	t(Cq−;Gp+)	Cpqdup;Gqdel(2)	M, U, A, MGM	S	
3	t(Cq−;Gq+)	Cqdup;Gqdel	F	1TA	Long tapering skull, sloping forehead, domed occiput, strabismus. Low-set ears, flexion deformity. Bilateral luxation of hips, atrial septal defect.
t(D;D)					
1	t(Dq+;Dq−)	Dpqdup	M, 2A, 2U, MGF	S several abortions in family	Seizures, minor somatic anomalies, mental retardation, 10 simple arches on fingertips.
t(D;E)					
1	t(Dp+;16q−)	Dpdup;16pqdup	M (mosaic)	11 other spontaneous abortions	Spontaneously aborted fetus
2	t(Dp−s−;18p+s+)	Balanced	2S	–	Normal
3	t(Dq−;17q+)	Dpqdup;18qdup	M, MGF	S	Seizures, dolicocephaly, minor somatic anomalies, mental retardation.
4	t(Dq−;Ep+)	1. Dpqdup;Eqdup 2. Dqdup;Eqdel	M, S	S(2)	1. Microcephaly, hemangiomata, hernias, mental retardation. 2. Retardation, odd facies, multiple anomalies.
5	t(Dp+;Ep−)	Dpsdel;Epdup	F, PGM, S	–	Odd facies, low-set ears, hydronephrosis, ventricular septal defect, coarctation of the aorta, agenesis of most of corpus callosum and absent olfactory nerves.
6	t(Dp+;18q−)	Dpdel;18pdel	M, S	–	1. Mental retardation and short stature, microcephaly, epilepsy, speech defect. 2. Also mentally deficient but with balanced chromosome complement.
7	t(Dp+;18q−)	Dpsdel;18qdup	F	–	Some features of 18-trisomy, hypertelorism, high arched palate, malformed low-set ears, micrognathia, hypotonia, abnormal hip abduction.
t(D;G)					
1	G−t(Dq+)	Dqdel;Gqdup	M, 2U, MGM	S	Down's syndrome
2	t(Dp−;Gp+)	Balanced	M, U, S	–	Congenital heart disease
t(E;E)					
1	t(17p+;18p−)	17p?dup;18pdel	M, A, MGF	–	18p− syndrome
t(E;G)					
1	t(18q−;Gq+)	18qdup−Gqdel	M, A, MGF, MGA, Co, 2S	2S	Failure to thrive, hypertonia, odd facies, skeletal, renal and cardiac anomalies, mental retardation.

2	t(18p−;21p+)	(1) Epdel;Gps?dup (2) Epdup;Gps?del	M, MA, MGM	C, 2S, 2MU	1. Retardation of physical and mental development, short stature. 2. Short stature, otherwise normal.
t(G;G)					
1	t(21q−;22q+)	21qdup;22qdel	M, MU, MGM	S, 7AB	Down's syndrome

[a]Source of reciprocal translocations referred to in this table:

t(A;A)
1. Summitt (1966)
2. Lee *et al.* (1964)
3. Lejeune *et al.* (1968c)

t(A;B)
1. De Grouchy (1965a)
2. Walzer *et al.* (1966a)
3. De Grouchy *et al.* (1966b)
4. Court Brown *et al.* (1964)

t(A;C)
1. Court Brown *et al.* (1966); Court Brown (1967)
2. Edwards *et al.* (1962)
3. Zaremba *et al.* (1965)
4. Clarke *et al.* (1964)
5. Gropp *et al.* (1965)
6. Hulten *et al.* (1966)
7. Cooke (1968)

t(A;G)
1. Falek *et al.* (1966)
2. Kontras *et al.* (1966)
3. Laurent and Robert (1968)

t(B;B)
1. Shaw *et al.* (1965)

t(B;C)
1. Edwards *et al.* (1962)
2. Lejeune and Berger (1965)
3. Makino *et al.* (1965)
4. Court Brown *et al.* (1966); Court Brown (1967)
5. McIntyre (1965)
6. Laurent and Robert (1966a)
7. De Grouchy *et al.* (1967a)

t(B;D)
1. Pfeiffer *et al.* (1966)
2. Lejeune *et al.* (1965)
3. Hamerton, unpublished data
4. Brimblecombe and Lewis (1966)
5. Koulischer and Quersin (1965)
6. Rumpler *et al.* (1967)
7. DeCapoa *et al.* (1967)

t(B;E)
1. PRU 1039
2. Firschein *et al.* (1966)
3. Court Brown *et al.* (1966); Court Brown (1967); Stewart *et al.* (1969)
4. Valdmanis *et al.* (1967)

t(B;G)
1. Gustavson *et al.* (1964b)
2. De Grouchy and Gabilan (1965)

t(B;?)
1. DeCapoa *et al.* (1967)
2. DeCapoa *et al.* (1967)

t(C;C)
1. Lindsten *et al.* (1965)
2. Lejeune and Berger (1965)
3. Rohde and Catz (1964)
4. Lejeune *et al.* (1968a)
5. McDermott *et al.* (1968)

t(C;D)
1. De Grouchy and Canet (1965)
2. Court Brown *et al.* (1966); Court Brown (1967)
3. Stalder *et al* (1964)
4. Pitt *et al.* (1967)
5. Insley *et al.* (1968)
6. Ruffie *et al.* (1966a)
7. Revasov and Russkikh (1966)
8. Pfeiffer and Meyer (1967)
9. De Grouchy *et al.* (1967b)
10. Blythe (1968)

t(C;E)
1. PRU 947
2. Punnett *et al.* (1966)
3. McDermott *et al.* (1968)

t(C;F)
1. Lejeune *et al.* (1966c)

t(C;G)
1. PRU 1389
2. Lord *et al.* (1967)
3. Mikkelsen *et al.* (1968)

t(D;D)
1. Jacobsen *et al.* (1966)

t(D;E)
1. PRU 2623
2. Court Brown *et al.* (1966)
3. Vislie *et al.* (1962); Brøgger (1967)
4. Hauschteck *et al.* (1966)
5. Migeon and Young (1964)
6. Fredga and Rayner (1967); Fredga (1968)
7. Meyer-Robisch and Schwanitz (1967)

t(D;G)
1. Laurent and Robert (1966b)
2. Court Brown and Jacobs (1966); Stewart *et al.* (1969)

t(E;E)
1. Lejeune *et al.* (1966b)

t(E;G)
1. Uchida *et al.* (1964a)
2. Jacobsen and Mikkelsen (1968a)

t(G;G)
1. Cohen and Davidson (1967)

[b]The standardized nomenclature recommended by the Chicago Conference (1966) is used throughout.

[c]Abbreviations: M, mother; F, father; PGM, MGM, paternal/maternal grandmother; PGF, MGF, paternal/maternal grandfather; MGA, maternal great aunt; A, aunt; U, uncle; MGGM, maternal great grandmother; Co, cousin; Ch, child; S, sib; AB, abortion; Prob, proband; TA, therapeutic abortion; dup, duplication; and del, deletion. Balanced, indicates no obvious chromosome imbalance as detected by morphological examination of karyotype. Does not necessarily indicate a normal phenotype (see last column of table).

anced chromosome rearrangements, suggests that the loss or gain of whole segments of the genome leads to a nonspecific effect on all or most of the processes of cellular metabolism and may affect many of the organ systems in the body. There is also evidence of an effect on cellular regulation, for instance, a delay in the switching mechanisms involved in the change from the production of fetal to adult hemoglobins.

III. Location of Specific Gene Loci

Singularly little success has accompanied attempts to map specific gene loci. A considerable volume of negative evidence recently summarized by Race and Sanger (1968) indicates that particular gene loci are not on a specific chromosome region (Table 8-9). This indicates how little is known and how essential it is that complete genetic studies are carried out on all families which are found to have segregating chromosome abnormalities.

Very recently an autosomal locus has been located. The Duffy locus is on chromosome No. 1 (Donahue *et al.*, 1968) and is fairly closely linked to the secondary constriction which lies close to the centromere. Finally, it is possible (see above) that the locus for the Hageman factor (clotting factor XII) is on the short arm of one of the larger C group (6?) autosomes, but this is not conclusive.

Thus, after 10 years of work and the discovery of many cytogenetic abnormalities, we have a realistic map of the X chromosome and a little evidence for some autosomal linkages (Table 8-10) but almost nothing but negative evidence on the relation of linkage groups to specific chromosomes. (See Addendum, Volume II.)

TABLE 8-9

Where Some Genetic Marker Loci Are Not Sited[a,b,c]

Marker system	Marker locus not on
ABO	Short arm, 5, 13
MNSs	Extremities 1 Short arm, 5, 13, 14, 15, 16, 17, 18 1/3 long arm, 13, 14, 15 Extremities, 14, 18 Part long arm 18
Rh	Short arm, 4, 5, 13, 14, 15, 16, 17, 18 1/3 long arm, 13, 14, 15 Part long arm 18 Extremities 18, 21, 22
Kell	Short arm, 5 Part long arm, 18 Extremities, 18
Duffy[c]	Short arm, 5, 13, 18 Extremities, 21, 22
Kidd	Extremities, 1, 18, 21, 22 Short arm, 5, 13, 18 Part long arm, 18
Haptoglobins	Short arm, 4, 5, 13, 18 1/3 long arm, 13, 14, 15 Extremities, 14, 18, 21, 22 1/2 long arm, 18
GM group	Short arm, 5, 13, 18 Part long arm, 18 Extremities, 18
Serum cholinesterase	Short arm, 13
Red cell acid phosphatase	Short arm, 5, 13 1/2 long arm, 13, 14, 15, 18 Extremities, 21, 22
Phosphoglucomutase	Short arm, 5, 13 1/2 long arm, 18
6PGD	1/2 long arm, 13,14, 15
Red cell adenylate kinase	Extremities, 21, 22

[a] Modified from Race and Sanger, 1968.

[b] There are hints that the haptoglobin locus may be sited on one of the D group of chromosomes 13, 14, or 15 (Gerald *et al.*, 1967; De Grouchy *et al.*, 1966c). Bloom *et al.* (1967) found evidence suggesting that the locus is at one or the other end of 13, but it cannot be on the short arm. The possibility therefore remains that the haptoglobin locus is sited toward the end of the long arm of chromosome 13. If this proves correct it will be the first locus to be assigned to a particular human autosome (see Chapter 7).

[c] Duffy is now known to be located on chromosome No. 1 (see text and Table 8-10).

TABLE 8-10

Autosomal Linkages in Man

Linked loci	Recombination rates	Reference
Lutheran and secretor	0.15 ♀ > ♂	Mohr, 1951a,b; Sanger and Race, 1958; Lawler and Renwick, 1959; Metaxas *et al.*, 1959; Greenwalt, 1961
Rh and elliptocytosis	0.033 0.029	Chalmers and Lawler, 1953; Goodall *et al.*, 1953, 1954; Lawler and Sandler, 1954
ABO and nail patella syndrome[a]	0.096 0.089 ♂ 0.146 ♀	Renwick and Lawler, 1955; Lawler *et al.*, 1957, 1958; Jameson *et al.*, 1956; Renwick, 1956; Renwick and Izatt, 1965
Duffy and congenital cataract		Renwick and Lawler, 1963
Duffy and chromosome 1		Donahue *et al.*, 1968
MNSs and a rare skin condition (gerodermatose scléro-atrophiante et kératodermique des extremités)	0.02	Mennecier, 1967
ABO and adenylate kinase[a]	0.21	Rapley *et al.*, 1968
? ABO and xeroderma pigmentosa	0.18	El Hefnawi *et al.*, 1965
Transferrin and serum cholinesterase	0.16 0.19 ♀ 0.12 ♂	Robson *et al.*, 1966
GC serum groups and albumin variants	0.015	Weitkamp *et al.*, 1966

[a] Order probably ABO-Np-AK rather than Np-ABO-AK.

Chapter 9

CYTOGENETICS OF HUMAN PREGNANCY WASTAGE

I. Introduction

Spontaneous abortion is generally considered to account for between 15 and 20% of all conceptions, and this figure may be considerably increased if losses during the pre-implantation period of pregnancy are included. Recent studies have shown that between 20 and 30% of all abortuses have a chromosome abnormality (Geneva Conference, 1966). Chromosome abnormalities are not the only, nor perhaps the most important factor, in the etiology of spontaneous abortion; Hertig *et al.* (1959) estimated that the greatest loss of fertilized ova was during the pre-implantation stage of development. Recent studies on the pig indicated that pre-implantation blastocysts showed a high frequency of chromosome abnormality and particularly triploidy (McFeely, 1967). It is possible that in man a high proportion of pre-implantation zygotes are abnormal, although there is no direct data available for this early stage of pregnancy. The data reported here concerns a highly selected series of abortuses which implanted and provided a recognizable conceptus for study.

II. Types of Chromosome Abnormality in Spontaneously Aborted Fetuses

Data are available from 22 separate series of abortuses (Table 9-1), the majority of which have gestational ages from 6 weeks to 5-6 months.

This is an extremely heterogeneous collection of material, particularly in relation to the criteria used for selection as well as assessment of spontaneity and frequency with which successful cultures were obtained. This ranges from 24-78% with a mean figure of slightly less than 60%. The reasons for this variation may be in the type of material collected and the different methods of handling it, and it is difficult, if not impossible, to separate these factors. Irrespective of these factors, however, about 20-30% of cultured spontaneous abortions fail to provide an adequate chromosome analysis with our present techniques. About 60-75% of cultured spontaneous abortions provided useful results (Machin and Dhadial, 1969). The type of abortus which failed to grow in culture was usually that in which no embryonic material was detected, as well as missed abortions and macerated fetuses. This suggested that the failure of growth *in vitro* might result from an early intrauterine death or a complete failure of development. This indicated the possibility that these fetuses might have a higher frequency of malformation and possibly therefore of chromosome anomaly than those providing results. On the other hand, Carr *et al.* (1966) have analyzed the data on 149 abortuses which failed to provide chromosome results in his series. They found little difference between abortion material which failed to grow *in vitro* and that which did provide results with respect to maternal age or length of gestation. Abortuses which failed to give results, however, differed from those with both normal and abnormal chromosomes with respect to duration of pregnancy, the "failed cultures" falling between the other two classes in this respect. Other factors analyzed were the previous obstetric histories and frequency of habitual abortion. No differences were found between these groups. Carr *et al.* concluded that there was no justification for assuming that the abortions which failed to grow contained any different range of chromosome abnormality than those which grew and were analyzed.

The range of chromosome abnormalities detected among these 1291 abortions is summarized in Table 9-2. The most common single abnormality is the 45,X group which comprises 20% of all chromosomally abnormal fetuses or about 5.0% of all spontaneous abortions. Triploids (Fig. 9-1) are the second most frequent class comprising 16.5% of abnormal fetuses and 4.1% of all abortions. The most frequent group of anomalies were the autosomal trisomics. Trisomic abortuses include A-, B-, C-, 16-, and F-trisomics (Fig. 9-2) as well as D-, 18-, and G-trisomics and comprise 47.8% of all chromosomally abnormal fetuses and 11.9% of all abortions. The three most common trisomics are those also found among live-born children, the D-, 18-, and G-trisomics. E-trisomics, which comprise about 15% of the chromosomally abnormal

TABLE 9-1

A Summary of the Chromosome Abnormalities Found in 22 Separate Series of Spontaneous Abortions

No.	Cultures started	No. karyotyped	Proportion successful	No. chromosomally normal	No. abnormal	Proportion abnormal	45,X	Autosomal trisomics							Polyploids		Autosomal monosomy	Double trisomics and tetrasomics	Mixoploids	Translocations	Other	Reference[a]
								A	B	C	D	E	F	G	69	92						
1	–	35	–	27	8	0.23	2	–	–	1	–	1	–	1	–	–	3(F–,F–)	–	–	–	–	Jacobson and Barter, 1967
2	370	274	0.74	149	125	0.46	18	1	1	14	17	20	2	16	25	5	–	4	2	–	–	J. G. Boué and Boué, 1966;
3	179	54	0.30	30	24	0.44	5	2	–	–	2	7	–	4	1	3	–	–	–	–	–	A. Boué and Boué, 1968; J. G. Boué *et al.*, 1967; J.G. Boué, 1967.
4	376	227	0.60	177	50	0.22	12	1	1	2	6	9	1	6	9	2	–	1	–	–	–	Thiede and Metcalfe, 1966.
5	?73	39	0.53	23	16	0.41	2	–	–	1	–	2	–	6	–	–	–	–	–	1	4	Carr, 1965, 1967
6	67	30	0.45	27	3	0.10	–	–	–	–	–	–	–	–	2	–	–	–	1	–	–	Clendenin and Benirschke, 1963; Benirschke (G.C.)
7	–	35	–	29	6	0.17	2	–	–	–	–	1	–	–	–	–	–	1	2	–	–	Schlegel *et al.*, 1966a
8	135	82	0.61	74	8	0.10	3	–	–	–	–	–	1	–	2	2	–	–	–	–	–	Kerr and Rashad, 1966
9	75	25	0.33	9	16	0.64	5	–	–	1	–	2	–	3	5	–	–	–	–	–	–	Inhorn *et al.*, 1964
10	16	8	0.50	6	2	0.25	–	2	–	–	–	–	–	–	–	–	–	–	–	–	–	Szulman, 1965
11	?	7	–	6	1	0.14	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	Hall and Kallen, 1964
12	?	14	–	12	2	0.14	1	–	1	–	–	–	–	–	–	–	–	–	–	–	–	Makino *et al.*, 1962; Sasaki (G.C.)
13	43	22	0.51	19	3	0.14	1	–	–	–	–	–	–	–	–	1	–	–	1	–	–	Sato, 1965 (G.C.)
14	?12	8	0.67	7	1	0.12	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	Warburton and Miller (G.C.)
15	118	28	0.24	25	3	0.11	–	–	–	–	–	–	–	–	2	–	–	–	1	–	–	Valenti (G.C.)
16	?	10	–	9	1	0.10	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	Rushton and Edwards (G.C.)
17	200	81	0.40	73	8	0.09	1	–	–	–	–	–	–	–	2	–	–	–	4	1	–	Profofkieva-Belgofvskaja (G.C.)
18	?	13	–	12	1	0.08	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Stenchever *et al.* (G.C.)
19	?	16	–	15	1	0.06	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	Gropp (G.C.)
20	43	31	0.72	29	2	0.06	–	–	–	–	–	–	–	–	2	–	–	–	–	–	–	Klinger *et al.* (G.C.)
21	64	50	0.78	49	1	0.02	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	Delhanty (G.C.)
22	342	202	0.59	162	40	0.20	11	1	–	1	4	6	–	5	3	2	–	1	4	1	1	Wingate (G.C.)
Total	?2113	1291	0.24–0.78	969	322	0.25 range 0.02–0.60	64	7	3	20	30	48	4	42	53	16	3	7	16	3	6	Machin and Dhadial, 1969

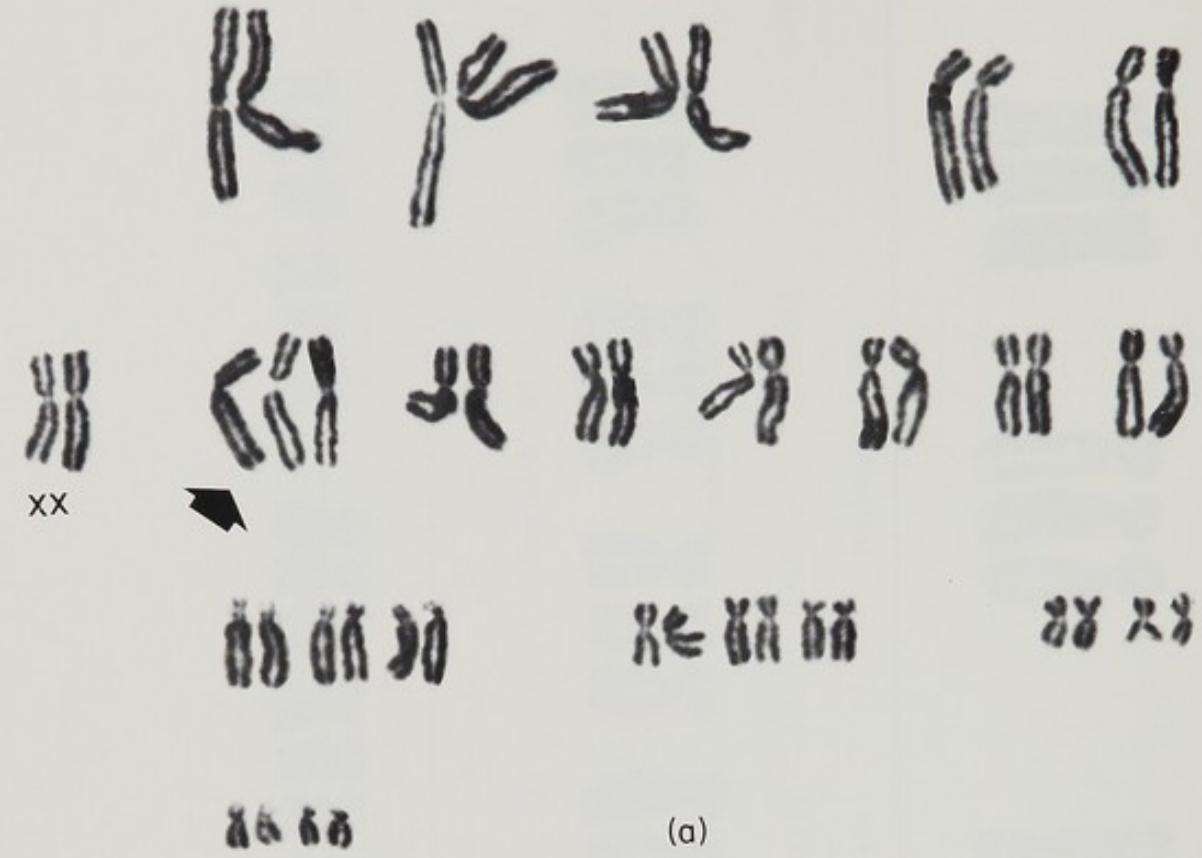
[a] Here G.C. stands for quoted in report of Geneva Conference (1966).

TABLE 9-2

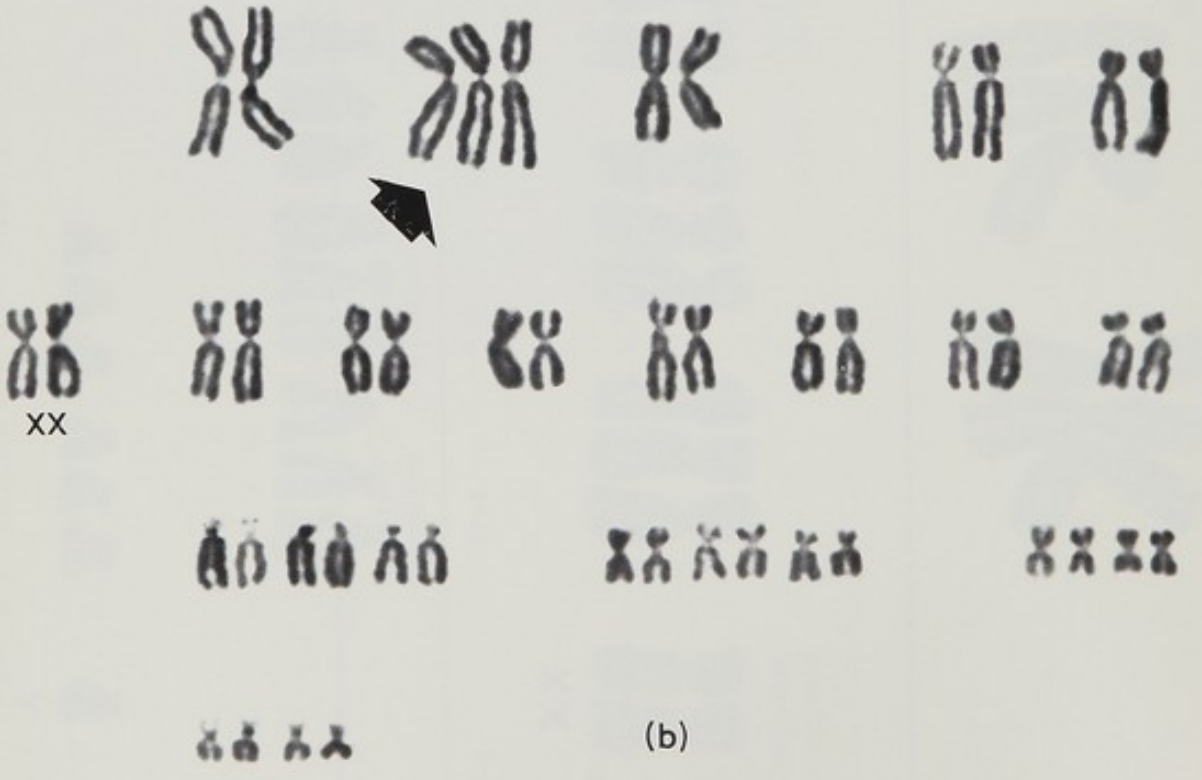
The Frequency of Different Types of Chromosome Abnormalities Found in Spontaneous Abortions

	Abortions karyotyped	Abnormal karyotypes	45,X	Autosomal trisomics							Triploids	Tetraploids	Mixoploid trisomics	Others
				A	B	C	D	E	F	G				
No.	1291	322	64	7	3	20	30	48	4	42	53	16	16	19
				All trisomics = 154							Polyploids = 69			
Proportion total	–	0.25	0.05	A,B,F 0.01		0.015	0.023	0.037	–	0.032	0.041	0.012		0.027
				All trisomics 0.119							Polyploids = 0.053			
Proportion abnormal	–	1.00	0.199	A,B,F 0.043		0.062	0.093	0.149	–	0.130	0.165	0.050		0.109
				All trisomics 0.478							Polyploids = 0.214			

FIG. 9-1. 69,XXY karyotype (F728) from an aborted conception at 13 weeks consisting of an empty ruptured sac (orcein ×1440). (Reproduced by courtesy of Dr. R. Dhadial and Dr. A. M. Machin.)



(a)



(b)

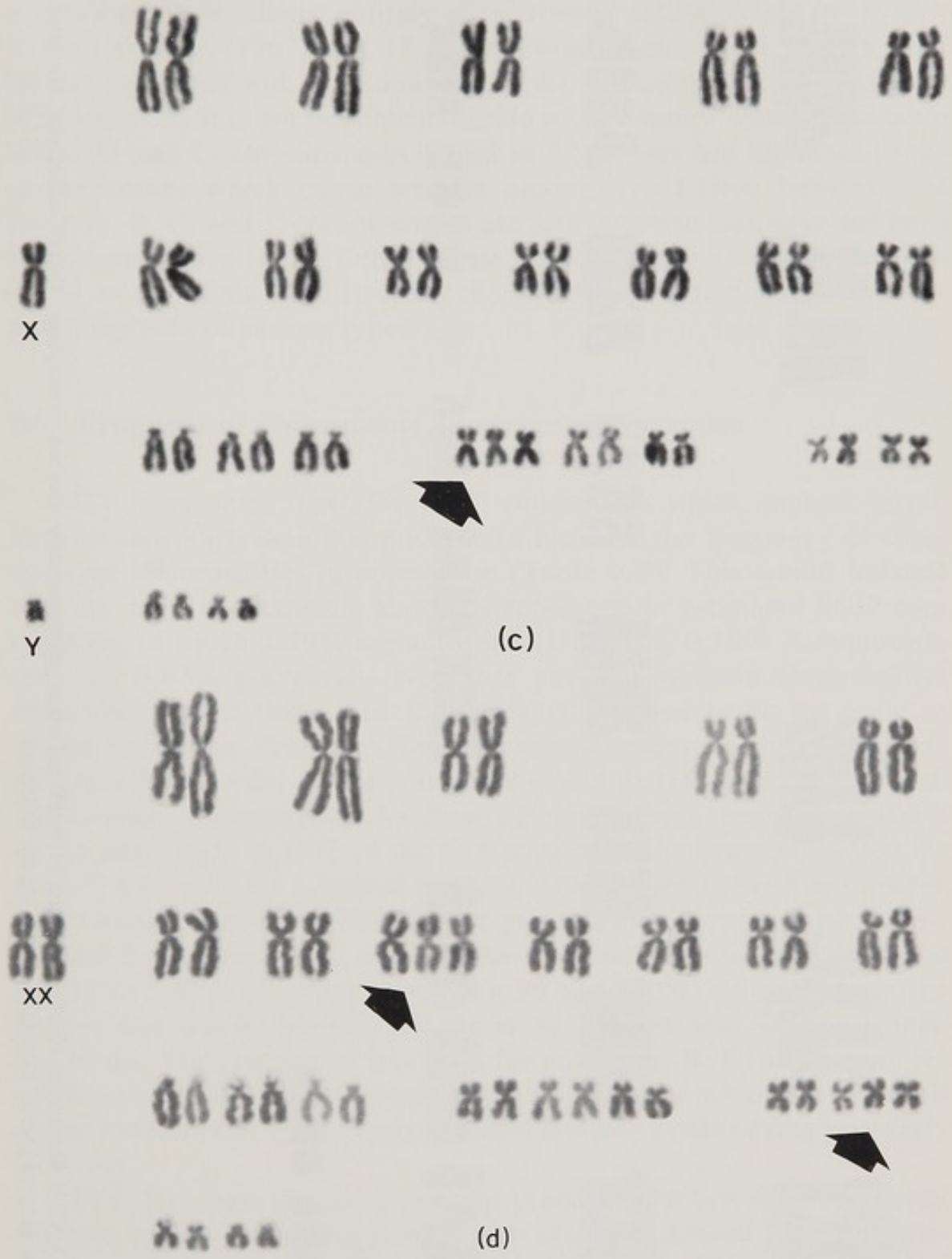


FIG. 9-2. Karyotypes of trisomic abortuses: (a) 47,XX,C+ (F739) from an intact sac containing a 6-cm embryo aborted at a gestational age of about 3 weeks. (b) 47,XX,2+ (F586) from a small intact sac containing a minute 2-mm embryonic nodule gestational age about 3-4 weeks. (c) 47,XY,16+ (F781) from an incomplete empty sac. (d) 48,XX,C+,F+ (F611) from a 10-week gestation spontaneously aborted conception. (Reproduced by courtesy of Dr. R. Dhadial and Dr. A. M. Machin.)

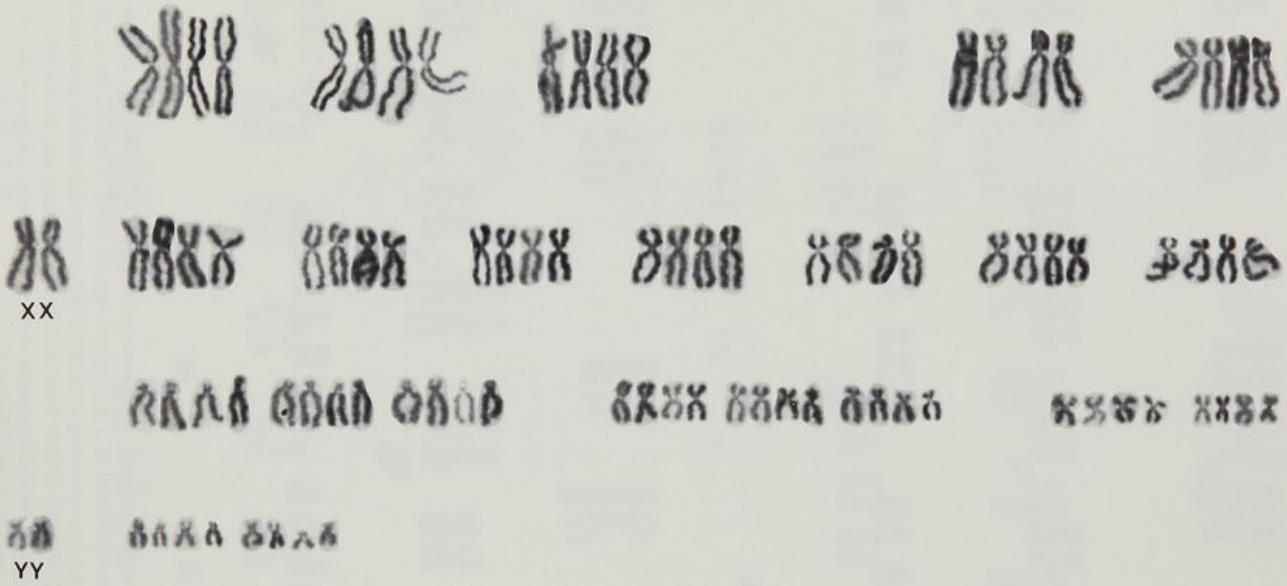


FIG. 9-3. 92,XXYY karyotype (F443) from an 11-week gestation spontaneously aborted conception. Empty intact sac. No fetus. (Reproduced by courtesy of Dr. R. Dhadial and Dr. A. M. Machin.)

abortions, consist almost entirely of 16-trisomic fetuses (eight out of nine in Carr's series (1967) and 17 out of 20 in A. Boué and Boué's 1968 series), compared with E-trisomic live births which almost entirely consist of trisomy-18. It is not possible to decide with certainty whether the additional D and G chromosomes found in 72 fetuses are identical to the chromosomes which cause trisomy among live births. Fetuses with extra A, B, C, and F chromosomes are less common and have not been found among live births. Other chromosome anomalies which have been found in 51 of the 322 fetuses (16%) included tetraploids (Fig. 9-3), and mixploids of various types.

III. Frequency of Chromosome Anomalies at Conception

If it is assumed that 15% of all conceptions which implant, terminate as abortions, then it is possible to estimate the frequency of chromosome abnormalities at conception (Table 9-3). This would indicate that the 1291 spontaneous abortions represent an estimated 8607 conceptions, of which 1.79% are autosomal trisomics, 0.75% X-monosomics, and 0.80% polyploids. No other sex chromosome abnormalities have been found; thus, their frequency is assumed to be the same as among live births. Alternatively, other sex chromosome aneuploids may be lethal much earlier in pregnancy and would therefore not be included. The estimated prenatal loss for these different groups ranges from 100% of the polyploids to 63% of the G-trisomics on the assumption that the fetal G-trisomics are identical to those which come to term as children with Down's syndrome. The highest prenatal loss occurs in the A-, B-, C-, and F-trisomics, none of which have so far been found at term. The loss of D- and E-trisomics is between 90 and 100%, although again the fetuses may not be trisomic for the same chromosome as the trisomic live births. The sparsity of trisomics for groups A, B, C, and F may result from a low frequency of mitotic or meiotic error within these groups of chromosomes or from a high degree of lethality predisposing very early fetal loss.

It is clear from the foregoing that prenatal selection is an extremely effective barrier against the introduction of any significant load of deleterious chromosome imbalance into the population. This selection continues in the postnatal period since the majority of chromosome anomalies are lethal early in the neonatal period or effective genetic lethals, in that affected subjects rarely breed. Down's syndrome and most sex chromosome anomalies fall into this category.

Assuming that the same chromosome is trisomic in abortions as in live births in groups D and G and in some E-trisomics, it is not clear

TABLE 9-3

Estimated Frequency of Chromosome Abnormalities among Conceptions Which Implant and an Estimate of Prenatal Loss

Chromosome anomalies	Autosomal trisomics					Sex chromosome anomalies		Triploids and tetraploids	Others	Total
	A,B,F	C	D	E	G	XO	Excluding XO			
Estimate in all conceptions which implant (A) (%)[a]	0.15	0.23	0.35	0.56	0.48	0.75	0.16 (?)	0.80	0.41	3.91
	Total trisomics 1.79									
In survivors at birth (%)	Nil	Nil	0.02	0.02	0.15[b]	0.02	0.16	? Nil	0.01	0.38
	Total trisomics 0.19									
Estimated prenatal loss of (A) as abortions (%)[a]	100		91	96	63	97	? Nil	100	97	88
	All trisomics 86.7									

[a] (A) is estimated from the data given in Tables 9-1 and 9-2 assuming that 15% of all conceptions which implant terminate as abortions.
[b] Down's syndrome.

why a small proportion of fetuses with identical chromosome anomalies survive to term while a greater proportion is lost prenatally. A number of explanations are possible. First, it is possible that different chromosomes are involved in fact. This undoubtedly applies to group E in which 16-trisomy is more frequently found in abortuses than either 17- or 18-trisomy. Second, it is possible that an interaction between the individual genetic background and the trisomic state may result in a variable phenotype. This may well be one reason for the variability exhibited by the three trisomic states in the postnatal period and could also account for the variable lethality. It is, however, even more difficult to account for the high lethality of the 45,X state. The majority of the 45,X fetuses studied have been shown to be chromatin negative; thus, loss of the active X in the fetuses and the inactive X or Y among the live births cannot be invoked to account for this differential lethality. Again perhaps some genomes can survive X-monosomy better than others, or perhaps these fetuses may be monosomic for a C− autosome which is likely to be highly lethal; if so, they should be 45,XX,C− and therefore chromatin positive. It is thus clear that while many of the facts are known very little is known of the causes; perhaps, however, the most likely explanation is the simplest, at least insofar as the autosomal trisomies are concerned, that different chromosomes are involved in fetal and live-born trisomics, or if not, that spontaneous abortion represents the extreme range of the phenotype in which the extra chromosome material leads to complete developmental blockage and hence death.

IV. Etiological and Other Factors in Spontaneous Abortion

Data on maternal age, parity, and abortion history in relation to karyotype have been analyzed on a number of occasions (Carr, 1965, 1967; Polani, 1966; Geneva Conference, 1966). There have also been several series analyzed in relation to these factors in which karyotype was not considered (Peckham, 1936; Javert, 1957; Stevenson and Warnock, 1959; Stevenson *et al.*, 1959; Stevenson, 1959; Shapiro *et al.*, 1962; James, 1963; Dekaban *et al.*, 1962). Only data on chromosomally studied abortuses will be analyzed in the present section.

A. *Maternal Age*

The available data on the maternal ages of 320 spontaneous abortions are summarized in Table 9-4. Two groups showed a significant

TABLE 9-4

Mean Maternal Age among Different Classes of Spontaneous Abortions[a]

Chromosome complement	No.	Mean maternal age
Chromosomes normal	219	27.9
Chromosomes abnormal	101	28.8
Trisomic	56	31.1
45,X	22	27.6
Polyploid	23	25.9

[a] Data from Carr (1965), Szulman (1965), Thiede and Metcalfe (1966), Kerr and Rashad (1966), and Machin and Dhadial (1969); Pediatric Research Unit series to September 1968.

departure from the control value for chromosomally normal abortuses. The trisomic group showed a slightly raised maternal age, while the mean maternal age at the birth of polyploids was considerably reduced. The trisomic data are analyzed in Table 9-5; the D- and G-trisomics showed a clear maternal age increase over those fetuses with normal chromosomes. However, the E-trisomics did not, and this might be because the majority of these were trisomic for chromosome No. 16. On the other hand, the increased maternal age for E-trisomic live births is not so great as either for the D- or the G-trisomics and this may simply be reflected among abortuses as well. The lowering of maternal age in the polyploid group is of interest since this group consists largely of triploids and this reduction might be related to the mechanism by which these arise. The most likely route is the suppression of the second polar body and fertilization of a diploid ovum by a haploid sperm (see Volume I, Fig. 7-21). It is not, however, clear why the second maturation division should be affected at a lower maternal age; but a suggestion has been made that delayed fertilization results in an increase in the frequency of chromosome abnormalities and particularly triploids among the resulting zygotes, and perhaps some relationship exists here.

B. *Other Factors*

Various other factors have been analyzed in relation to spontaneous abortion. These include length of pregnancy, previous obstetrical history, sex ratio, and fetal malformation. So far the only series of chromosomally analyzed and unselected spontaneous abortions sufficiently large to give some information on these topics is that of Carr (1965, 1967). Some additional data were also summarized by the Geneva Conference (1966).

TABLE 9-5

Maternal Age at Conception of 56 Trisomic Abortuses[a]

Chromosomes	No.	Maternal age
G+	15	33.1
D+	10	35.1
E+	18	26.4
Others[b]	13	31.0
Total	56	31.1

[a]Same data as Table 9-4.
[b]Includes double autosomal trisomics.

1. Length of Pregnancy

Carr (1965, 1967) found that the mean duration of pregnancy was significantly shorter for the 44 chromosomally abnormal fetuses when compared with the 144 specimens with normal chromosomes. Forty-six out of 50 of his specimens with abnormal chromosomes aborted between the beginning of the third and the end of the fourth month. Despite this he was unable to find a correlation between length of pregnancy and incidence of chromosome anomalies, owing to the shortage of fetuses of less than 56 days gestational age. Of the eight abortions in this age group, only one had a chromosome anomaly. Szulman (1965) found that 16 out of 25 (64%) early spontaneous abortions had a chromosome anomaly and of these 14 had a gestational age of 15 weeks or less. The data are highly suggestive and indicate that chromosomally abnormal specimens are likely to be eliminated earlier than the normal ones. Carr (1967) suggested that the incidence of chromosome abnormalities in the zygote is considerably higher than the 20% found in available spontaneous abortions. In other mammals there is probably a zygote loss of at least 30% which is twice the figure for spontaneous abortion in man, and there is little reason to suppose that man has a lower zygotic loss. If so, the stage of implantation provides one of the many barriers to the establishment of abnormal chromosome complements in the population. The next barrier is spontaneous abortion usually occurring between 6 and 15 weeks, which eliminates between 60 and 100% of chromosomally abnormal fetuses (see Table 9-3). During the first weeks of life many of the remaining chromosome abnormalities which survive to term are eliminated as neonatal deaths. The ultimate selection barrier occurs among those surviving to maturity, the majority of whom are sterile. This category includes the various sex chromosome anomalies with the

possible exception of the triplo-X and possibly XYY states; alternatively, if the survivors are not sterile they are often mentally defective and consequently less likely to breed. This group therefore comprises the genetic lethals. A few children with Down's syndrome survive to reproduce. These produce approximately 50% Down's syndrome progeny so that the selective pressures begin again. Some 47,XXX females breed but in general seem to have normal children. A possible meiotic mechanism exists here to eliminate the abnormal chromosome complements. Balanced heterozygotes survive and may breed; some of these may be habitual aborters, or have congenitally malformed children, or even show some degree of involuntary infertility (see Volume I, Chapter 8) so that again there may be selection against the spread of unbalanced chromosome complements. This may, however, be balanced by the production of an excess of heterozygotes in some of these families thus ensuring the survival of the rearranged but balanced chromosome complement.

2. Previous Obstetric History

Carr *et al.* (1966) and Carr (1967) have been unable to show any significant difference between the obstetric histories of mothers with chromosomally normal as compared to abnormal fetuses. The same comment applies to habitual aborters which Carr has defined as women having three or more abortions. Finally, chromosome defect appears to be no more common among women having several abortions than among women having only a single abortion.

The Geneva Conference (1966) analyzed some of these data and this analysis is given in Table 9-6. The number of previous pregnancies appears to be slightly higher among women having the trisomic or trip-

TABLE 9-6

Karyotype of Spontaneous Abortuses in Relation to Parity and Frequency of Previous Abortions[a]

	45,X	Trisomic	Triploid
Number of previous pregnancies	32	112	30
Number of previous abortions	3	28	8
Mean No. of previous pregnancies	1.8	2.9	2.0
Mean No. of live births	1.6	2.2	1.8
Frequency of previous abortions	0.09	0.25	0.27

[a] Data from report of Geneva Conference (1966).

loid fetuses than among those with a 45,X fetus. Women who have had a triploid or trisomic abortus appear to have a higher frequency of previous abortions (Table 9-6). The numbers are, however, extremely small, and it is doubtful whether a great deal of significance can be placed on these observations.

3. Sex Ratio

Data from 15 separate series are analyzed by trimester and karyotype in Table 9-7. There appeared to be an excess of female abortuses in most series. This applied equally to chromosomally normal and abnormal fetuses, although in neither was the difference significant from the usual one-to-one ratio. At birth the ratio varies geographically and invariably shows an excess of males to females. In North America the sex ratio was 106 males to 100 females. Stevenson (1966) summarized the sex chromatin findings in early abortions in eight studies comprising more than a hundred specimens each, the sex ratio male/female varied from 1.34 to 4.06. Other series have given similar results; for instance, Serr and Ismajovich (1963) found a sex ratio of 1.36. The only series which showed an excess of females to males is that of K. L. Moore and Hyrnuick (1960) who studied 276 abortions and found 145 females (chromatin positive) and 131 males (chromatin negative), a ratio of 0.9. A number of errors are likely in the analysis of sex chromatin data, including too high a figure for males since this category will include the chromatin-negative 45,X fetuses. A similar excess of chromatin-negative observations will result from sex chromatin studies of chorionic villi or the anatomical sexing of early abortions.

If the 45,X fetuses were to be included with the males in the series studied chromosomally (Table 9-7) then the sex ratio becomes 0.94 or very close to 1:1, and this should be remembered when the sex chromatin data are considered. Stevenson's summary (1966) gave an over-all sex ratio of 1733 chromatin-negative and only 754 chromatin-positive abortuses, which is undoubtedly too high an estimate of negative fetuses.

The most reliable data are, of course, the series in which full chromosome analyses have been undertaken and these showed a slight excess of 46,XX abortuses, which might account for the slight excess of males at term. However, until much more data are available on the primary sex ratio, this conclusion can only be tentative.

4. Clinical Data on Abortuses

It is well known that abortuses show a higher frequency of congenital malformations than live-born children. This has now been partly ex-

TABLE 9-7

Sex Ratio of Spontaneous Abortuses in Relation to Karyotype[a]

Trimester	Normal karyotype			Abnormal karyotype			XO	$\frac{(XO + \text{total XY})}{\text{total XX}} \times 100$
	XY	XX	Sex ratio	XY	XX	Sex ratio		
First	24	28	86	12	26	46	17	98
Second	16	11	146	3	1	–	2	175
Unspecified	131	155	85	8	10	80	5	87
Total	171	194	88	23	37	62	24	94

[a] Data from report of Geneva Conference (1966).

plained by the chromosome findings. The Geneva Conference (1966) summarized the clinical status of 788 chromosomally studied aborted fetuses (Table 9-8). The frequency of chromosomally abnormal abortuses was significantly higher when there was an abnormal embryo or blighted ovum than when the embryo was normal. Carr (1965) had shown that in his series of 200 spontaneous abortions, 50% of the specimens with intact sacs but without recognizable embryonic remnants (blighted ova) had a chromosome anomaly; in that series blighted ova accounted for 11.5% of the chromosomally normal fetuses but over 40% of those with an abnormality. Thiede and Salm (1964) selected their series for blighted ova and raised the frequency of chromosome anomalies to 65%. Szulman (1965) found recognizable embryonic remnants in 9 out of 15 chromosomally normal or 45,X fetuses, while in 11 trisomic or triploid fetuses only two had recognizable embryonic remnants and one was a hydatidiform mole.

TABLE 9-8

Type of Conception in Relation to Chromosome Abnormality

Type of specimen	Total No.	No. with abnormal karyotype	
		No.	Frequency
Abnormal embryo	10	8	0.80
Blighted ovum[a]	72	42	0.58
Normal fetus[b]	88	6	0.07
Unspecified	618	97	0.16
Total	788	153	0.19

[a] Included cases with intact empty sac and cases with an abnormal embryo.

[b] Usually examination relatively superficial.

Thus, it is clear that chromosome abnormalities contribute to a high frequency of congenitally malformed fetuses and in many cases to a complete failure of development of the fetus itself. Selection for blighted ova or malformed fetuses should therefore result in a very high frequency of chromosome anomaly.

The clinical features of 134 abortuses are summarized in Tables 9-9, 9-10, and 9-11. These 134 abortuses comprise the three major chromosome groups—trisomic, triploid, and 45,X—and examination of Table 9-12 shows that there are clear differences between these three groups. The highest frequency of embryos or fetuses are found in the 45,X group where 69.7% of the abortuses contain a recognizable fetus (Fig. 9-4). This compares with the trisomic group in which only 34.3% of the abortuses have a recognizable fetus (Fig. 9-5), and the majority are empty, intact, or ruptured gestational sacs. Hydatidiform or other types of moles are found only in the triploid group where they comprised 23.5% of the recovered abortuses (Fig. 9-6, 9-7). Where esti-

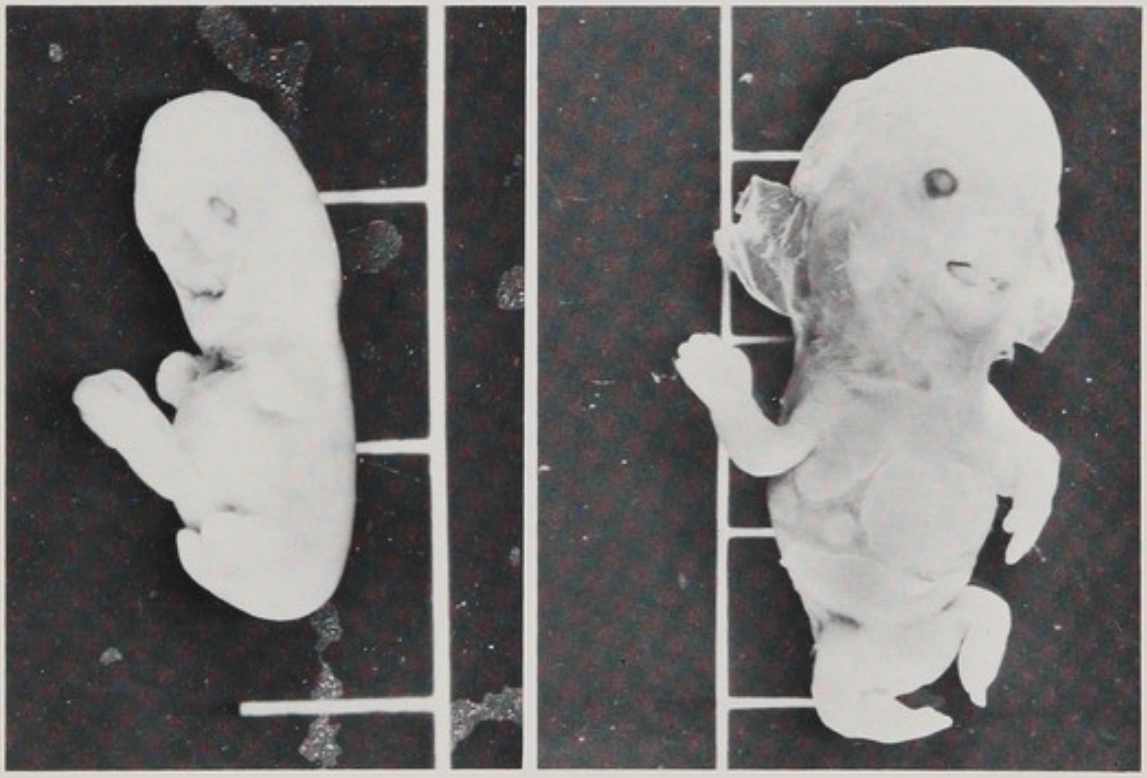


FIG. 9-4. 45,X abortuses. (a) F637. Small macerated embryo 18 mm CR length aborted at 7 weeks gestational age. (b) F880. Macerated fetus, 36 mm CR length, broad neck with cystic hygromas. Gestational age 14 weeks. (Reproduced by courtesy of Dr. R. Dhadial and Dr. A. M. Machin.)

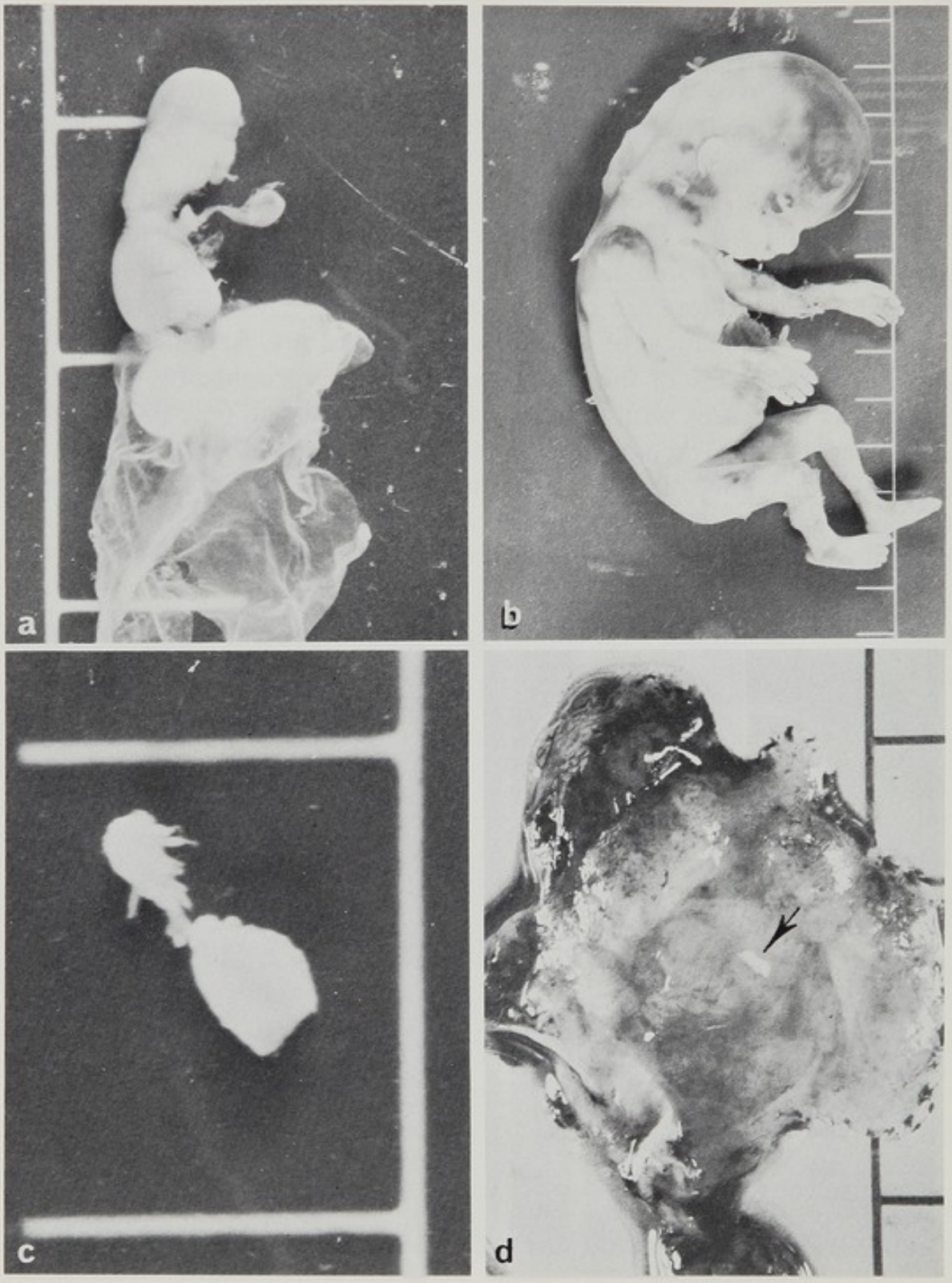


FIG. 9-5. Trisomic fetuses. (a) 47,XX,D+(F650). Small macerated embryo aborted at 10½ weeks gestation, approximately 10 mm CR length. (b) 47,XX,G+(F857). Macerated fetus aborted at 16 weeks gestation, 133 mm CR. (c) 47,XX,C+(F739). Small macerated embryo about 5-6 mm. Three to four weeks gestation. (d) 47,XY,E+(F893). 2-3 mm embryo in complete intact sac. (Reproduced by courtesy of Dr. R. Dhadial and Dr. A. M. Machin.)

TABLE 9-9

Morphology of Some Known Trisomic Abortuses

Chromosomes	Estimated age of fetus or embryo	Age from last menstrual period	Estimated age from ovulation	Brief description of specimen	Ref. No.[a]	Reference
Group A						
47,XY,A+	–	10 weeks	–	Empty intact chorionic sac	198	Kerr and Rashad; 1966
47,XX,A+	–	11 weeks	–	Empty intact chorionic sac	242	
47,XX,3+	–	64 days	–	Empty intact chorionic sac	44	Carr, 1965; Singh and Carr, 1967
Group B						
47,XX,B+	–	65 days	About 22 days	Empty intact sac containing nodular embryo, degenerating cellular mass ? nervous tissue.	24	Carr, 1965; Singh and Carr, 1967
47,XY,B+	–	8 weeks	–	Placenta and cord	115	J. G. Boué *et al.*, 1967
Group C						
47,XX,C+	–	10 weeks	–	Complete sac containing macerated embryo. 11 mm C.R. well preserved villi.	–	Szulman, 1965
47,XX,C+	–	72 days	–	One specimen an intact empty sac and the other a ruptured sac.	13	Carr, 1965; Singh and Carr, 1967
47,XY,C+	–	65 days	–		19	
47,XX,C+	> 28 days	–	–	Empty complete sac	209	J. G. Boué *et al.*, 1967
47,XX,C+	40 and 35 days	–	–	Twins. Complete sac with two embryos 15 mm C.R.	214	
47,XX,C+	28 days	–	–	Complete sac with 2 mm embryo	247	
47,XX,C+	–	–	–	Membranes only	329	
Group D						
47,XX,D+	40 days	58 days	44 days	Intact sac with 17 mm embryo of grossly normal appearance	3	Carr, 1965; Singh and Carr, 1967
47,XX,D+		70 days		See description for specimens 16, 29, and 39.	4	
47,XX,D+	*ca.* 31 days	85 days		Twin of triploid headless embryo 7 mm. Asynchrony in development of limb buds.	8	
47,XY,D+	–	86 days	–	Two ruptured sacs and one empty intact sac and one ruptured sac with a macerated fetus. See also No. 4.	16	Carr, 1965; Singh and Carr, 1967
47,XY,D+	–	85 days	–		29	
47,XX,D+	–	70 days	–		39	

TABLE 9-9 (cont'd.)

Chromosomes	Estimated ag of fetus or embryo	Age from last menstrual period	Estimated age from ovulation	Brief description of specimen	Ref. No.[a]	Reference
47,XX,D+	–	10 weeks	–	Ruptured sac–fragment	166	J. G. Boué *et al.*, 1967
47,XX,D+	–	10 weeks	–	Ruptured sac. Structureless embryonic nodule 4 mm	184	
47,XX,D+	–	11 weeks	–	Fragments ?	248	
47,XY,D+	40 days	14 weeks	–	Intact sac with embryo. Abnormal head, failure midline closures, anencephaly.	264	
47,XX,D+	45-47 days	*ca.* 7 weeks	–	Intact sac, embryo about 22 mm, abnormal face with harelip, five digits on each hand.	272	
47,XX,D+	–	9 weeks	–	Fragment of placenta	301	
47,XY,D+	25 days	9 weeks	–	Intact chorionic sac; 4 mm embryo	313	
47,XY,D+	7 weeks	10 weeks	–	Small macerated fetus	F206	Machin and Dhadial, 1969
Group E						
47,XX,16+	–	11 weeks	–	Curettage specimen, fragments of membranes, fibrosing villi.	–	Szulman, 1965
47,XY,16+	–	114 days	–	Empty intact sac or ruptured sac	12	Carr, 1965; Singh and Carr, 1967
47,XY,16+	–	70 days	–		17	
47,XX,16+	–	–	–		20	
47,XY,16+	–	69 days	–		28	
47,XY,16+	–	102 days	–		36	
47,XX,16+	–	65 days	–		43	
47,XY,16+	–	6 weeks	–	Membrane fragments	148	J. G. Boué *et al.*, 1967
47,XX,16+	–	9 weeks	–	Intact sac with nodular embryo	169	
47,XX,16+	–	12 weeks	–	Intact sac with nodular embryo about 2 mm	187	
47,XY,16+	–	8 weeks	–	Empty intact sac	231	
47,XX,16+	–	10 weeks	–	Empty intact sac with abnormal membranes	296	
47,XY,16+	–	10 weeks	–	Small fragments of membranes	304	
47,XX,16+	–	12 weeks	–	Fragments of placenta	319	
47,XY,E+	–	11 weeks	–	Ruptured sac, no embryo	79	Kerr and Rashad, 1966
47,XX,E+	–	9½ weeks	–	Intact sac, no embryo, villi with early fibrosis and local hydropic change.	–	Szulman, 1965
47,XX,E+	–	108 days	–	Ruptured or intact sacs	2	Carr, 1965; Singh and Carr, 1967
47,?XX or XY,E+	–	–	–		–	
47,?XX or XY,E+	–	–	–		–	
47,XY,E+	–	7-8 weeks	–	Intact sac with blood clot and disorganized tissue	F149	Machin and Dhadial, 1969
47,XX,E+	–	8-9 weeks	–	Intact fluid-filled sac. No fetus.	F166	
47,XY,E+	–	8-9 weeks	–	Placenta and fragments of membrane	F222	

Group F						
47,XX,F+	–	10 weeks	–	Intact sac without fetus	139	J. G. Boué and Boué, 1966
Group G						
47,XX,G+	–	9½ weeks	–	Curettage fragments of membrane. Fibrosis of some villi.	–	Szulman, 1965
47,XY,G+		13 weeks	–	Curettage fragments of amnion and chorion.	–	
47,XY,G+	–	9½ weeks	–	Intact sac with amnion and chorion. No embryo.	–	
47,XX,G+	–	89 days	–	Three intact sacs, two ruptured sacs. No. 6, 6 mm embryo. Small head and only first pharyngeal arch seen, heart and liver masses prominent and somites visible. Fore limbs retarded, hind limbs normal. Eye smaller than normal. [Carr, (1965) refers to five abortions in this group; Singh and Carr (1966) to six.]	6	Carr, 1965; Singh and Carr, 1967
47,XY,G+	–	71 days	–		18	
47,XX,G+	–	92 days	–		26	
47,XX,G+	–	90 days	–		33	
47,XX,G+	–	64 days	–		40	
47,XX,G+	35 days	12 weeks	–	Monozygotic twins 6.5(116) and 3 mm [116(2)]. Monoamniotic. Twins	116	J. G. Boué *et al.*, 1967.
47,XX,G+	35 days	12 weeks	–		116(2)	
47,XY,G+	<30 days	7 weeks	–	Intact sac with 2.5 mm embryo, of normal appearance.	138	
47,XY,G+	47 days	*ca.* 9 weeks	–	Ruptured sac with 30 mm embryo macerated	170	
47,XY,G+	45-47 days	6 weeks	–	Intact sac with 22 mm embryo	221	
47,XX,G+	40-45 days	13 weeks	–	Ruptured sac with embryo	267	
47,XX,G+	–	9 weeks	–	Small sac with inversion or invagination of membranes	268	
47,XX,G+	–	12 weeks	–	Fragments of membranes and cord	341	
47,XX,?G+	3-4 weeks	12 weeks	–	Intact sac with 2 mm embryo	F248	Machin and Dhadial, 1969
47,XY,G+	6 weeks	12 weeks	–	Intact sac with embryo	F168	

[a] This is the reference number in the original series.

TABLE 9-10

Morphology of Some Triploid and Tetraploid Abortuses

Chromosomes	Estimated age of fetus or embryo	Duration of pregnancy from LMP[a]	Estimated age from ovulation	Brief description of specimen	Ref. No.[b]	Reference
69,XXY	–	8 weeks	–	Pocket of decidual tissue edematous chorionic villi	51	J. G. Boué *et al.*, 1967
69,XXY	–	7 weeks	–	Pocket of decidual tissue with blood clot and chorion. Vesicular appearance.	59	
69,XYY	–	12 weeks	–	Chorion and amnion with 10 mm macerated fetus.	107	
69,XXY	–	23 weeks	–	Intact sac with 6 mm embryo with spina bifida.	120	
69,XXX	–	15 weeks	–	Partial hydatidiform mole	163	
69,XXY	35 days	23 weeks	–	Intact sac with 12 mm fetus, surrounding tissue resembles Breus mole.	174	
69,XXX	8 weeks	12 weeks	–	Macerated fetus	246	
69,XXX	8 weeks	? 9 weeks	–	Macerated fetus	311	
69,XXY	40 days	14 weeks	–	Ruptured sac. Large amniotic pocket with very small fetus	322	
69,XXY	–	14 weeks (C)	–	Curettage segments of amnion and chorion	–	Szulman, 1965
69,XXY	"Missed abortion." bleeding 15 weeks, evacuation 22 weeks.			Segments of amnion and chorion. Fragments of macerated fetus. Fibrosed avascular villi.	–	
69,XXY	Bleeding in pregnancy. Small uterus. 20 weeks evacuation.			Necrotic placenta. Segments of amnion.	–	
69,?	–	13½ weeks (C)	–	Ruptured sac, amnion and chorion, villi with poor vascularity and early fibrosis.	–	
69,XXY	–	20 weeks (E) after bleeding	–	Transitional hydatidiform mole. Fetal remnant macerated <20 mm.	–	
69,XXY	35 days	85 days	71 days	Twin to 8. Intact sac with 15 mm embryo. Grossly normal.	7	Carr, 1965; Singh and Carr, 1967
69,XXY	–	58 days	–	Intact empty sac	10	
69,XXY	25 days	87 days	73 days	Intact sac with 3 mm C R embryo, cylindrical	14	
69,XXY	–	87 days	–	Intact empty sac	25	
69,XXY	–	106 days	–	Stunted macerated fetus in intact sac	30	
69,XXX	–	103 days	–	Empty ruptured sac	32	
69,XXY	–	110 days	–	Intact sac with nodular embryo	34	
69,XXY	–	95 days	–	Empty ruptured sac	15	
69,XXX	40 days	56 days	42 days	Intact sac with 18 mm C R fetus. Large anterior encephalocoel.	37	

69,XXY	–	<12 weeks (C)	–	Abnormal swollen chorionic villi, small vesicles similar to hydatidiform moles. No fetus.	A B C	Makino *et al.*, 1964c
69,XXY		<12 weeks (C)	–			
69,XXY	–	<12 weeks (C)	–			
69,XXY	–	Bleeding 6 weeks D and C 4 months		Disorganized fetal tissues	–	Penrose and Delhanty, 1961
69,XXX	8 weeks	134 days		Amnion chorion with 19 mm fetus; amnion with arborizing polyps.	2	Schlegel *et al.*, 1966b
69,XYY	8 weeks	86 days (C)		Amnion chorion with 16 mm fetus; amnion with arborizing polyps.	–	
46,XY/69,XXY	–	44 days (C)		Amnion chorion. No fetus.	1	
92,XXXX	–	10 weeks		Intact sac, no fetus, intrachorionic hematomas.	275	Boué *et al.*, 1967
92,XXXX	–	97 days		Intact empty sac	11	Carr, 1965; Singh and Carr, 1967
92,XXYY	–	80 days		Intact empty sac with small tissue nodule	35	
92,XXXX	–	9 weeks		Placenta and membranes only	F233	Machin and Dhadial, 1969

[a] Here (C) stands for curettage and (E) for evacuation.
[b] Reference number in original series.

TABLE 9-11

Morphology of Some 45,X Abortuses

Chromosomes	Estimated age of fetus or embryo	Duration of pregnancy from LMP[a]	Estimated age from ovulation	Brief description of specimen	Ref. No.[b]	Reference
45,X	–	10 weeks (D and C)	–	Intact sac, 17 mm embryo macerated. Villi immature, some fibrosed.	–	
45,X	–	11½ weeks (B), (D and C)	–	Ruptured sac, fragment umbilical cord. Villi with moderate vascularity.	–	
45,X	–	11 weeks (B), (D and C)	–	Ruptured sac with macerated fetus. 27 mm C.R. Villi well vascularized.	–	Szulman, 1965
45,X	–	12 weeks (B), (D and C)	–	Intact sac with 5 mm cylindrical embryo. Villi poorly vascularized.	–	
45,X	–	12 weeks (B), (D and C)	–	Ruptured sac with 10 mm macerated fetus. Avascular and fibrosed villi.	–	
45,X	–	70 days	–	–	5	
45,X	–	82 days	–	–	9	
45,X	–	78 days	–	–	21	
45,X	–	94 days	–	Intact sac with 20 mm C.R. embryo. No gross abnormalities.	22	
45,X	–	152 days	–	75 mm C.R. fetus. Loose skin, thin umbilical cord. Cystic hygroma in nuchal region. Horseshoe kidney. Single umbilical artery.	23	
45,X	–	98 days	–	64 mm C.R. fetus. Normal externally. Horseshoe kidney. Unicornate uterus.	27	
45,X	–	159 days	–	134 mm C.R. fetus. Bilateral cystic hygromata. No other abnormalities.	31	Carr, 1965; Singh and Carr, 1966; Singh and Carr, 1967; Carr, 1969
45,X	–	101 days	–	Intact sac with 15 mm C.R. embryo. Abdominal wall missing, otherwise grossly normal.	38	
45,X	–	86 days	–	Intact sac with 17 mm C.R. embryo. No gross abnormalities.	41	
45,X	–	83 days	–	–	42	
45,X	–	80 days	–	Ruptured sac with 25 mm C.R. embryo. Damaged and macerated. No gross abnormalities.	1	
45,X	–	123 days	–	90 mm C.R. fetus. Cystic hygroma in nuchal region.	228	

45,X	–	15 weeks	–	Intact sac without embryo	40	J. G. Boué *et al.*, 1967
45,X	< 1 month	10 weeks	–	Intact sac with embryonic plaque	127	
45,X	40 days	13 weeks	–	Membranes and embryo with abnormal head	188	
45,X	< 1 month	9 weeks	–	Intact sac with embryo of 1.5 mm	240	
45,X	–	17 weeks	–	Ruptured sac, no embryo, hematomas under the chorion.	266	
45,X	–	11 weeks	–	Ruptured sac with macerated embryo, placenta with hematomas.	270	
45,X	47 days	12 weeks	–	25 mm embryo macerated	305	
45,X	35-40 days	23 weeks	–	Intact sac 13 mm embryo	339	
45,X	–	12 weeks		Placenta and membranes only	F126	Machin and Dhadial, 1969
45,X	8 weeks	9-10 weeks	–	Slightly macerated fetus	F140	
45,X	7-8 weeks	8-9 weeks	–	Intact sac with embryo	F170	
45,X	7 weeks	14 weeks	–	Macerated fetus	F231	
45,X	12-13 weeks	15 weeks	–	Macerated fetus with bilateral cystic hygroma, low-set ears and short sternum.	F253	
45,X	7 weeks	8-9 weeks	–	Intact sac with macerated fetus	F283	
45,X	–	8-9 weeks	–	Membranes and placenta only. No fetus.	F307	
45,X	–	11 weeks	–	Membrane, placenta and stump of umbilical cord only. No fetus.	F341	

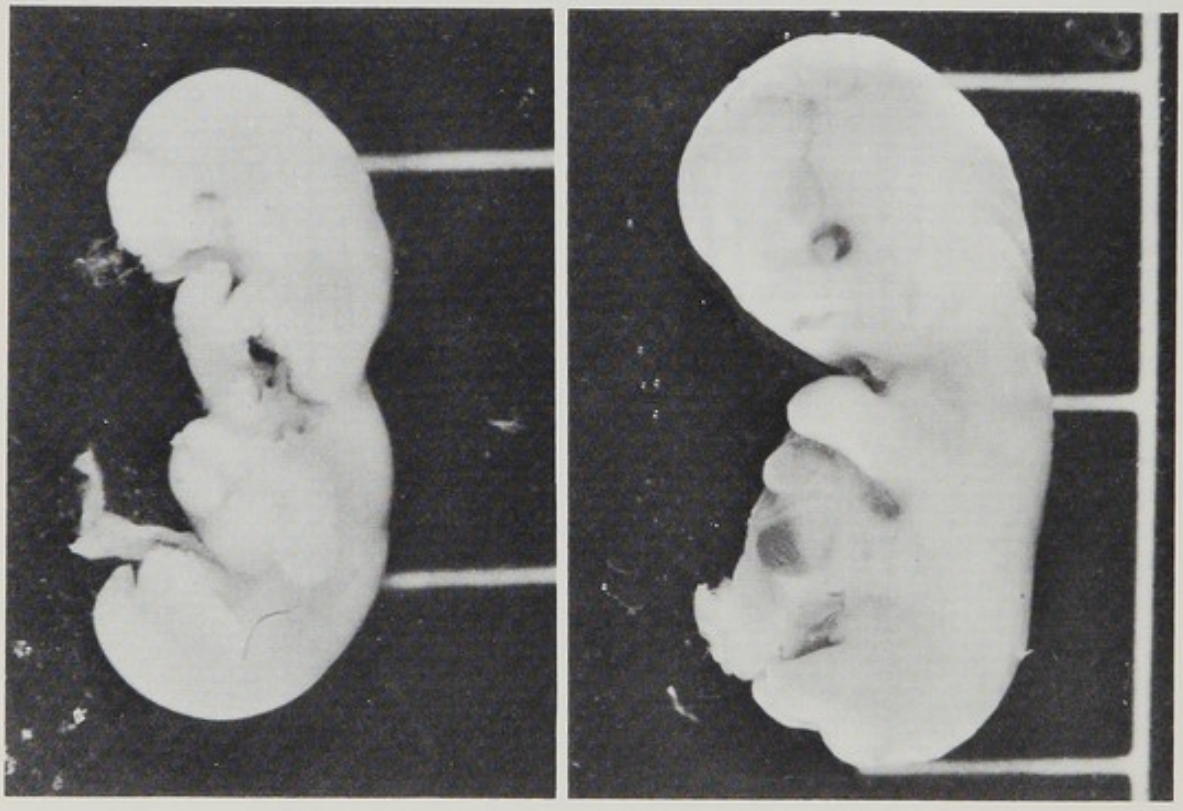
[a] Here (B) stands for Bleeding and (D and C) for dilatation and curettage.
[b] Reference number in original series.

TABLE 9-12

Type of Conception in Relation to the Chromosome Abnormality

Chromosome complement	Empty sac (intact or ruptured)	Embryo or fetus	Mole	Placenta and cord or remnants only	No data	Total
Trisomic	32 (47.8)[a]	23 (34.3)	–	12 (17.9)	–	67
45,X	3 9.1	23 69.7	–	3 9.1	4	33
Polyploid	7 (20.6)	15 (44.1)	8 (23.5)	4 (11.8)	–	34
Total	42 31.3	61 45.5	8 (5.9)	19 14.2	4	134

[a]Figures in parentheses are percentages.



a b

FIG. 9-6. Triploid embryos. (a) 69,XXX (F913). 12 mm CR embryo age about 5 weeks in complete sac. (b) 69,XXY (F802). 22 cm CR length fetus age about 8 weeks gestation. (L.M.P. 14 weeks). (Reproduced by courtesy of Dr. R. Dhadial and Dr. A. M. Machin.)

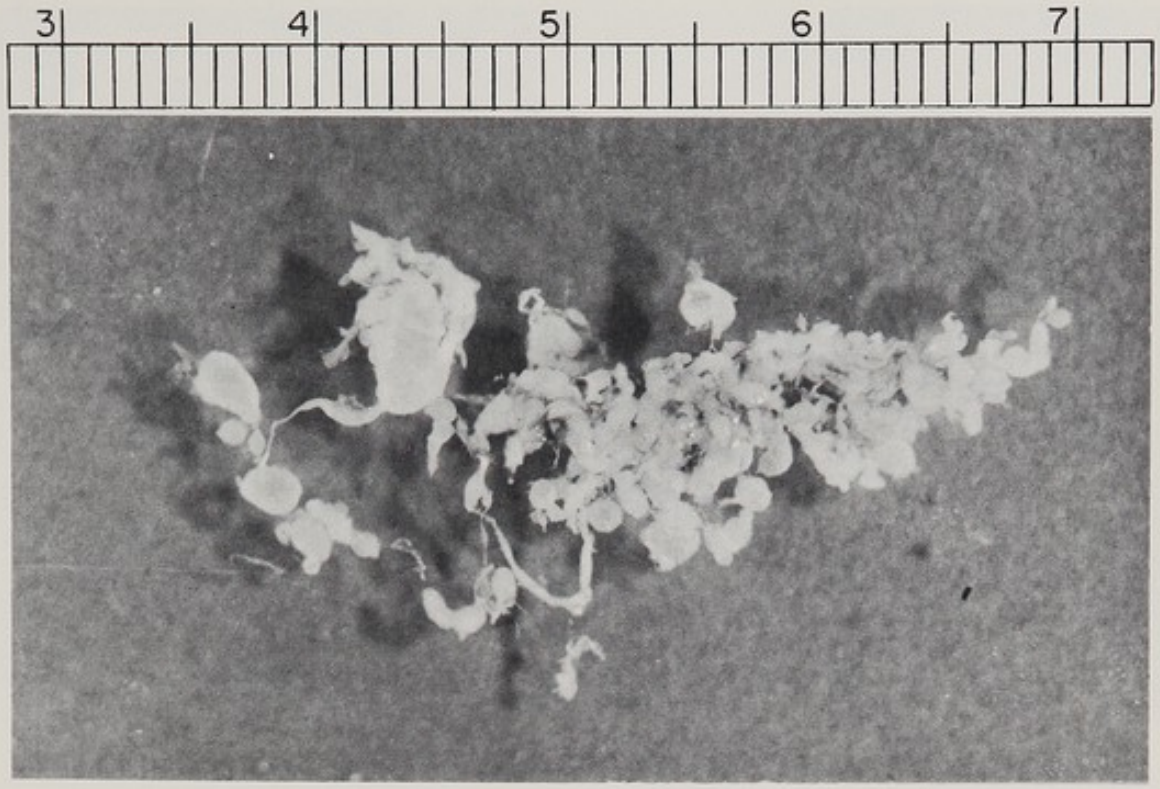


FIG. 9-7. Triploid hydatidiform degeneration of villi (69,XXY). (Reproduced by courtesy of Professor D. Carr.)

mates are available both for the duration of pregnancy from the last menstrual period as well as for the age of the fetus it becomes clear, especially in the trisomic and triploid groups, that death or a stoppage of fetal development occurs at a much earlier stage than the termination of the pregnancy. The most detailed anatomical study has been carried out by Singh and Carr (1966, 1967) on 51 abortuses with abnormal chromosomes. Thirteen of these were 45,X of which three were empty sacs while the remaining 10 contained a recognizable fetus; of these 10 fetuses four had no obvious abnormalities while the remaining six had a variety of anomalies including cystic hygromas, horseshoe kidneys, unicornate uterus, and single umbilical artery. In all of them the ovaries were grossly normal and contained germ cells (Fig. 9-8) and only after 12 weeks of gestation was any reduction seen in the number of germ cells as compared to 46,XX ovaries of the same age.

V. Summary and Conclusions

The frequency of chromosomally abnormal abortuses is about 20%, and it is thought that the frequency of chromosome anomaly in the zy-

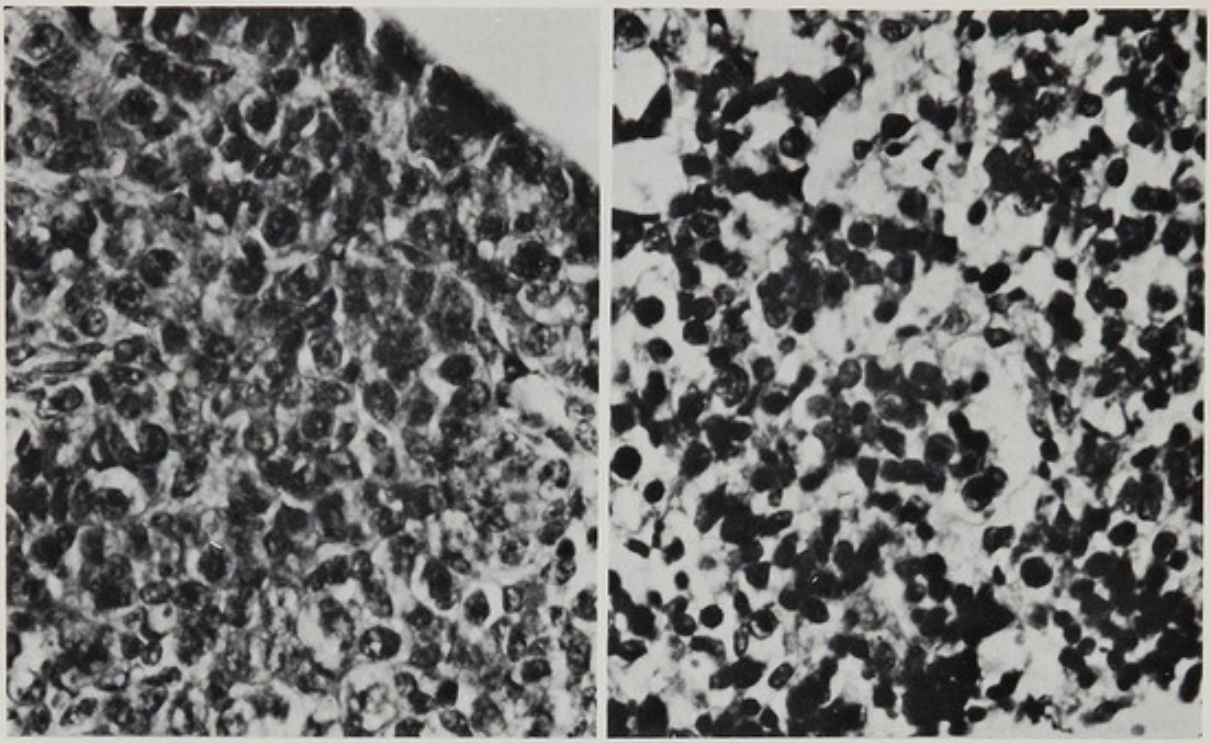


FIG. 9-8. Histological section from fetal ovaries (a) 46,XX fetus 61 mm CR. (b) 45,X fetus 64 mm CR, gestational age 98 days. (Reproduced by courtesy of Professor D. Carr.)

gote is much higher. The most frequent type of abnormality is trisomy, followed by triploidy. 45,X fetuses are the most common single type found. Spontaneous abortion is thus one selective mechanism for the elimination of between 60 and 100% chromosomally abnormal fetuses.

Chapter 10

CHROMOSOMES AND NEOPLASTIC DISEASE

I. Introduction

Chromosome abnormalities of various kinds are common in most types of neoplastic disease. The possibility that neoplasia might be caused by a chromosome abnormality was first suggested by Boveri (1902), and this question is still unanswered 68 years later. Direct evidence concerning the cause of a neoplastic transformation, which may have occurred in a single cell, is extremely difficult to obtain because by the time the tumor has reached a stage where clinical diagnosis is possible, the neoplastic cells have undergone numerous divisions and, in any one of these, a change in the chromosome constitution might have occurred. In the altered tumor environment a change in the karyotype may confer a selective advantage on the chromosomally distinct cell line. The development of a primary neoplasm can therefore be divided into two phases: first, the neoplastic transformation resulting in a cell capable of unlimited growth and possessing invasive properties; second, the progression of the tumor from a single cell to a multicellular tissue, the cells of which very frequently contain a chromosome abnormality. Makino (1957) first put forward the stem line theory of tumor progression in which the basic or stem line in a tumor is clonal in origin and contains a particular but constant chromosome abnormality. From this stem line, as a result of abnormal divisions, cells containing other chromosome complements arise. These may, if they have sufficient selective advantage, overgrow the original stem line and become the basic stem line of the

tumor. On this hypothesis the tumor is considered as a natural population of cells in which chromosome abnormalities interact with selective forces and may be eliminated or favored. An *in vitro* parallel is the transformation from a senile degenerating diploid cell strain with a finite life span to a heteroploid cell line with an infinite life span. A study of this process and in particular the loss of contact inhibition (Abercrombie and Heaysman, 1954; Abercrombie, 1962; Levine *et al.*, 1965) which prevents the overgrowth of diploid strains might throw considerable light onto neoplastic transformations which occur *in vivo*.

There is now considerable circumstantial evidence from studies both of human neoplasia and experimental neoplasia in animals that the primary change in a neoplastic transformation may be some form of chromosome mutation; for instance, many agents including oncogenic viruses also cause chromosome aberrations, and in man identical tumors with similar chromosome abnormalities are being found in different individuals. In the present chapter the data which are available on chromosome aberrations in human tumors will be discussed in relation to the hypothesis that the primary change in a neoplastic transformation is a chromosome mutation usually occurring in a single cell. This chromosome change leads to genetic imbalance in that cell allowing it to undergo indefinite cell division and to become invasive. During tumor progression this abnormal cell population becomes subject to selective pressures which in turn may select other and more successful chromosome variants.

II. Chromosome Abnormalities in Human Tumors

A. *Tumors of the Reticuloendothelial System*

1. Chronic Myeloid Leukemia

Nowell and Hungerford (1960) demonstrated a specific chromosome abnormality in chronic myeloid leukemia (CML), and this was rapidly confirmed (Baikie *et al.*, 1960; Tough *et al.*, 1961). The abnormality found in blood and marrow cells in the great majority of CML patients is a small chromosome replacing one of the G group chromosomes and resulting from a presumptive deletion of about one-half to two-thirds of the long arm (46,XX or XY,Gq−). This chromosome is also known as the Philadelphia or Ph^1 chromosome (Fig. 10-1). In tissues other than the hemopoietic system such as skin fibroblasts the chromosome com-

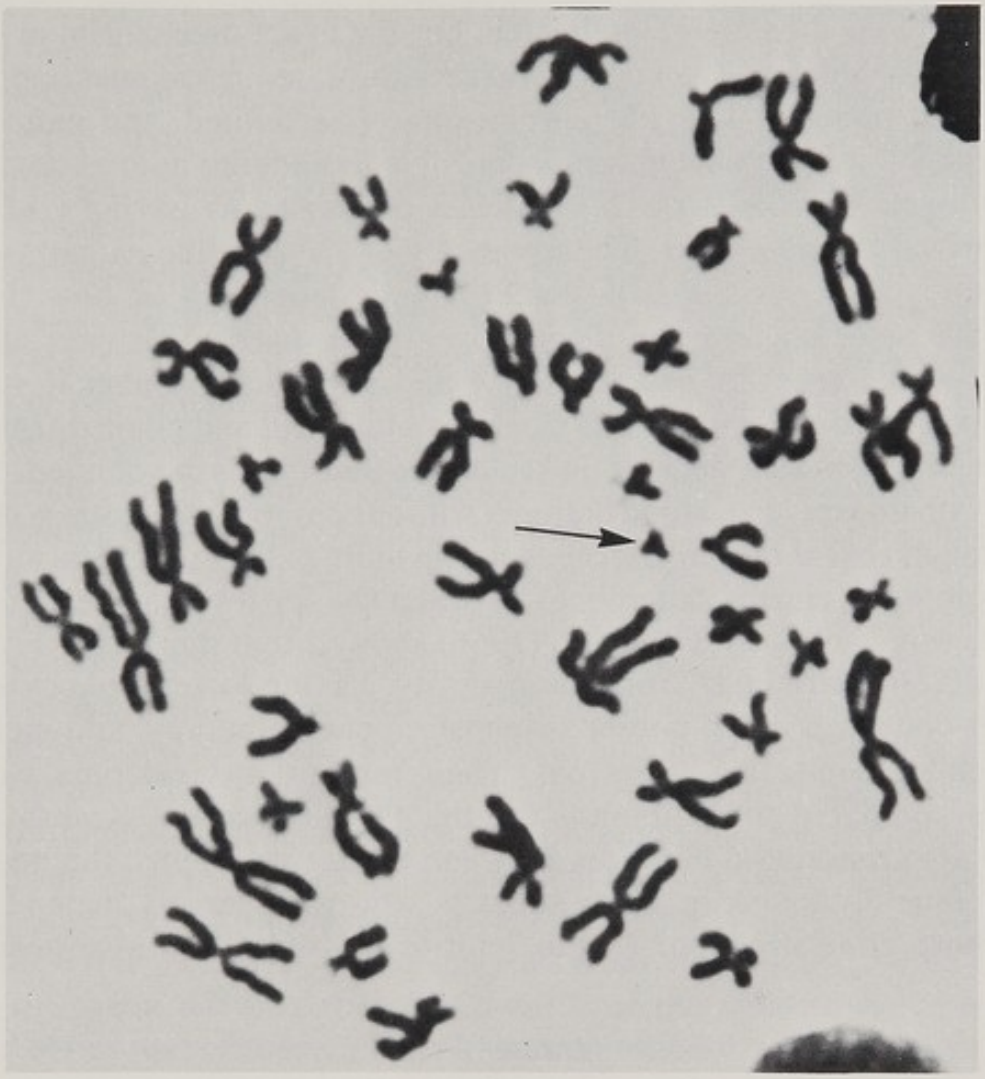


FIG. 10-1. Metaphase plate from bone marrow of a female patient with chronic myeloid leukemia. The Ph^1 (Gq–) chromosome is indicated by an arrow. (Reproduced by courtesy of Dr. S. Lawler.)

plement is invariably normal (Tough *et al.*, 1961). The evidence that this abnormal chromosome is No. 21 is by no means conclusive and consists of the following: (1) that 47,XX or XY,G+ Down's syndrome patients show a higher frequency of leukemia and (2) that the level of leukocyte alkaline phosphatase is raised in 21-trisomic Down's syndrome and lowered in CML. The fact that a variety of enzymatic levels have been shown to be raised in Down's syndrome (Chapter 5) including X-linked glucose-6-phosphate dehydrogenase reduces the weight of this evidence. It is therefore by no means clear whether the deleted chromosome is the same one which in the trisomic state causes Down's syndrome. Morphologically the chromosome resembles a G chromosome in which a greater

part of the long arm has been deleted, but the exact mechanism of origin cannot be stated nor is it known whether the same mechanism operates in different patients. The Ph^1 chromosome is satellited, and judging by its frequency it is a stable chromosome able to undergo mitosis normally. The cytogenetic results on 229 patients diagnosed as having CML are summarized in Table 10-1. The frequency of Ph^1-positive patients varies from series to series and is probably largely dependent on how the patients are selected and the diagnostic criteria used. The over-all frequency would seem to be about 84% and is probably higher if studies are restricted to patients with typical hematological and clinical features. Differences may also depend on technique and the tissue studied. Bone marrow or shorter term blood cultures without phytohemagglutinin stimulation might reveal the Ph^1 chromosome in more patients. Several authors have pointed to clinical differences between the Ph^1 +ve and −ve groups. An extensive study by Tjio *et al.* (1966) showed that the 13 Ph^1 −ve patients differed strikingly from the majority, having lower leukocyte and platelet counts, a much poorer response to chemotherapy, and included more children under 7 years old. Their median survival time was 18 months compared to 45 months for the Ph^1 +ve group. Krauss *et al.* (1964) also reported differences between these two groups, the negative group generally including older subjects who were largely male (11/12) and whose clinical picture was difficult to classify. They also generally

TABLE 10-1

Frequency of the Ph^1 Chromosome in Subjects with Chronic Myeloid Leukemia

References	No. of cases	Ph^1+	Ph^1−	Other	+ve (%)	Comment
Tough *et al.*, 1961	18	13	5	–	72.2	Five −ve subjects. Two have acute leukemic transformation; three benign.
De Nava *et al.*, 1966	39	36	3	–	92.3	
Tjio *et al.*, 1966	73	60	13	–	82.2	
Elves and Israels, 1967	11	11	–	–	100.0	
Speed and Lawler, 1964	26	22	4	–	84.6	
Krause *et al.*, 1964	28	16	12	–	57.1	Atypical features in −ve group
Pedersen, 1966a	29	29	–	–	100.0	
Kemp *et al.*, 1964	5	5	–	–	100.0	
Total	229	192	37		83.8	

showed a poorer response to therapy and had a shorter survival time. There is now little doubt that most, if not all, adequately diagnosed and studied cases of CML carry the Ph¹ chromosome, at least in the myelogenous precursor cells of the bone marrow; and it seems likely that the abnormal chromosome is closely related to the etiology and progression of the disease.

The finding of definite clinical differences between the Ph¹ positive and negative patients (Krauss *et al.*, 1964; Tjio *et al.*, 1966) suggests that these may be a different nosological category or perhaps different stages of the same disease. One patient in this series showed a wide variety of karyotypes, a finding more typical of the acute transformation than of chronic leukemia. The poorer prognosis and failure of response to chemotherapy, suggests that the Ph¹—ve cells are less sensitive to therapeutic treatment than the Ph¹+ve cells.

The failure to find the Ph¹ chromosome in any tissue except the hemopoietic elements; the finding of monozygotic twins, one of whom had Ph¹+ve CML while the other had normal chromosomes and no CML (Goh and Swisher, 1965); and the finding of the Ph¹ chromosome in early pre-CML states (Kemp *et al.*, 1964) all indicate that the Ph¹ chromosome results from a specific chromosome rearrangement in a myelogenous or even more primitive stem cell and that this change leads to the development of the disease. The finding of Whang *et al.* (1963) of 90-100% Ph¹+ve cells in the marrow from 13 patients, while smears from the same patients showed 25-60% of the cells to be of the erythroid series and of these 30-80% were in mitosis, suggests that the Ph¹ chromosome is present in the erythroid as well as the myeloid series. There is some evidence that it may also be found in dividing megakaryocytes. If so, the chromosome rearrangement must have occurred either in a primitive precursor of both the erythroid and the myeloid series or independently in several cells of the different series. The latter seems less likely.

The acute blast transformation in patients with CML is usually accompanied by considerable increase in karyotype instability. During the chronic phase serial studies of blood or bone marrow usually show a fairly constant karyotype (Tjio *et al.*, 1966) although aneuploid clones have been reported which often contain more than one Ph¹ chromosome. Treatment frequently reduces the proportion of Ph¹-positive cells. However, with the onset of the acute phase of the disease, aneuploidy with loss or gain of chromosomes unrelated to the Ph¹ becomes frequent (Kemp *et al.*, 1964; Lawler, 1967). Pedersen (1966a,b) has suggested that the progression of the disease from the chronic to the acute stage is dependent to a large degree on the development of aneuploid clones. He

also considered hyperdiploid Ph¹-positive cells to be selected at the expense of other cell types and that chemotherapy might increase the selection of these more resistant cells. De Grouchy *et al.* (1966d) have made a study of the karyotype evolution in eight cases of CML and have defined three models: (1) gain of supernumerary chromosomes, (2) loss of chromosomes, and (3) the presence of structural changes. A further model might be the acquisition of polyploidy and subsequent loss or gain of chromosomes within the basic polyploid cell line.

It seems probable that the finding of other chromosome abnormalities, either together with or without the Ph¹ chromosome in patients with CML, may be evidence for the beginning of blast transformation. Examples of this have been reported by Wahrman *et al.* (1962), Pedersen and Videbaek (1964), Houston *et al.* (1964a), Makino and Awa (1964), Goh *et al.* (1964), Sanchez Cascos and Barreiro (1964), and Erkman *et al.* (1966).

Several patients with typical CML have been found in which there are two Ph¹ chromosomes, and as far as can be determined this has no effect on the course or characteristics of the disease (Dougan and Woodliff, 1965). Chronic myeloid leukemia associated with lymphadenopathy as a result of infiltration of the lymph nodes with leukemic cells containing two Ph¹ chromosomes has been reported in three patients (Duvall *et al.*, 1967). A further variant with 45 chromosomes and one G chromosome missing and one Ph¹ chromosome [45,X?Y,?G−,(Gq−)+] is reported by Engel *et al.* (1965b), while two cases, one of CML in blast crisis and the other of acute myeloid leukemia, are reported by Kiossoglou *et al.* (1965a). The CML in blast crisis had two Ph¹ chromosomes but otherwise a normal karyotype. The patient with acute myeloid leukemia also had two Ph¹ chromosomes, but was missing a D and E chromosome, and had structurally abnormal Nos. 2, 5, and 18. Finally, Goh and Swisher (1964) compared 10 cases of CML with 10 cases of myeloid metaplasia and showed that the Ph¹ chromosome was specific to the patients with CML (see earlier in this section). It would seem most likely that the variant karyotypes observed in a few cases of CML represent progression of the disease to the acute phase and that in this phase the Ph¹ chromosome may be lost or retained along with other chromosome anomalies.

2. Other Myeloproliferative Disorders

Myeloproliferative disorders result from abnormal proliferation of one or more of the myeloid elements in the bone marrow and can be

subdivided into at least six entities: polycythemia vera (PV), CML, myeloid metaplasia (MM), thrombocytopenia (T), acute myeloid leukemia (AML), and Di Guglielmo's syndrome (erythemic myelosis; EM). Chronic myeloid leukemia has already been dealt with because it is one of the few malignant conditions to show a specific chromosome abnormality. Chromosome studies on the other five conditions will be discussed here.

a. POLYCYTHEMIA VERA. Nowell and Hungerford (1962) and Nowell (1965) studied the chromosomes of five patients with PV who had been treated with ^{32}P and found chromosomally abnormal cell lines in four, one of whom subsequently developed leukemia. Two of these patients had hypodiploid cell lines (45,XX or XY,C− or E− and 44,XX or XY,D−,G−) and one pseudodiploid with a deleted D chromosome. Kemp *et al.* (1962) found normal chromosomes in the marrow of seven out of nine patients with PV. One patient had a hyperdiploid line with 48 chromosomes and one, who subsequently developed CML, had a Ph^1 chromosome. In other patients a C group deletion and hyperdiploid cell lines have been observed (Solari *et al.*, 1962; Levan *et al.*, 1964). These patients had all been treated with either ^{32}P or ionizing radiation.

The most extensive survey is that of Kay *et al.* (1966) on the bone marrow chromosomes of 43 patients with PV (Table 10-2). Of 11 patients untreated at the time of study, seven showed some aneuploidy in the bone marrow, and in three of these all cells were found to be aneuploid. Among the treated patients nine had normal chromosomes, 12 showed some aneuploidy, and eight carried definite abnormal clones of cells characterized by specific marker chromosomes. Three patients who subsequently developed leukemia showed a variety of chromosome abnormalities. The high degree of aneuploidy found in the bone marrow of untreated patients is of some interest. In four such patients 55 hyperdip-

TABLE 10-2

Summary of the Chromosome Data on 43 Patients with Polycythemia Vera[a]

Treatment	No. of cases	All cells normal	No. of cases with Some aneuploid cells	No. of cases with All aneuploid cells	Abnormal clones detected	Leukemia variable chromosome abnormalities
Untreated	11	4	4	3	–	–
^{32}P	32	9	12	–	8	3

[a]Data from Kay *et al.*, (1966).

loid cells accounted for 43% of the cells examined and of these 55 cells, 54 had an additional C group chromosome and one an additional marker chromosome of unknown origin (Table 10-3). The possibility that the C group chromosome was an X is unlikely but is not excluded. In one untreated male (No. 8), all the bone marrow cells were 45,X while the blood was 46,XY. A further analysis of bone marrow cells 4 months after treatment showed a partial reversion to 46,XY cells. There are three possibilities which might account for this high level of aneuploidy: (1) aneuploidy predisposes development of PV (2) PV predisposes the development of aneuploidy, and (3) both arise independently from the same common cause. If the sex chromosomes are involved (1) above is unlikely since subjects with a constitutional sex chromosome abnormality have not been shown to have a predisposition to PV. This possibility remains tenable, however, if the additional C group chromosome is an autosome. On the other hand, if PV predisposes aneuploidy, then the low frequency of aneuploid cells among treated patients is surprising since the disease persists despite treatment, and under these circumstances aneuploid cells might be expected to increase in frequency. If, however, aneuploidy and PV are both caused by the same factor, which is considered most likely by Kay *et al.* (1966), then why has such a low frequency of aneuploidy been found in treated subjects (hypodiploid 6%, hyperdiploid 0.7%)? Kay *et al.* (1966) suggested that this may result from selection of patients; perhaps patients with an initial high

TABLE 10-3

Chromosome Analysis of Hyperdiploid Cells in Bone Marrow of Four Patients with Polyethemia Vera (Nos. 3, 9, 10, and 11)[a]

Number of cells			Analysis		
			47	48	49
Counted and analyzed (BM only)[b]	Total hyper-diploid	Proportion hyper-diploid			
127	55	0.433	46 (43) C+ (1) C+,F−,G+ (1) C+,D−,G+ (1) mar+,	7 (6) C+,C+ (1) C+,mar+	2 (1) C+,C+,E+ (1) C+,16−,16−,17+,F+,G+

[a]Data from Kay *et al.* (1966). Patient numbers in parentheses.
[b]Bone marrow.

frequency of aneuploids either die rapidly or are more easily cured, so that either way they are not seen at follow-up clinics. Aneuploid cells may be more radiosensitive so that there is a selective reversion to euploidy after treatment.

In the treated groups the most likely explanation for the sporadic changes was radiation damage, and the type of change seen (deletions, translocations, and occasionally fragments) was typical of radiation. The eight patients with specific clones of cells have all had fairly extensive long-term fractional treatments with ^{32}P. Four of these patients had a similar deletion in the F group (F?−) (Fig. 10-2). In two of the remaining four cases there was a Dq−, in one a Cq−, and in one a Gq−p+ marker chromosome. It seemed doubtful whether these changes were specifically connected with the disease and were likely the result of selection of specific radioresistant aneuploid clones. The F deletion may, however, be more specific, and a further three patients with PV who carried this deletion in a proportion of bone marrow cells have been reported (Millard *et al.*, 1968). F?− cells constituted 22-100% of the bone marrow cells but were only rarely seen in blood cultures. De Grouchy *et al.* (1966e) have found a similar chromosome defect in cases of idiopathic sideroblastic anemia, and because of this Millard *et al.* (1968) studied the excretion of tryptophan metabolites in five of their patients with PV. It was found to be abnormally high in four and reduced following pyridoxine loading (Table 10-4). This suggests a relative deficiency of pyridoxine and that possibly cells with F?− have a proliferative advantage under these conditions. It seems unlikely that the F− deletion causes PV because it is only found in a relatively few affected patients and also because it is often not present at the onset of the disease but arises during its progression.

In the three cases which developed acute leukemia the variety of chromosome changes were unlike those found in other patients, and the authors considered that there was no evidence for the direct clonal evolution of the leukemic cell lines from the chromosome complements found in PV. They considered that perhaps these resulted from the selection of radioresistant cell lines. This argument is not entirely convincing and a more likely explanation may be an increase in the general level of aneuploidy during the leukemic transformation and subsequent selection of those cells which are most suited for the new leukemic environment.

b. Myeloid Metaplasia. Several studies of patients affected with MM have failed to reveal any specific chromosome abnormality (Goh and Swisher, 1964; Better *et al.*, 1964). Among the 12 patients

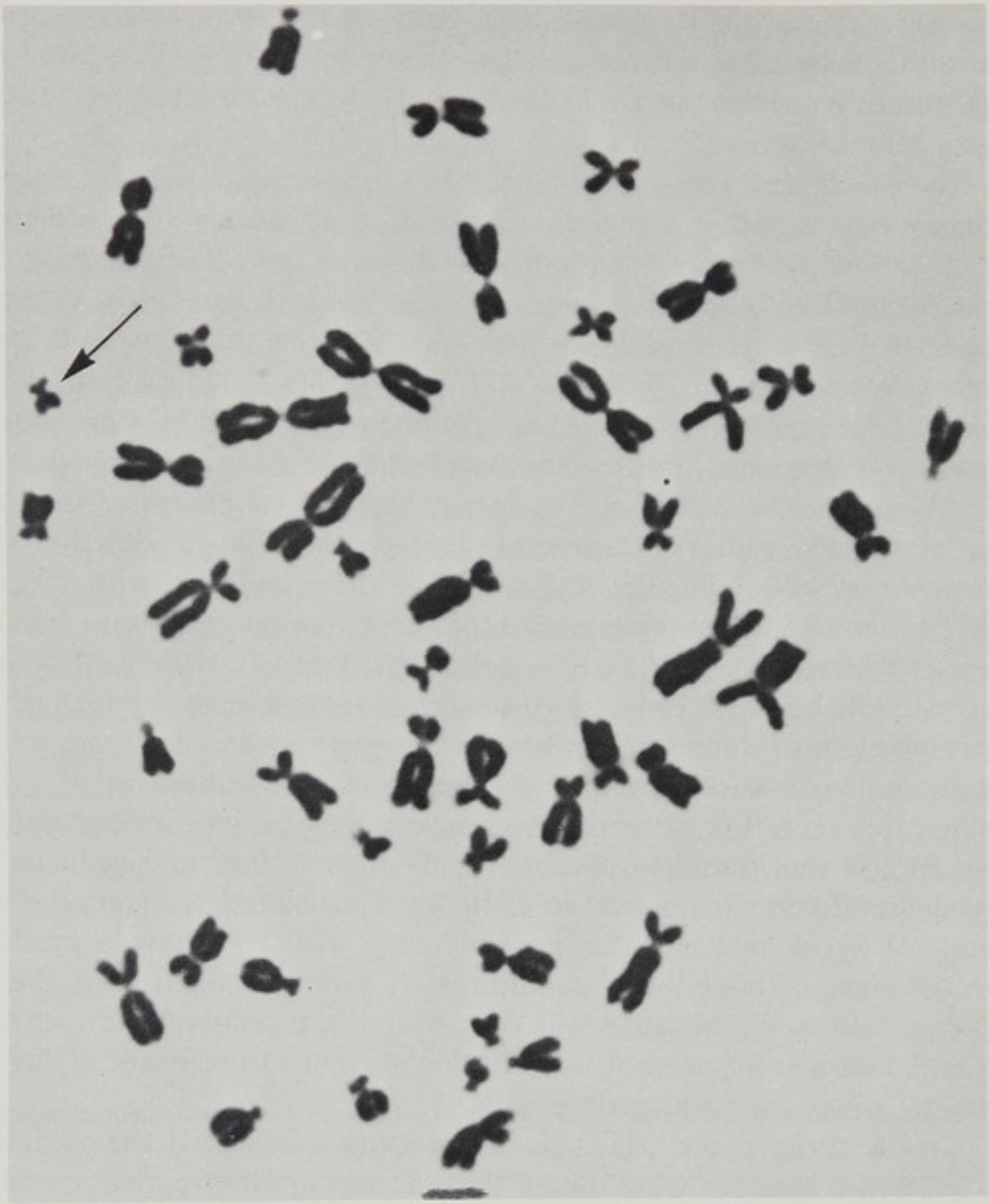


FIG. 10-2. Metaphase plate from bone marrow of a female patient with polycythemia vera showing the deleted F group chromosome (F?–). (Reproduced by courtesy of Dr. S. Lawler.)

studied using peripheral blood culture, one showed a high frequency of aneuploid cells with counts ranging from 36 to more than 47 chromosomes; 80% of the hypodiploid cells had counts of less than 40. In four other untreated patients two types of abnormality were observed, these were a dimorphism in the length of No. 3 and chromatid breakage in the C group; one cell had an additional C group chromosome. A single case reported by Sandberg *et al.* (1964a) initially had a 47,XX,C+ chromosome complement in the majority of marrow and blood cells; 3 months

TABLE 10-4

Excretion of Tryptophan Metabolites in Fdel Patients with PV Compared with Controls with and without Pyridoxine Treatment[a]

Metabolite	Mean excretion ± SD[b] (μM/8 hr) after 2 gm tryptophan load		P	Reduction in Fdel group receiving 100 mg pyridoxine for 7 days after 2 gm tryptophan load (%)
	Fdel group	PV (no Fdel)		
Number of patients	5	6		
Anthranilic acid	42 ± 20	15 ± 12	0.02	58.5 ± 2.5
3-Hydroxy anthranilic acid	26 ± 36	108 ± 118	>0.10	NS[b]
Kynurenine	315 ± 151	67 ± 15	<0.01	64 ± 16
3-Hydroxy kynurenine	160 ± 105	43 ± 17	0.02	84 ± 3.5
Kynurenic acid	128 ± 29	95 ± 61	>0.20	NS
Xanthurenic acid	40 ± 27	16 ± 13	>0.05	80 ± 18.5
Total	711 ± 247	344 ± 188	0.02	51 ± 15.5

[a]Data from Millard *et al.* (1968).

[b]SD = Standard Deviation; NS = Not Significant.

later, however, the marrow still had a 47,XX,C+ karyotype while the leukocytes were normal (46,XX). Twelve other cases studied by these authors had normal chromosomes (Sandberg *et al.*, 1962a). A case of agnogenic myeloid metaplasia had a 46,XY,Gq− chromosome complement, and it is possible that in this patient the disease was progressing toward CML. The interrelationships of the myeloproliferative disorders are imperfectly understood and the finding of a Ph^1 +ve case, which is apparently not CML, is of considerable interest.

c. Acute Myeloid Leukemia. The distinction between AML and the blast crisis in CML is not always clear so that the two situations can be discussed together. Chromosome findings are extremely variable and there is usually a high degree of numerical variation, often with evidence of clonal selection of a particular cell type (Ford and Clarke, 1963; De Grouchy *et al.*, 1965b, 1966d; De Grouchy, 1967). Patients with acute leukemia can be separated into three groups: patients with apparently normal chromosomes, patients with a specific chromosome abnormality, and patients in which there are a wide variety of chromosome abnormalities which do not apparently conform to a clonal pattern. Such changes include numerical aneuploidy and polyploidy, structural

rearrangements, and the finding of abnormal marker chromosomes of unknown origin (Sandberg *et al.*, 1962b; Baikie *et al.*, 1961b). Among other changes endoreduplication has been reported in acute leukemia, and this may be one mechanism for the origin of polyploids (Bottura and Ferrari, 1963; Reisman *et al.*, 1963; Houston *et al.*, 1964b).

There have been a number of reports of abnormalities in the G group in acute leukemia. Khan and Martin (1967) reported a case of AML with two cell lines (46,XX,C−G+/47,XX,G+) in direct preparations from bone marrow. Kiossoglou *et al.* (1965b) have reported G-trisomy in some hyperdiploid cells accompanied by other anomalies, and it is of course well known that patients with Down's syndrome have a predisposition to acute leukemia. Other patients with definite mixoploidy in bone marrow and AML have been reported (Ruffié and Lejeune, 1962; Ruffié *et al.*, 1964a,b). These all have 45,XX or XY,G−/46,XX or XY, or in one case three cell lines were present (45,XY,G−/46,XY,C+,G−/46, XY). In one patient some evidence of selective reduction in the proportion of aneuploid cells was observed after treatment, falling from 90% to nil over a period of 1 year.

Jensen (1967) studied 18 patients with AML and found specific chromosome abnormalities in six. These included a deleted number 3 (3?−). In two patients serial chromosome studies were made before and during treatment and various changes in the cell lines observed (Table 10-5). Other examples of hypo- and hypermodal cell lines in AML include a 45,XY,C−,D+,G− and a 47,XX,C+ (Forteza *et al.*, 1963b; A. W. Weinstein and Weinstein, 1963). In two patients reported by Awa *et al.* (1965) the G group was abnormal; in the first a 45,XY,G−,G−,D+ cell line was found in bone marrow before treatment, which was replaced after treatment by 46,XY pseudodiploid cells with various karyotypes. In the second patient a pseudodiploid cell line was found (46,XY,G−mar+*). The marker chromosome (mar*) was submetacentric and resembled a satellited F group chromosome. In both these patients it seems reasonable to suggest that the abnormal chromosome (?D+ and ?Fsat+) was derived from a structural rearrangement in the G group. The finding of a hypodiploid mode seems to be not uncommon in AML, and Erkman *et al.* (1967) reported a case with a modal number in bone marrow of 43 with chromosome counts ranging from 38 to 175 and with secondary modes at 46 and 86 chromosomes. The constitution of the modal cell line was 43,X?Y,2p+,B−,?Cq+p−,?D+,17−,F−,G−, min+. The 46 cell line was normal with the exception that it carried the abnormal C group chromosome (46,XY,?Cq+p−). A patient with a modal chromosome number of 41 was reported by Jensen (1967).

TABLE 10-5

The Effect of Treatment on the Chromosome Findings in Bone Marrow in Two Patients with AML[a]

Date	Chromosome complement	Treatment and dates
	Case No. 11	
June 1965	45,XX,C−,D+,G−	None
September 1965	45,XX,C−,D+,G−/<u>46,XX</u>[b]	6-Mercaptopurine June 4-22, 1965
January 1966	46,XX,D+,G−/<u>46,XX</u>[b]	Amethopterin Sept. 15, 1965-Mar. 3, 1966
March 1966	46,XX,D+,G−	Prednisone Mar. 30-Apr. 16, 1966
April 1966	46,XX,D+,G−	
	Case No. 13	
October 1965	<u>46,XY</u>/47,XY,C+[b]	None
November 1965	45,XY,E−/<u>46,XY</u>/47,XY,C+[b]	Prednisone Oct. 2-Nov. 11, 1965. 6-Mercaptopurine Oct. 9-Nov. 11, 1965.

[a] Data from Jensen (1967).
[b] <u> </u> indicates modal cell line.

These data show that there is a wide range of karyotype variability in subjects with AML and indicate how little consistent variation has been observed. An increasing proportion of cases seem to have abnormalities in the C group and G group, but much more carefully analyzed data are required. The increased frequency of leukemia in patients with Down's syndrome has already been discussed (Chapter 5), and the chromosome findings in relation to the leukemia will be discussed below.

d. THROMBOCYTHEMIA. Rowley and Blaisdell (1966) reported a single untreated case with two cell lines (46,XX/48,XX,C+,C+) in the bone marrow; after treatment the abnormal 48,XX,C+,C+ line disappeared. Thrombocythemia is one of a group of "preleukemic" conditions which have a high chance of terminating in leukemia, and the finding of an abnormal cell line indicates an unstable karyotype. This, perhaps, provides further evidence of the causative nature of chromosome abnormalities in leukemia.

e. ERYTHEMIC MYELOSIS (EM) (DI GUGLIELMO'S SYNDROME). Di Grado *et al.* (1964) reported a patient with erythroleukemia whose

bone marrow showed a wide range of chromosome counts with a modal number of 45 and submodes at 44 and 46. Variable chromosome loss was observed together with trisomy of chromosomes 3 or 4 in some cells. In 90% of the cells a large ring chromosome was seen. Weatherall and Walker (1965) reported chromosome studies on a patient with a constitutional hypoplastic anemia during the transitional phase to acute erythroleukemia. Chromosome analyses were mainly carried out on blood cultures but were confirmed by a single marrow sample. During the anemic stage the modal number of chromosomes was 46 with a normal karyotype (46,XX). These cells were, however, characterized by a high frequency of chromatid breakage, secondary constrictions and gaps, and there was also a high frequency of polyploidy in the bone marrow. After the transformation to erythroleukemia a secondary cell line appeared which produced fetal hemoglobin and had an additional C chromosome (47,XX,C+). Chromosome aberrations of various types have also been reported in other types of anemia. Kiossoglou *et al.* (1965c) have reported a variety of chromosome changes including chromatid breaks, gaps, fragments, and the presence of giant chromosomes in bone marrow cells from three subjects with pernicious anemia (PA). A proportion of the cells had only 45 chromosomes and lacked a member of the G group. Out of a further series of 12 patients with PA reported by these authors chromosome abnormalities were found in six, five of which had hypodiploid cell lines lacking a G group chromosome. The remaining six patients had normal chromosomes. Hypodiploidy, chromosome breakage, and rearrangement have also been reported in Cooley's anemia (Bosi *et al.*, 1962) Fanconi's anemia (Schmid *et al.*, 1965; Schmid, 1967; Swift and Hirschhorn, 1966; Schroeder, 1966a,b), and in Bloom's syndrome (German *et al.*, 1965; Sawitsky *et al.*, 1966).

f. Other Forms of Myeloproliferative Disease. C-Trisomy is reported in a single case of an atypical myeloproliferative syndrome and myeloid immaturity (Winkelstein *et al.*, 1966). A variety of chromosome abnormalities have been reported in multiple myeloma and Waldenstrom's macroglobulinemia. These include cells with abnormal chromosome numbers rising in some cases into the polyploid range as well as abnormal marker chromosomes (Castoldi *et al.*, 1963; F. J. W. Lewis *et al.*, 1963d; Bottura *et al.*, 1961; German *et al.*, 1961). One of the most striking observations has been the finding of a large abnormal marker chromosome in several unrelated cases of Waldenstrom's macroglobulinemia (Bottura *et al.*, 1961; German *et al.*, 1961; Benirschke *et al.*, 1962c; Pfeiffer *et al.*, 1962b; Elves and Israëls, 1963; Heni and Siebner, 1964; Moretti *et al.*, 1965). This chromosome ranges in the size of group A or larger and may be metacentric or submetacentric.

3. Lymphocytic Leukemia

Gunz *et al.* (1962) found an abnormal G group chromosome (Fig. 10-3) segregating in a family in which two members were affected with chronic lymphocytic leukemia (CLL); several other members also carried the abnormal chromosome but were otherwise unaffected. They suggested that this chromosome predisposed to the development of CLL. This, however, has never been confirmed and it seems likely that the abnormal chromosome, which was termed the *Christchurch chromosome* (Ch^1) and appeared telocentric (Gp−), was a normal variant of the karyotype with little clinical significance (Volume I, Chapter 4). Fitzgerald and Gunz (1964) have reported four additional families in which two sibs had died from CLL or some other form of leukemia; the Gp− chromosome was not observed in any of these. A further 28 cases of CLL have been studied and relatively few chromosome abnormalities have been found. It seems likely that chromosome abnormalities are not common in this condition (Fitzgerald and Adams, 1965). However, marker chromosomes have been found by other authors; for instance, De Grouchy and Lamy (1962) found two cell lines (46,XY/46,XY,Cq−) in a child with CLL, the abnormal (Cq−) chromosome being found in about 12% of mitoses in blood culture. The apparent rarity of chromosome abnormalities in CLL may, at least in part, result from technical problems related to the use of peripheral blood culture. Several authors have reported that leukemic lymphocytes respond poorly to PHA stimu-



Fig. 10-3. Abnormal G group chromosome (arrow) found in a family in which several heterozygotes had chronic lymphocytic leukemia (Gp−Ch^1 chromosome).

lation (Bernard *et al.*, 1964; Winter *et al.*, 1964; Ruffié *et al.*, 1966b; Goh, 1967). Goh (1967) cultured peripheral blood from 6 CLL patients for 4, 5, and 6 days and obtained a higher percentage of pseudodiploid cells compared with controls after the longer period of culture; the modal number was 46, and between 20 and 80% of the cells were pseudodiploid compared with frequencies of between 0 and 6.7% in thirteen 5- and 6-day control blood cultures. He also showed that the peak mitotic index in the leukemic cultures was reached after 5-6 days compared with a 3-day peak for the controls. These observations suggest that the lower response to PHA by leukemic lymphocytes in standard 3-day cultures may result from a slowing down of the processes of DNA and RNA synthesis. The pseudodiploidy seen in CLL by Goh (1967) included abnormalities in the A, B, D, and E groups as well as a small metacentric marker chromosome which could have resulted from a structural rearrangement. It seems clear from these observations that aneuploidy is far less frequent than pseudodiploidy in both CLL and CML. The low frequency of abnormalities found in 3-day blood cultures from CLL patients seems to result from lack of response by the leukemic lymphocytes to PHA at this time and a dilution of the leukemic lymphocytes by the normal lymphocytes which have responded. No specific chromosome abnormality has yet been found in CLL to compare with the Ph^1 chromosome found in CML. Jensen (1967) looked at the bone marrow chromosomes from six patients with acute lymphocytic leukemia (ALL) and found a lower frequency of aneuploidy than in AML. Only one patient had a distinct cell line and this became evident after 15 months of treatment. Two marrow biopsies taken during the first 3 months showed only diploid cells; after 12 months two cell lines were found (46,XY/47,XY,D+), and at this stage the bone marrow was dominated by lymphoblasts. The normal findings in the other five patients and in the early cultures of this patient may have resulted from dividing myeloblasts and erythroblasts dominating the marrow.

4. Lymphosarcomas and Lymphomas

Several studies are available on solid tumors of the reticuloendothelial system, and these are of considerable interest because at least one of these—Burkitt's lymphoma—is thought to be virus induced. Spiers and Baikie (1966) have studied lymph node cells from 10 patients with malignant lymphomas and found hyperdiploid and polyploid cell lines in eight. Three cases of Hodgkin's disease had a diploid modal cell line (Table 10-6); hyperdiploid cells had additional C and G group chromosomes and in two cases an abnormal chromosome was present in the

TABLE 10-6

Chromosome Analysis of Tumor Cells in 10 Patients with Malignant Lymphoma[a]

Case	Type of Tumor	Chromosome analysis
1	Follicular lymphoma	48,XY,C+,G+
2	Follicular lymphoma type 2-3	47,XY,(Ep−)+
3	Follicular lymphoma type 4	Chromosome No. 83-98,XX. Mode $2n = 89$.
4	Reticulum cell sarcoma	Chromosome No. 89-96,XY. Several modes.
5	Reticulum cell sarcoma	Chromosome No. 89-96,XY. Several modes.
6	Reticulum cell sarcoma	Diploid or hypodiploid. Mitotic index low.
7	Lymphosarcoma	46,XX/47,XX,fra*+[b]
8	Hodgkin's granuloma	46,XY/47,XX,G+ 3%,49,G−
9	Hodgkin's granuloma	46,XY (57%); 25% analyzable cells normal, half with (17 or 18p−)+.
10	Hodgkin's granuloma	46,XY (63%). Most with normal karyotype, 5% with 17 or 18p−, 11% hypo- or hyper-triploid.

[a] After Spiers and Baikie (1966).
[b] ═══ indicates modal cell line.

17-18 group (Ep−). Millard and Sief (1967) found six out of 29 cases of malignant lymphomas of different histological types to have a similar 18q− chromosome in the majority of cells studied. One of their patients also had an 18p− chromosome similar to that reported by Spiers and Baikie (1966). Other examples of involvement of the E group in lymphoma cells include a 17 or 18i, 17-18-trisomy and 17-18-monosomy (Ricci *et al.*, 1962; Sandberg *et al.*, 1964b; Sasaki *et al.*, 1965). In these patients several other less specific abnormalities were also reported. Lawler *et al.* (1967) have studied the circulating lymphocytes in 20 patients with Hodgkin's disease. They found a variety of chromosome abnormalities, the majority of which could be attributed to treatment, and were unable to detect a circulating lymphocyte population with a specific chromosome anomaly.

Several studies have been made on the Sternberg-Reed cells in Hodgkin's disease (Spriggs and Boddington, 1962; Ricci *et al.*, 1962; Galan *et al.*, 1963); polyploidy, aneuploidy, and, in some cases, specific marker chromosomes have been found. Several chromosome studies on blood, skin, bone marrow, and lymph node aspirates from a woman with a malignant lymphoma have shown a predominantly normal diploid karyotype (46,XX) in blood and skin and a pseudodiploid karyotype in marrow and lymph node aspirate (46,XX,C−,D−,mar+*,mar+*). One marker chromosome was mediocentric and about the size of No. 3,

while the other was acrocentric and slightly larger than the G group. The two abnormal chromosomes could have arisen by translocation from the missing C and D group chromosomes.

Burkitt's lymphoma is of particular interest because of its regional distribution (Burkitt, 1962a; Haddow, 1963) and possible viral etiology (Burkitt, 1962b; Jacobs *et al.*, 1963). It is confined to regions of Africa with a rainfall greater than 20 in. per annum and a mean temperature above 60°F. These areas correspond to the distribution of the "wet tropics group" of mosquitoes, and all the tribes and races within these regions appear to be susceptible. Jacobs *et al.* (1963) studied the chromosomes from the blood, bone marrow, and tumors of 19 East African patients of whom 15 were untreated at the time of examination. Satisfactory tumor preparations were obtained from 12 subjects, four of whom showed no chromosome abnormality while eight had abnormal chromosomes (Table 10-7). In most patients the modal chromosome number was 46, and five out of the eight subjects with abnormal chromosomes carried a morphologically similar, if not identical, marker chromosome (Fig. 10-4). This was a long acrocentric chromosome similar in size to the long arms of No. 2. Two patients had abnormal chromosome numbers, one with 47 and the other with 49 chromosomes. Of these eight patients, five were untreated and three treated with Cyclophosphamide. Rabson *et al.* (1966) reported a similar pseudodiploid karyotype from a Nigerian child. This was in cultured material and chromosome counts ranged from 40 to 77 with a mode at 46. The analysis of the modal cells showed 46,XY,2−,mar+*,mar+* chromosome complement, the two marker chromosomes being very similar to those seen by Jacobs *et al.* (1963), one was a long acrocentric resembling in size the long arm of No. 2 and the other a submetacentric resembling a B group chromosome. E. W. Chu *et al.* (1966) reported direct chromosome studies on the ascitic fluid from a poorly differentiated lymphocytic lymphoma involving both ovaries in an American Caucasian female. This tumor had similar features to Burkitt's lymphoma as seen among Africans. Two cell lines were found −46,XX,1−,mar+****/47,XX,1−,D+,mar+**** (mar**** metacentric chromosome larger than any normal human chromosome).

Burkitt's lymphoma is characterized by indefinite growth in *in vitro* suspension cultures and the maintenance of a similar pseudodiploid karyotype (Epstein and Barr, 1964; Epstein *et al.*, 1964a; Kohn *et al.*, 1967; Miles and O'Neill, 1967; Hughes, 1968). Replicating virus-like particles similar to herpes virus have also been found in some of the cultured lymphoblasts (Epstein *et al.*, 1964a,b; S. E. Stewart *et al.*, 1965).

TABLE 10-7

Chromosome Findings in 19 African Patients with Burkitt's Lymphoma[a]

Case No.	Sex	Age (years)	Treatment[b]	Modal chromosome No.	Chromosome analysis[c]	
1	M	4	U	46	46,XY	
2	M	6	Cycl	46	46,XY,C+,G–	Six cells. Large acrocentric marker, replacing a C group chromosome.
3	M	51	U	No results	–	
4	M	49	U	No results	–	
5	F	5	Cycl	46,48,50	3 cell lines	46,XX,2–,C–,mar*+,mar**+ 48,XX,2–,mar*+,mar**+,mar***+ 50,XX,2–,B+,16+,mar*+,mar**+,mar***+
6	F	4	Cycl	45,46	2 cell lines	45,XX,G– plus various other anomalies 46,XX
7	F	5	U	47	47,XX,C+	
8	F	4	U	46	46,XX	
9	M	6	U	46	46,XY	
10	M	7	U	46	46,XX (2 cells)	46,XX,D–,mar*+ 46,XX,3–,mar****+
11	M	6	U	Results unsatisfactory	? 2 cell lines	46,48. ?48,XY,2–,mar*+,mar*****+
12	M	4	U	46	46,XY	
13	F	8	U	46,47	47,XX,2–,mar*+,mar******+	
14	M	6	U	No results	–	
15	M	18	U	46	46,XY,1–,2–,mar*+,mar****+	
16	M	6	U	49	49,XY? mar****+	
17	M	13	U	No results	–	
18	M	19	Mu hyd	No results	–	
19	M	5	U	No results	–	

[a] After Jacobs *et al.*, 1963.

[b] Here U stands for untreated, Cycl for cyclophosphamide, and Mu hyd for Mustine Hydrochloride.

[c] *Large acrocentric size long arm No. 2; **submetacentric size Nos. 4-5; ***small metacentric size Nos. 19-20; **** large metacentric, larger than any normal human chromosome; *****similar but larger than Nos. 4-5; and ******abnormal chromosome Nos. 4-5 but more acrocentric.



FIG. 10-4A

5. LEUKEMIA ASSOCIATED WITH DOWN'S SYNDROME

There is an increased frequency of leukemia in patients with Down's syndrome (see also Chapter 5). This condition may be either congenital leukemia occurring within a few hours of birth or acute myeloid leukemia occurring later in life. Chromosome studies have revealed



FIG. 10-4B



FIG. 10-4C. Karyotypes from three cell lines from a female African patient with Burkitt's lymphoma. (A) 46,XX,A−,G−,mar*+,mar**+. (B) 48,XX,A−,mar*+,mar**+, mar***+. (C) 50,XX,A−,B+,16+,mar*+,mar**+,mar***+. (Reproduced by courtesy of Dr. P. Jacobs.)

no consistent chromosome abnormality apart from the G-trisomy which is associated with Down's syndrome. Several studies have revealed the presence of an additional C group chromosome (Mercer *et al.*, 1963; Honda *et al.*, 1964), additional chromosomes in the G group (Ross and Atkins, 1962), as well as a subject with variable aneuploidy together with chromosome breakage (Johnston, 1961).

B. *Neoplastic Disease in Other Tissues*

1. Carcinomas

a. Intra-epithelial Carcinoma of the Cervix Uteri (carcinoma *in situ* and dysplasia). This disease involves changes in the cervical epithelium without conclusive histological evidence of invasion of adjacent structures. The major changes are nuclear and involve variation in size and shape, loss of orderly maturation, and numerous normal and abnormal mitoses in all layers of the epithelium. This condition, which is presumed to be the histologically recognizable precursor of an invasive carcinoma, is localized and curable. Chromosome studies should, therefore, give an indication of the type of finding to be expected in an early carcinomatous condition. Studies on four groups of patients who were all ascertained by routine cervical smear are summarized (Boddington *et al.*, 1965; Wakonig-Vaartaja and Hughes, 1965; Richart and Wilbanks, 1966; Kirkland, 1966). In each patient the chromosome

analyses were made directly from biopsy material in which the presence of carcinoma *in situ* was confirmed by histological study. Forty-five patients with carcinoma *in situ* and 18 with mild-to-severe dysplasia were included. The chromosome counts ranged from less than 40 to more than 100, with peaks in the diploid, hyperdiploid, hypotetraploid and hypertetraploid regions. A few tumors, particularly in the series of Boddington *et al.*, showed peaks in the hypodiploid range. Other irregularities included the presence of abnormal marker chromosomes and abnormal mitoses, including multipolar spindles, chromosome lagging, etc. No consistent chromosome change has been reported in this type of tumor.

b. Invasive Carcinoma of the Cervix. Modal chromosome counts range from the hypodiploid to the hypo- and hypertetraploid (Wakonig-Vaartaja and Hughes, 1965). Kirkland (1966) found a predominance of cells with hypodiploid and diploid chromosome numbers, as well as some with chromosome numbers in the tetraploid range. Similar findings were reported by Makino *et al.* (1964b) in 13 cases of uterine carcinoma. Eight uterine carcinomas studied by Atkin and Baker (1966) and Atkin *et al.* (1967) had counts ranging from 41 to 54 chromosomes. In one a predominantly normal karyotype was observed, while in four tumors specific marker chromosomes were found in all cells. In six uterine carcinomas these investigators found modal chromosome numbers to range from 47 to 59 with one exception, in which the modal number was 77 chromosomes. In four tumors the mode was 47, 48, 44, and 54 chromosomes, and in one a near diploid mode of between 44 and 48 chromosomes was found. Specific marker chromosomes were found in five out of these six tumors, the one exception being the tumor with a modal chromosome number of 48 (48,XX,3+,3+,B−,C+). The presence of these specific marker chromosomes suggests a clonal origin for these cell lines. In four out of the five tumors in which distinct marker chromosomes were found, the markers were large, metacentric or submetacentric chromosomes, often as large or larger than normal A group chromosomes (Fig. 10-5).

c. Other Types of Carcinoma. A similar range of chromosome counts have been obtained from the majority of other carcinomas which have been studied including gastric, rectal, mammary, ovarian, and endometrial carcinomas (Makino *et al.*, 1964b; Lubs and Clark, 1963; Yamada and Sandberg, 1966; Katayama and Jones, 1967). Lamb (1967), in a study of transitional-cell carcinomas of the bladder, has shown a wide range of chromosome counts in invasive tumors in contrast to the sharp diploid mode found in noninvasive tumors. This



FIG. 10-5. Larger marker chromosomes seen in metaphase from a carcinoma of the uterine cervix: (a) metaphase plate showing large marker chromosome and (b) marker chromosomes from six metaphases with the normal No. 1. (Reproduced from Atkin and Baker, 1966.)

perhaps suggests that there is a direct correlation between malignancy and variation in chromosome count.

2. EFFUSIONS

Pleural and peritoneal effusions provide excellent material for the study of the chromosomes of malignant cells. The modal chromosome count in 49 different effusions varied from less than 40 to over 100 chromosomes and a similar variation was found within each tumor (Table 10-8) (Spriggs *et al.*, 1962; Ishihara and Sandberg, 1963; Ishihara *et al.*, 1963; J. F. Jackson, 1967). Thirteen tumors in this series had a modal

TABLE 10-8

Variation in Modal Chromosome Numbers Found in Some Cancerous Effusions

Reference	<40	40-45	46	47-49	50-59	60-69	70-79	80-89	90-99	100-200	Total
Spriggs *et al.*, 1962	1	2	3	2	–	1	8	–	–	1	18
Ishihara and Sandberg, 1963	1	2	8	–	1	1	5	–	–	1	19
Ishihara *et al.*, 1963											
J. F. Jackson, 1967		2	2		2	2	2	1	–	1	12
Total	2	6	13	2	3	4	15	1	–	3	49

number of 46 and 15 a mode of between 70 and 79 chromosomes. Eight were hypodiploid and three had modes of over 100 chromosomes. With a few exceptions abnormal marker chromosomes were present as well as abnormal numbers of chromosomes.

Sandberg *et al.* (1963b) reported an effusion from a carcinoma of the colon in which the mode was 77 while more than 50% of the cells had 600 or more chromosomes. Two highly malignant effusions (lung carcinoma, stomach carcinoma,) with modal numbers lying between 70 and 80 chromosomes are reported by Ising and Levan (1957). Both show a variety of marker chromosomes as well as one or more ring chromosomes in some cells.

3. Specialized Tumor Types

a. Glial Cell Tumors, (*gliomas*). Gliomas are tumors derived from one of the cell types forming the parenchyma of the brain and include astroblastoma, astrocytoma, glioblastoma multiforme, spongioblastoma, medulloblastoma, and oligodendroglioma.

Chromosome results are available (Table 10-9) on 19 gliomas of various types (D. Cox *et al.*, 1965; Lubs *et al.*, 1966; Lubs and Salmon, 1965; Conen and Falk, 1967; Hansteen, 1967). The most significant results were those obtained by direct chromosome study of the excised tumors after operation without any intervening period of *in vitro* culture. Unfortunately, the low frequency of mitosis in some of these tumors makes direct preparations difficult. Hansteen (1967) compared direct preparations with various types and periods of *in vitro* culture and found that in general there is a relationship between the results of direct and culture methods, particularly in the types of marker chromosomes found but not necessarily in the range of chromosome counts. Conen and Falk (1967) studied seven gliomas of various types (Table 10-9) using *in vitro* culture and obtained modes of 46 chromosomes in every case. In con-

TABLE 10-9

Chromosome Findings in 13 Different Glial Cell Tumors

Type	Modal chromosome No.	Range chromosome Nos.	Presence of minutes	Marker chromosomes	Additional chromosomes	Type of preparation	Reference
Medulloblastoma	–	75-85	++	–	–	Direct	D. Cox *et al.*, 1965
Medulloblastoma	46	45-51	++	–	–	Direct	Lubs and Salmon, 1965
Oligodendroglioma	92	–	–	–	C+B+	Direct	Lubs and Salmon, 1965
Glioblastoma multiforme	–	42-47 86-89	–	+	–	Direct	Lubs and Salmon, 1965
Medulloblastoma	49	49	++	–	B+ (?r+)	Direct	Lubs *et al.*, 1966
Medulloblastoma	46	–	–	–	–	Culture	Conen and Falk, 1967
Medulloblastoma	46	–	–	–	–	Culture	Conen and Falk, 1967
Epidendyoma	46	–	–	–	–	Culture	Conen and Falk, 1967
Epidendyoma	46	–	–	–	–	Culture	Conen and Falk, 1967
Astrocytoma	46	–	–	–	–	Culture	Conen and Falk, 1967
Glioma of optic nerve	46	–	–	–	–	Culture	Conen and Falk, 1967
Papilloma	46	–	–	–	–	Culture	Conen and Falk, 1967
Astrocytoma	48 96	40-97	1 cell	–	E+F+	Direct	Hansteen, 1967
Astrocytoma	46 92	–	–	–	–	Direct	Very variable group of tumors, no consistent findings. After culture mainly diploid cells found, usually direct preparations give low yield.
Astrocytoma	47	Very variable karyotype		–	(17 or 18q+)(E+E+)F–	Direct	
Astrocytoma	Mostly pseudodiploid				D–G+ C+E–	Direct	
Astrocytoma	49-93	–	–	+ 1-2 metacentric markers		Direct	
Astrocytoma	43-56	–	–	+ minute metacentric marker		Direct	
Astrocytoma	61 (2 cells)	–	–	–		Direct	

trast, the range of chromosome counts in twelve tumors studied directly was from 40 to 97 chromosomes. Modal numbers of 46 and 92 chromosomes were found in two tumors while one tumor had two cell lines, one with 48 and the other with 96 chromosomes (D. Cox *et al.*, 1965; Lubs and Salmon, 1965; Lubs *et al.*, 1966; Hansteen, 1967). In three out of these twelve cases a high frequency of double minutes was found in most cells (Fig. 10-6).

b. NEUROBLASTOMAS. D. Cox *et al.* (1965) studied the chromosomes of three neuroblastomas. The first had a modal chromosome



Fig. 10-6. Metaphase from neuroblastoma from a 20-month-old boy showing a high frequency of double minutes. (Reproduced from D. Cox *et al.*, 1965.)

number of 46 with counts ranging from 37 to 58 chromosomes. The cells with the modal number of chromosomes had abnormal karyotypes and were characterized by the presence of varying numbers of double minutes. The second tumor had a modal chromosome number of 54 (range 49-55), and in some cells a large number of double minutes were again observed. In a third tumor the modal number was 75 (range 56-79), and double minutes were present in the majority of cells (see Fig. 10-6). The tumors were all in children between 20 months and 4 years of age.

c. NEPHROBLASTOMAS. The chromosomes of seven nephroblastomas were studied by D. Cox (1966). Chromosome counts ranged from less than 44 to 58. One tumor had a modal chromosome number of 57. Five of the remaining six tumors had modal numbers of 46, and one a modal number of 47. Three of the tumors with modes of 46 chromosomes apparently had normal karyotypes; one had a 46,XX,1−,C+ chromosome complement, and one an increased amount of aneuploidy with counts ranging from 46 to 49 chromosomes. One tumor with a modal number of 47 and counts ranging from 46-48 chromosomes had the following analysis: 46,XX/47,XX,1+/47,XX,?C+/48,XX,1+,1+. Finally, one tumor in this series with a modal number of 57 chromosomes showed an increase in the number of C and D group chromosomes.

d. TERATOMAS. Chromosome studies of teratomas have usually been carried out after an intervening period of tissue culture, and under these conditions the majority have been found to have a modal chromosome number of 46 with a normal karyotype (Corfman and Richart, 1964; Rashad *et al.*, 1966). Sex chromatin studies on 520 female gonadal teratomas were summarized by Rashad *et al.* (1966) who showed that 475 were chromatin positive and 21 negative. Six testicular teratomas studied by means of short-term *in vitro* culture had modal numbers ranging from 53 to 111 chromosomes with corresponding variation in DNA values (Galton *et al.*, 1966). Sex chromatin-positive stromal, endothelial, and epithelial cells with near diploid and near triploid DNA values were found in five of these tumors. DNA replication studies failed to reveal a late labeling X chromosome in two cases in which chromatin-positive cells were found. Specific marker chromosomes were observed in most cells from the five tumors. Chromosome studies without an intervening period of tissue culture on four testicular tumors (one seminoma, one seminoma combined with malignant teratoma, and two malignant teratomas) have recently been reported (Martineau,

TABLE 10-10

Chromosome Findings in Four Gonadal Tumors

Type of tumor and case No.	No. of cells	Diploid cells	Aneuploid range	Modal chromosome number	Marker chromosomes (large)	Additional chromosomes
Seminoma (1)	69	4	63-74	73	Dicentric; submetacentric; acrocentric.	All groups, D+G+ most usual. G+ is probably Y+ in some cells.
Seminoma and malignant teratoma (2)	68	–	45-127	–	Submetacentric; fragment.	No karyotype constancy
Malignant teratoma (3)	34	2	44-160	–	Submetacentric; ?dicentric.	All groups; D+G+ constant.
Malignant teratoma (4)	24	–	41-68 (one cell with 125 chromosomes)	–	Metacentric.	All groups; A– often found.

1966).[17] These findings are of considerable interest because in each tumor there was evidence for a clonal origin of cell lines which carried similar marker chromosomes (Table 10-10). Counts ranged from between 41 to 160 chromosomes in three tumors, while in one a clear modal number of 73 chromosomes was found. The markers were large submetacentric or metacentric chromosomes (Fig. 10-7), and in one instance a long dicentric marker chromosome was seen. The most striking finding was the presence of these large marker chromosomes of similar morphology in most of the cells examined in the different tumors irrespective of chromosome number. Similar markers were also found in two more tumors, the first a combined seminoma and malignant teratoma and the second a malignant teratoma. Galton *et al.* (1966) studied a further eight malignant testicular teratomas and found a similar metacentric or submetacentric marker chromosome in five of these tumors. The significance of these findings is not clear, but it seems unlikely that the finding of very similar marker chromosomes in 10 out of 14 malignant testicular tumors can be dismissed as insignificant. Other findings in these tumors include a variety of aberrant marker chromosomes which show little similarity from tumor to tumor.

III. The Significance of Chromosome Abnormalities in Malignant Disease

There are three ways of considering the relationship of a chromosome abnormality to a malignant change and these can be summarized as follows: (1) the chromosome change caused the malignant transformation, (2) the malignant transformation resulted in the chromosome abnormality, and (3) the same common factor which caused the malignant change also caused the chromosome abnormality.

Neoplasia can be produced by a variety of factors, for instance, oncogenic viruses, ionizing radiation, and a variety of carcinogenic chemicals; many of these factors also cause chromosome abnormalities. Koprowski *et al.* (1962) have shown that the oncogenic virus SV40 also

[17]Martineau (1969) reported that since describing the apparently similar markers in testicular tumors she has carried out a more exact study on the markers in a larger sample of these tumors. She has calculated the relative length and centromeric index for each marker and tested the similarities between chromosomes from different tumors by statistical methods. Most of the markers, including those described in the 1966 paper, were peculiar to each tumor. However, each of nine tumors contained similar markers, which did not differ significantly from each other. These looked like B group chromosomes but were longer.

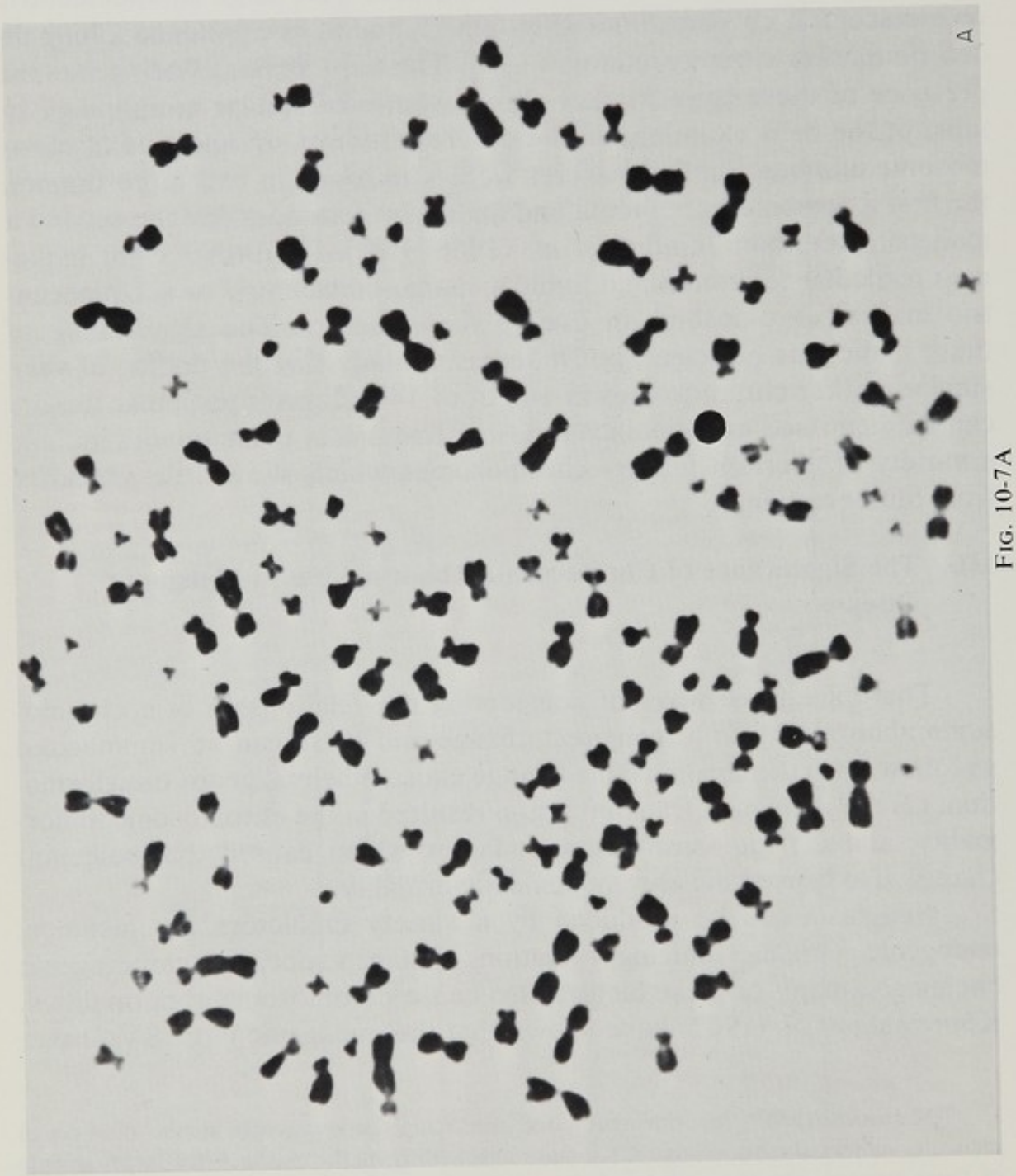


FIG. 10-7A

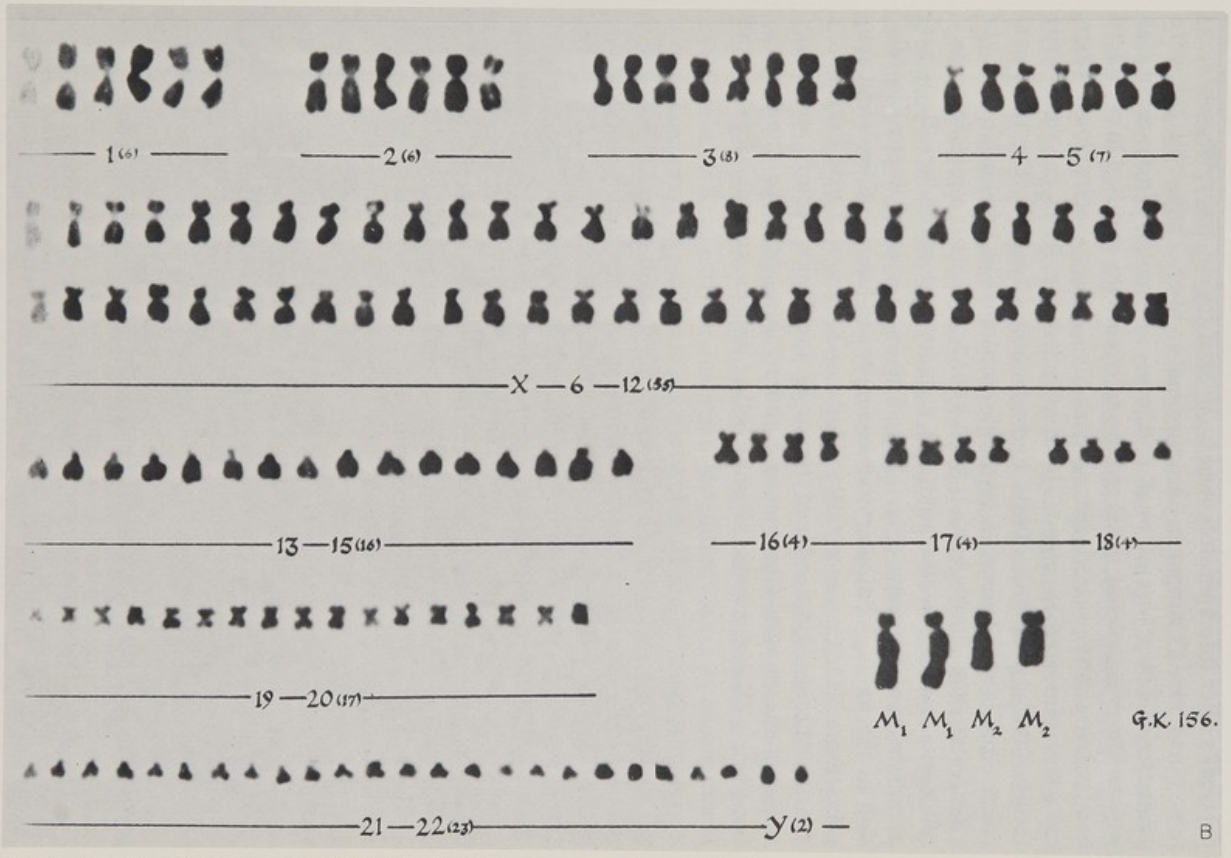


FIG. 10-7. (A) Metaphase plate with 156 chromosomes from a seminoma. The four marker chromosomes can be seen. (B) Analysis of this cell reveals that the numbers of chromosomes in each group varies from 4*n* (group E) to 12*n* (group G). (Reproduced by courtesy of Dr. M. Martineau.)

caused chromosome abnormalities; chromatid breaks appeared at about 11 weeks after infection, followed by di- and tricentrics, rings, and fragments, as well as changes in chromosome number. These changes were characterized by a loss of small and large acrocentric chromosomes as well as chromosomes of the E group and eventually resulted in complete heteroploidy. Other oncogenic viruses also caused heteroploidy when cells were infected *in vitro*. These included the Rous sarcoma virus (Mark, 1967a,b), polyoma virus, and adenovirus type 12. The Rous sarcoma virus is also known to break chromosomes in human lymphocyte cultures after *in vitro* infection. Mark (1967c) reported a high frequency of double minutes in virus-induced primary and secondary Rous sarcomas in newborn mice (Fig. 10-8). This is of special interest in relation to the finding of similar double minutes in human gliomas and neuroblastomas (D. Cox *et al.*, 1965; Lubs and Salmon, 1965; Lubs *et al.*, 1966). Another virus-induced tumor is the "milk factor" mammary tumor in the mouse. Chromosome abnormalities in these tumors have been less well documented. Finally, other viruses, such as measles, and

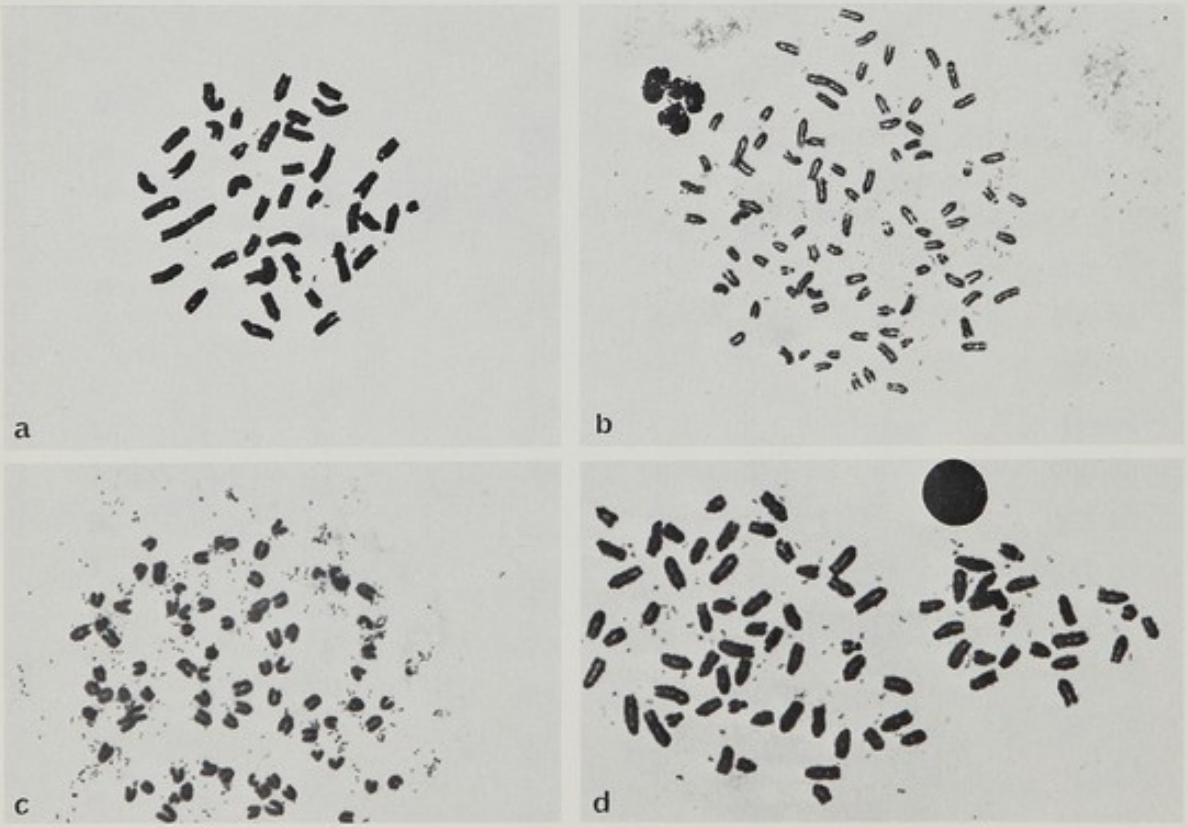


FIG. 10-8. Double minutes seen in virus-induced primary and secondary Rous sarcomas in newborn mice. (a) From primary tumor in CBA mouse; 41 chromosomes, 8 double minutes. (b) From same tumor; 86 chromosomes, 71 double minutes. (c) CBA Rous sarcoma. *In vivo* passage 10; 80 chromosomes, 200 double minutes. (d) *In vivo* passage 43; 75 chromosomes, 70 double minutes. (From Mark, 1967c.)

chicken pox, which are not known to be oncogenic, are known to cause chromosome breakage (Nichols, 1963; Aula, 1965).

Ionizing radiation and chemical carcinogens both cause chromosome aberrations as well as neoplasia (see Lea, 1955; Kihlman, 1966). Genetic factors may also predispose to both neoplasia and chromosome aberrations. Two conditions in particular, both resulting from single gene defects, are known to lead to the development of leukemia as well as to a high incidence of chromatid breakage. These are congenital telangiectatic erythemia (Bloom's disease) and Fanconi's anemia (German *et al.*, 1965; Sawitsky *et al.*, 1966; Schroeder *et al.*, 1964; Schmid, 1967). Fraccaro *et al.* (1965) and Perkins *et al.* (1969) have reported a high frequency of spontaneous chromosome rearrangement and breakage in an untreated papillary cystadenocarcinoma of the ovary. The risk of leukemia is increased in Down's syndrome (Chapter 5) and perhaps in other trisomics. The finding of a specific chromosome abnormality (Gq−) in chronic myeloid leukemia, of various chromosome abnormalities in certain "pre-leukemic" conditions such as myeloid metaplasia and polycythaemia vera, in early premalignant conditions such as carcinoma *in situ* of the cervix as well as in a variety of early and untreated tumors is anecdotal evidence that chromosome change may be important in the initial cellular malignant transformation. Apart from these findings, the observation of marker chromosomes in many tumors suggests that at least some tumors are characterized by specific clones of cells; it is not, however, clear if these clones comprise the primary tumor cells or have arisen secondarily to the origin of the tumor.

What then is the cause of cancer? It may be an external biological agent, an external physical or chemical agent, an internal hormonal substance, or a genetic factor, possibly congenital or possibly somatic, acting probably on a single cell and resulting in a breakdown of the inhibitory processes which control the rate of cell division and the invasive properties of the cell. Such an agent may at the same time lead to chromosome damage, including breakage and rearrangement of the genome as well as heteroploidy and polyploidy. If this is so then conditions are ripe for the selection of cells containing a karyotypically altered genome which are capable of rapid multiplication and invasion in an altered tumor environment.

It would thus seem unimportant whether the chromosome alteration came before, after, or at the same time as the neoplastic transformation. What is important is that the production of an altered genome in the tumor provides a population of cells from which lines capable of unlimited growth in an ever-changing tumor environment can be selected. All the evidence suggests that the chromosome and neoplastic change oc-

curred at the same time, or at least very close to each other, and that the changed chromosome complements immediately become important in the progression of the tumor.

The stem cell concept of tumor progression (see Section I) is supported by most of the data presented here. The significance of heteroploidy in tumor cells may be that such cells possess a greater potentiality for a loss or gain of chromosomes than their simple diploid progenitors. Polyploid cells have a greater potential variability and can give rise to a higher frequency of viable cell types on which selection can act. Wide variation in chromosome number and karyotype without any specific mode as is found in some tumors and effusions (Sandberg and Yamada, 1966) may simply indicate a tumor which is undergoing intensive evolution of the cell population and producing a large number of variants. A similar explanation could account for the finding of cytogenetic polymorphism in certain cell populations *in vitro* (Hughes, 1968). There are a number of difficulties attached to any attempt to associate the presence of a particular chromosome or chromosomes with malignancy, or the capability of a cell strain to divide indefinitely and to lose the characteristic contact inhibition.

Recently, Levan (1966) studied the nonrandom representation of chromosomes in tumor stem cell lines from 40 human cancers and concluded that chromosomes of C group were over-represented while those of D and G groups were under-represented. More recently, Gorman *et al.* (1967) showed that chromosome No. 16, and to a lesser extent No. 17, was over-represented in six heteroploid and one quasi-diploid cell line and two human cancers; they concluded from this that a relative increase in the number of chromosome 16's always occurs during the development of malignancy irrespective of the primary cause.

Both these studies were based on morphology of the chromosomes, and there was no evidence that the chromosomes involved were not structurally altered chromosomes resembling those of the groups to which they were assigned. However, even if the chromosome identification was correct, there is no evidence to relate these chromosome changes to the primary malignant change. All the tumors studied by Levan (1966) were old and far advanced. Gorman *et al.* (1967) studied cell lines which had been transferred *in vitro* for many generations, and the two tumor cell populations studied consisted of secondary effusions which bear little resemblance to the primary tumor. Thus these studies throw no further light on the primary event in a malignant change but only on the chromosome change which may be relevant to tumor or cell line progression.

The studies which have been outlined in the present chapter fail to provide any evidence that a specific chromosome abnormality is related to the primary malignant change. A possible exception to this is the Gq− chromosome in CML and possibly some of the changes in PV. The finding of similar marker chromosomes in certain tumors suggests that these may originally be of clonal origin arising from a similar cell type under similar environmental conditions; they do not, however, provide evidence that the chromosome change is primary to the malignant change or vice versa. Thus, at present, we still have little evidence about the primary malignant change and much more data are required about chromosome abnormalities in pre- and early malignant conditions before any realistic statement can be made.

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ADDENDUM

No attempt has been made to make this addendum exhaustive. Only those observations thought to be important and to lend support to a principle discussed in the text are included. Numerous case reports have been published since the text was completed. The majority of these have been omitted intentionally.

Chapter 1

Frequency of Sex Chromosome Aneuploidy in Males

A summary of data from five neonatal chromosome surveys (Lubs and Lubs, 1971) shows that out of a total of 11,039 consecutive male births, 31 were found with a sex chromosome abnormality, an incidence of 2.81/1,000 male births. Seventeen of these babies were 47,XYY (1.5/1,000); thirteen, 47,XXY (1.2/1,000); and one, 46,XX (0.1/1,000). No other aneuploid males were found.

XXY Males

Several endocrinological, psychiatric, and cytogenetic studies of groups of 47,XXY males have been published recently (Nielsen, 1969; Nielsen *et al.*, 1969; Frøland, 1969).

Maternal Age

The results of a recent study by Court Brown *et al.* (1969) are summarized in Table A1-1. There was a significant increase in maternal age for 47,XXY males and double aneuploids but not for the 49,XXXXY or 48,XXXY males, although the maternal age distribution for the latter group was consistent with bimodality. As expected, neither the 47,XYY nor the 48,XXYY males show any significant change in frequency or distribution. Postzygotic nondisjunction is suggested to account for the findings on 49,XXXXY males. This would also fit the available Xg blood group data.

Dermatoglyphic analysis of 55 unrelated patients with Klinefelter's syndrome (47,XXY) (Cushman and Soltan, 1969) revealed a closer resemblance between patients with Klinefelter's syndrome and female controls rather than male controls for six traits. One trait showed closer resemblance to male controls while no significant difference was found for any of the other 13 traits.

TABLE A1-1

PARENTAL AGE OF ANEUPLOID MALES

Chromosome complement	Mean maternal age	Mean paternal age	n^a	p-m[a]
47,XXY	32.47	35.38	159	2.91
47,XYY	27.91	30.19	53	2.28
48,XXXY	29.89	34.00	19	4.11
48,XXYY	29.06	32.71	35	3.65
49,XXXXY	28.49	30.33	43	1.84
Double aneuploids	36.16	37.26	25	1.08
Control	28.60	30.90	–	2.36

[a]Here p indicates paternal and m indicates maternal, n = number of individuals.

XX Males

Xg blood groups have been determined on 34 XX males (Sanger *et al.*, 1971). Twenty-eight were Xg(a+) (0.824). This distribution fits the XXY distribution slightly better than the female and much better than the male. These results do not support the X;Y translocation hypothesis (see text p. 25) (Ferguson-Smith, 1966). Only three informative families were found out of 21 in which both the 46,XX proband and

his parents were studied. These indicated that both X chromosomes must be maternal in origin.

Fluorescent staining of the chromosomes with quinacrine or its mustard (see Addendum, Vol. I) of three 46,XX males (George and Polani, 1970; Philip *et al.*, 1971) has failed to demonstrate any brightly fluorescent region which might be seen if a translocation involving Yq had occurred, indicating that if such a translocation had occurred, it did not involve the distal two-thirds of the long arm of the Y chromosome.

XYY Males

Numerous attempts to locate additional 47,XYY males have been reported in the past 18 months. Because of the initial reports of a supposed association between the 47,XYY karyotype, criminality and height, many of these studies were of selected tall prisoners. The most significant of these related to penal institutions and approved schools in Scotland (Jacobs *et al.*, 1971). This comprised a chromosome study of 2,258 male prisoners selected in various ways and concluded that in Scotland there was no significant difference between the frequency of 47,XYY males in the institutions studied than in the newborn population. The authors stated:

> In Scotland, the increased criminal behaviour in the 47,XYY male is confined to those that are mentally disordered and liable to be admitted as patient offenders to the state hospital.

A study was done by Melnyk *et al.* (1969), of 200 patients over six feet tall in the Atascadero State Hospital, California, a maximum security facility for the care of mentally disordered sexual offenders (MDSO) and the mentally ill criminally insane (MICI). Seventy-nine MDSO patients were studied and seven (8.9%) were 47,XYY; two of the 121 MICI patients studied were 47,XYY (1.6%). Thus, in the tall MDSO group the frequency of the 47,XYY karyotype is 89 times that in the general newborn population. Other studies are difficult to summarize because of different in-patient selection and the handling of criminals and criminally insane patients in different countries.

It is, however, clear that it is too early to generalize about the prognosis for a 47,XYY infant; there is, however, very little evidence of an association between criminality and the 47,XYY state.

Recently, Sumner *et al.* (1971) have shown that 1.26% of human sperm have two fluorescent bodies (see Addendum, Vol. I, p. 380) and that the DNA content of these sperm lies between those with one F body (23,Y) and no F bodies (23,X). They interpret these as 24,YY

spermatozoa and the complementary class as 22,O. If both classes of sperm were successful in fertilization, then 12.6/1,000 births would be 47,XYY and 12.6/1,000 would be 45,X. In fact, the incidence is about 1.7/1,000 live male births (47,XYY) and 0.2/1,000 live female births (45,X). More than 90% of 45,X zygotes are lost during gestation, but there is no evidence of prenatal loss of 47,XYY zygotes. Sumner *et al.* (1971) therefore suggested a diminished efficiency of 24,YY sperm compared to normal sperm in achieving fertilization. Fluorescent studies of sperm from a 47,XYY male showed that about 70% contained one F body, 5% two, and the remainder none. Meiotic studies on 47,XYY males (Addendum, Vol. I, p. 383) suggest meiotic loss of the second Y in some males, but not in all; thus, the finding of 5% sperm with two F bodies is not inconsistent with these observations.

Chapter 2

Ovarian Dysgenesis

Zarate *et al.* (1969) reported a girl with 45,X ovarian dysgenesis, based on one blood culture and the analysis of 30 cells, and secondary amenorrhea. Menstruation commenced at 14 years and lasted for five years with decreasing frequency. Laparotomy revealed an enlarged left polycystic gonad and an atrophic right gonad. A few primordial follicles were found in the ovarian cortex.

Two of the 45,X/46,XYdic patients referred to briefly in the text (p. 84) and Table 2-5 have now been described in detail along with a third subject with the same chromosome complement (Angell *et al.*, 1970). Gonadal histology on two of these patients showed a single sterile testicular tubule in the right gonad of one, while the left gonad on that patient and the only gonad on the second were sterile "streaks." Ferguson-Smith *et al.* (1969) reported a further example of a patient with Turner's syndrome 45,X/46,XYqi. At autopsy an infantile uterus and fallopian tubes were found, while in the ovarian sites a number of small fimbrial cysts were seen. No seminiferous tissue was found. An epididymal-like structure was observed on the right in an anterior position. There was no right gonad; the left consisted of an ovarian streak. The presence of an epididymis on the right suggests that at one time there may have been sufficient testicular differentiation to induce some Wolffian development.

Wood *et al.* (1970) have estimated levels of γM and γG globulins in 46,XX and 46,XY female and male controls and a group of 45,X fe-

males with ovarian dysgenesis. Levels in the 46,XY and 45,X subjects were significantly lower than in the 46,XX controls. γG globulins were similar in the 46,XY and the 46,XX controls but low in 45,X subjects. Antibody titers against *Listeria monocytogenes* and *Escherichia coli* also showed similar differences.

McHardy-Young *et al.* (1970) have recently reported that two groups of patients with Turner's syndrome differ in their response to thyroid stimulating hormone. Patients with thyroid antibodies had a significantly lower response than those without antibodies which suggested that patients with Turner's syndrome had a low thyroid response and behaved like other patients with chronic focal thyroiditis and Hashimoto's disease.

There have been several attempts recently to correlate sex chromosome findings with phenotype in relation to gonadal dysgenesis and to develop a unified concept for the pathogenesis of this condition (German, 1970; Morishima and Grumbach, 1968; Hecht *et al.*, 1970; Polani, 1970a).

X Chromosome Origin, X-Inactivation, and the Xg Blood Group

It is still an open question whether the Xg locus is subject to random inactivation. The study of MacDiarmid *et al.* (1967) suggested that it was inactivated in a female heterozygous for an X-linked sideroblastic anemia and the Xg^a antigen. A similar study by Weatherall *et al.* (1970) was unable to confirm these results. Xg grouping of patients with chronic myeloid leukemia suggested either Ph′-positive cells are not clonal in origin or that Xg^a is not inactivated assuming that it is produced on the red cell precursors and not elsewhere (Lawler and Sanger, 1970; Fialkow *et al.*, 1970). Hsu *et al.* (1970) have studied a 46,XXq− patient and shown the Xq− to be late replicating in every cell and from this, they argued, totally inactivated. They pointed out, therefore, that the hypothesis locating the Xg^a locus on the short arm of the X is untenable (see text pp. 89-90). Fialkow (1970), studying double heterozygotes for HGPRTase deficiency and Xg, has reported evidence that either the Xg locus does not undergo random inactivation or that the Xg^a antigen is not synthesized in the red cells themselves.

Finally, a group of patients with both Xq− and Xp− deletions studied by Polani *et al.* (1970) suggested that when the Xg(a) allele at the Xg locus is on a structurally abnormal X chromosome it is invariably inactivated. They stressed that this conclusion applies only to abnormal X chromosomes.

Familial Gonadal Dysgenesis

Perez-Ballister *et al.* (1970) reported a family with three 46,XX sisters of normal stature with pure gonadal dysgenesis. Laparotomy of each revealed streak gonads consisting of typical stromal tissue and absence of primordial follicles. Espiner *et al.* (1970) reported a family in which five girls in three sibships have 46,XY chromosome complements and gonadal dysgenesis.

Chemke *et al.* (1971) reported a family in which two "sisters" are reported with 46,XY gonadal dysgenesis and a brother is a male pseudohermaphrodite.

Levy *et al.* (1970) reported an interesting family in which the propositus has the male Turner's syndrome phenotype, a paternal aunt the female Turner's phenotype but with normal 46,XX chromosomes, while the father and one female sib are partially affected. The authors suggested an autosomal dominant mode of inheritance. Nora and Sinha (1970) reported male-to-male transmission of the male Turner's phenotype which suggests again the possibility of autosomal dominant inheritance rather than X-linked dominance.

An interesting family reported by Hsu *et al.* (1970) contained two sisters with 45,X/46,XY/47,XYY mixoploidy and gonadal dysgenesis and a brother with male pseudohermaphroditism and 45,X/47,XYY mixoploidy; a third sister, who had normal chromosomes, had 5% aberrant cells. She was normally fertile and had one son.

These families provide further evidence in favor of a genetic etiology for some forms of gonadal dysgenesis, sex reversal, and true hermaphroditism (Chaps. 3 and 4, Fig. 4-11).

X Chromosome Polysomy

Eight triple X females have been reported in 5,608 newborn female infants in five neonatal chromosome surveys (Lubs and Lubs, 1971), an incidence of 1.8/1,000 female births.

Barr *et al.* (1969) have reviewed the 47,XXX phenotype primarily ascertained during sex chromatin surveys of the mentally retarded or mentally ill patients. One-third have congenital defects of various types, while the remainder are physically normal. Twenty-eight 47,XXX females have borne 67 children, 31 boys, 19 girls, and 17 for whom the sex was not recorded. Twenty-nine of the children were cytologically tested: 24 had normal chromosomes and one was 47,XXY. Four of the mothers who were 46,XX/47,XXX had between them two 47,XXY, one 46,XY/47,XXY, and one 46,XX/47,XXX children.

Two additional 48,XXXX females have been reported (Duncan *et al.*, 1970; Berkeley and Faed, 1970). Both were mentally retarded with slight physical abnormalities and some abnormal dermatoglyphic findings.

Chapter 3

Testicular Feminization

Recently, Polani (1970b) has reviewed in detail the hormone mechanisms in testicular feminization (TF). Studies of testosterone levels in the blood and the measurement of testosterone production rate have shown normal male values. The source of plasma testosterone in TF is almost certainly the testes, although some may be contributed by the adrenal cortex unlike normal males. In general, the idea of a target organ defect in respect to responsiveness to testosterone seems most likely. Mauvais-Jarvis *et al.* (1970) have shown that in normal males testosterone was 5α-hydrogenated outside the liver but that this seemed unlikely to occur in TF patients who are about ten times as sensitive to estrogen treatment as normal males. They suggested that the basic defect may be related to an abnormal synthesis of plasma bound protein(s) under the effect of circulating estrogens so that an abnormally small amount of unbound testosterone may be available in target cells for 5α-reduction.

Bruchovsky and Wilson (1968) have shown that in the rat testosterone concentrates rapidly in the nuclei of target cells and is converted enzymically by a 5α-reductase ($NADPH_2$:Δ^4-5α-3-ketosteroid oxidoreductase) into dihydrotestosterone (DHT). This enzyme is present in the nuclei of target organ cells and is associated with nucleochromatin. It is suggested that only DHT acts on the target organ, in whose cells it enhances RNA-polymerase activity and RNA production, and increases protein synthesis.

Northcutt *et al.* (1969) have compared the efficiency of DHT production by suprapubic skin, pubic hair follicle, epididymis, and vas deferens of normal males and TF subjects and suprapubic skin of females. The results showed a twentyfold greater efficiency of the normal male and female target organs to convert testosterone to DHT. These results were confirmed by Heinrichs *et al.* (1969), but it should be stressed that these studies were not exhaustive and that more work is needed to delineate the basic defect in TF.

Similar syndromes to that seen in man have now been reported for

rats, cattle, and mice (Nes, 1966; Bardin *et al.*, 1970; Short, 1970; Lyon and Hawkes, 1970). Lyon and Hawkes (1970) have clearly shown that the testicular feminization allele (*Tfm*) in the mouse is linked to the sex-linked alleles *Ta* and *Blo* and is about 1.3 ± 1.3 crossover units from *Ta*, thus indicating that *Tfm* is sex-linked in the mouse. Lyon and Hawkes (1970) argued that the condition in the mouse is probably homologous with the condition in rats and humans, and from this they concluded that the rat and human loci are also sex-linked.

The biochemical lesion has been investigated in the mouse, and it has been shown that hemizygous *Tfm*, XY mice fail to respond to the induction by testosterone of alcohol dehydrogenase (ADH) in the kidneys. It is suggested that this is not the result of a failure to form dihydrotestosterone (DHT) because DHT does not induce kidney ADH activity in normal mice. Ohno and Lyon (1970) suggested that *Tfm* is a noninducible mutation of a repressor regulator which controls the structural genes for testosterone inducible enzymes.

Chapter 4

The Action of the Y Chromosome

Mittwoch *et al.* (1969) and Mittwoch (1970) have suggested that the mammalian Y exerts its action on the indifferent gonad by stimulating mitosis at a critical point in the development of the gonadal primordium thus increasing growth rate and leading to a switch in the developmental pathway from an ovary to a testis. Mittwoch cited as evidence the fact that the primitive gonad in the rat is larger by about 40% in the male than in the female even before the stage at which the type of gonad can be determined histologically. Jost (1970a) pointed out that the basic mammalian sex is female and that the Y chromosome in some way imposed testicular development on a gonad which would otherwise develop into an ovary. He considered a simple burst of mitosis to be an insufficient explanation.

Evidence from a study of intersexual states and in particular the freemartin (see text and Short, 1970) suggests that the hypothesis put forward by Hamerton (see text) may be too complicated. Sex can be determined in mammals without postulating an active female determinant as suggested by Fig. 4-8. It is sufficient if there is a male determinant under the control of the Y chromosome. The evidence that this may be located elsewhere in the genome than on the Y chromosome but controlled by an element on the Y is quite strong. Thus, in the presence

of this controlling element, the male determinant causes the indifferent gonad to develop into a testis. In its absence the normal course of female development will proceed without interruption.

Jost (1970b) has stated the present position very clearly:

> The process of testicular organogenesis is probably controlled by one or more diffusable substance(s) produced by some cells and which influence other cells so as to impose male organogenesis. If the identity of the leading cells and the nature of the inducing substance(s) remain unknown, it could be conceived either that these cells participate in the elaboration of the main duct system or that they remain somewhat apart from it (as do interstitial cells or mesonephric elements). There is no indication that in those gonads which do not become testes (presumptive ovaries) there is any special mechanism or cortical inductor responsible for preserving the undifferentiated pattern of growth. The mere absence of the testicular inducing signal could explain their ovarian prospect.

Chapter 8

Location of Specific Gene Loci

A second family with an elongated No. 1 (1h) segregating in 6 out of 15 members is reported by Ying and Ives (1968). Blood grouping studies showed linkage between 1h and the *Fy* locus. Linkage studies in a family with a Dp− segregating shows that the *MN*, *Rh*, *Hp*, *Gc*, *Ag*, *Pi*, and *AK* alleles and the allele for erythrocytic acid phosphatase cannot be located on the short arm of the D chromosome (No. 13) (Brøgger, 1969). Fragile chromosome sites, which are useful as markers in linkage studies, have been reported recently on chromosome 9 (Schmid and Vischer, 1969) and on chromosome 16 (Magenis *et al.*, 1970). Linkage studies in the family with the fragile 16 segregating revealed linkage between this site on No. 16 and the α-*Hp* locus. Magenis *et al.* (1970) also stated that the α-*Hp* gene can probably be located to a discrete segment of the chromosome near the junction of the middle and distal thirds of the long arm of chromosome 16. Studies by Robson *et al.* (1969), using segregating translocation chromosomes, assigned the *Hp* locus to the long arm of 16 with a probability of 0.97. Amos *et al.* (1970) suggested linkage between *Hp* and the *HL-A* histocompatibility locus.

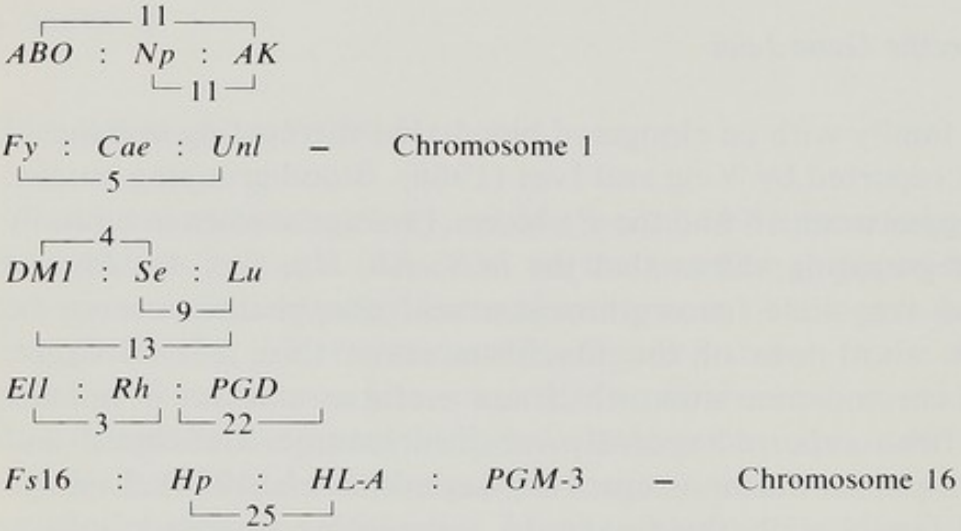
Finally, Renwick (quoted by Magenis *et al.*, 1970) stated:

> . . . extensive data from an Amish isolate suggested a recombination fraction of 0.25 between *Hp* and the *HL-A* histocompatibility region with a peak load of 4.0 and 95% probability limits of 0.19 and 0.33. There is a probability of 0.98 that *HL-A* is syntenic with *Hp* and therefore also on chromosome 16.

It is suggested that *HL-A* is on 16q near the fragile site, the order being either *HL-A*:fragilesite:*α-Hp* or fragilesite:*α-Hp*:*HL-A*. Renwick (1971a) assigned the gene loci to specific chromosomes in the accompanying table.

Locus	Chromosome No.	*p*
Duffy	1	0.98
Haptoglobin	16	0.98
HL-A histocompatibility locus	16	0.97
Acid phosphatase	2	0.63 (uncertain)
Rh blood group	D group	Uncertain because identity of specific D chromosome not clear
Group specific component (Gc)	?D	0.50 (uncertain)
Thymidine kinase	17 or 18	Cell hybridization studies

The following human linkage groups are now known:



Key: *Np*, nail patella syndrome; *AK*, adenylate kinase; *Fy*, duffy blood group; *Cae*, congenital cataract; *DM1*, dystrophica myotonica; *Se*, secretor; *PGM-3*, phosphoglucomutase 3; *PGD*, phosphogluconic dehydrogenase; *Unl*, uncoilea locus-chromosome 1; *Fs* 16, fragile site-chromosome 16; and *El* 1, elliptocytosis. Figures indicate distances given in crossover units.

Chapter 9

Spontaneous Abortions and Oral Contraceptives

Carr (1970) has shown a significant increase in triploidy among 54 abortuses from women conceiving within six months of discontinuing oral contraceptives. He suggested that this may result from an

abnormal timing of fertilization owing to hormonal imbalance. Carr (1971) has presented a detailed study of 37 polyploid abortus specimens. Very few of these contained an embryo or fetus and 87% showed hydatidiform degeneration. A study of specimens selected for hydatidiform degeneration (not mole) showed 70% to be triploid.

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