Human Cytogenetics: Its Present Place and Future Possibilities[1]

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THE NUMBER OF HUMAN CHROMOSOMES

I THINK IT WOULD BE FAIR to say that four years ago none would have foreseen the developments in human cytogenetics that have actually taken place. My own attitude at that time may have been typical. We had a visit one day from an Oxford surgeon, Mr. Moloney, who showed interest in the squash preparations of seminiferous tubules we were making at that time from Carter's mouse translocation stocks, and offered to provide us with human material. I thanked him, of course, and the thought that ran through my mind may have been something like this, "It would be interesting to see human chromosomes when there is a little less pressure of work, but everyone knows that the diploid number is 48 and there is probably very little more we can learn at present."

The following year I read with an amazement that I am sure I must have shared with many others, Tjio and Levan's short paper in Hereditas (1956), announcing their counts of 46 chromosomes in tissue cultures established from foetal lung. I immediately remembered Mr. Moloney's offer, and with his kind assistance, Hamerton and I (1956) were quickly able to confirm the new number by counting 23 bivalents regularly at first spermatocyte metaphase. Our work was therefore inspired solely by Tjio and Levan's discovery: it was in no sense independent.

The surprise had hardly subsided when Kodani's first paper (1957) appeared bringing an apparent reprieve for the number 48; an indication that the number might vary, at least among Japanese; the suggestion that the chromosomes in excess of 46 were inert supernumeraries; and the implication that human populations might differ from one another in respect of these additional chromosomes. Since then however, notwithstanding a further, confirmatory contribution from Kodani (1958), the evidence in favour of the diploid number 46, at least in persons of European ancestry, has continued to mount; (Bender 1957; Hsu et al., 1957; Ford, Jacobs and Lajtha, 1958; Tjio and Puck, 1958; Lejeune, Gautier and Turpin, 1959; Chu and Giles, 1959). Published evidence regarding the chromosomes of other ethnic groups is still very meagre, but there is a recent short paper by Makino and Sasaki (1959) reporting counts of 46 in tissue cultures established from six Japanese foetuses, and Professor Makino has kindly al-

[1] Part of a Symposium on Cytology in Human Genetics held on Sept. 2, 1959, under the joint sponsorship of the American Society of Human Genetics and the Genetics Society of America during the meetings of the American Institute of Biological Sciences at Pennsylvania State University, August 30 to Sept. 3, 1959.

lowed me to say that he and his colleagues have now made counts on tissue cultures from a total of 39 different Japanese foetuses and that in every one they find the diploid number 46. Taken at face value these observations are not reconcilable with Kodani's. But it must be remembered that Kodani's observations were made on testicular material, and until there is independent examination of the meiotic chromosomes Stern's suggestion (1959a) that supernumerary chromosomes might be confined to the germ tract cannot be rejected.

HUMAN CHROMOSOME MORPHOLOGY

Within the last 15 months idiograms of human somatic chromosomes have been published by three groups. Our own (Ford, Jacobs and Lajtha, 1958) was based on measurements of the chromosomes in 3 bone marrow mitoses and was not meant to be other than a guide for further work. Nevertheless there is a considerable measure of agreement between this and those of Tjio and Puck (1958) and Chu and Giles (1959) which were prepared from measurements of chromosomes in tissue-cultured cells. Such small differences as there are may well reflect differences in contraction of whole chromosomes or chromosomic arms brought about by differences of technique or in origin of the cells examined. Nevertheless we should bear in mind the possibility of true, structural polymorphism of the human chromosomes, perhaps particularly of the X and Y. Comparison of the chromosome sets of different ethnic groups immediately suggests itself as the most likely method of revealing polymorphism if it exists. It is unnecessary to stress the interest for anthropology if any form of chromosome polymorphism should be revealed.

ABNORMALITIES OF SEX-CHROMOSOME CONSTITUTION

Tjio and Puck (1958) on the one hand and Chu and Giles (1959) on the other claimed to be able to identify both X and Y as individual chromosomes. We originally were only able to define Y as one of 5 small acrocentric chromosomes in the male, and the X as one of 15 medium sized metacentric chromosomes (Ford et al. 1958). Nevertheless this was sufficient to justify beginning an investigation of the chromosomes in patients exhibiting anomalies of sex development. Now we can frequently identify Y as an individual chromosome in our marrow preparations and the X as one of 5, sometimes 3.

Interest in these anomalies had been greatly stimulated by the discovery of 'sex chromatin' by Barr and Bertram (1949) and by the interpretation placed on it, namely that it represented fused heterochromatic regions of the two X chromosomes. It was soon found that the essentially male patients with Klinefelter's Syndrome, or seminiferous tubule dysgenesis, mostly exhibited sex chromatin in buccal smears, or skin biopsy nuclei (Bradbury et al., 1956; Plunkett and Barr, 1956). The essentially female patients with gonadal dysgenesis (the more extreme forms of which are known as Turner's Syndrome) were mostly chromatin negative (Decourt et al., 1954; Polani et al., 1954; Wilkins et al., 1954). There were suggestions that these two classes of patient, in which the sex chromatin diagnosis did not conform with the apparent sex, might represent examples of reversal of the genetic or chromosomal sex.

In February, 1958, Miss Jacobs and I, in conjunction with Dr. W. M. Davidson and Dr. D. R. Robertson Smith examined the chromosomes of a chromatin-positive Klinefelter patient by the bone marrow method. The specimen was a poor one and we found only 5 reasonably 'good' cells in metaphase, all of which appeared to have the chromosomes of a normal female (Ford et al. 1958). It seemed as though those who spoke of 'reversal of genetic sex' might be right.

In the event this proved to be an unlucky observation. At the end of the year Jacobs and Strong (1959) and my associates and myself (1959) independently examined the chromosomes of two further chromatin-positive Klinefelter patients. The great majority of cells of both patients were recorded as containing 47 chromosomes, which were interpreted to include, almost certainly, two X chromosomes and a Y. The marrow specimen from our patient also contained a number of cells with 46 chromosomes and appeared to be a mosaic, as far as his marrow was concerned, of XXY cells and XX cells.

Subsequently we have examined the chromosomes of a further 6 chromatin-positive Klinefelter patients, including the remarkable mongol Klinefelter case I shall mention again later. In every one there is very little doubt that the patient developed from an XXY zygote. The cytological observations relating to one of these patients were made by Dr. D. G. Harnden (in press) using tissue cultures established from skin explants on to plasma clots.

Further chromatin-positive Klinefelter patients have also been examined at Edinburgh and Lund. Dr. Levan and Dr. Nowakowski have kindly informed me of the work at Lund, which was carried out by Drs. Bergman and Reitalu on tissue cultures established from skin biopsies performed on two of Dr. Nowakowski's patients. Again 47-chromosome cells, interpreted to be XXY, predominated, although in cultures from one of the patients some 30 per cent of cells contained an additional acrocentric chromosome with no counterpart in the normal set. Our first (?XX) case appears to be, therefore, the one exception among some 12 examined. I have checked the original records and have no reason to suspect that they may have been wrong. Obviously we should endeavour to re-examine material from the same patient. In the light of the one mosaic marrow I have already mentioned and other examples I shall discuss shortly I don't think it is too fanciful to suggest mosaicism as a possible explanation.

The other group of patients in which 'reversal' of genetic sex had been suggested as a result of sex chromatin studies I shall refer to collectively as cases of Turner's Syndrome. We started with the knowledge that on the basis of colour blindness studies Polani, Lessof and Bishop (1956) had suggested that the chromatin-negative group might be XO: also that Danon and Sachs (1957) had found that in two patients observations on skin sections had not been consistent in respect of sex chromatin, indicating, they suggested, that these patients might be XO/XX chromosomal mosaics.

The first chromatin-negative Turner patient whose marrow we examined confirmed the suggestion made by Polani and his colleagues: virtually all the cells counted contained 45 chromosomes and all that were studied in detail were consistent with the XO interpretation.

Subsequently we have examined bone marrow preparations from three other cases of Turner's Syndrome, all in conjunction with Dr. Polani, Dr. Briggs and Dr. Almeida of Guy's Hospital, London. One of these was chromatin negative and two chromatin-positive, but all the preparations proved to contain mixtures of 45-chromosome cells and 46-chromosome cells. The last of the three gave preparations of good technical quality and 12 of the cells were analysed in detail. These detailed observations left little doubt that the 46-chromosome cells contained two X chromosomes and the 45-chromosome cells only one. We therefore interpret this case as an XO/XX mosaic, as foreshadowed by Danon and Sachs, and consider it probable that the other two examples mentioned are also XO/XX mosaics.

If this is so, then I suggest that it is likely that all three developed from XO zygotes. There is evidence that strong selective forces can operate and bring about differential proliferation of distinct clones of cells in the haemopoietic tissues of irradiated mice (Ford, Micklem and Gray 1959); also that there is selective elimination of cells with unbalanced chromosome sets in irradiated testis and bone marrow of another species, *Poterous tridactylus* (Sharman 1959). It would therefore not be surprising if an XX cell, arising by non-disjunction in an XO embryo, should be favoured and multiply differentially. On the other hand although an XO cell might arise by non-disjunctional loss of an X chromosome in an XX embryo, elimination or, at most, a slower rate of multiplication would seem to be a more likely fate. In any case I hope I have said enough to indicate that the evidence is not inconsistent with developments of all three mosaic patients from XO zygotes.

The chromosomes of several other chromatin-negative cases of Turner's Syndrome have now been examined by Fraccaro and his colleagues (1959), Tjio, Puck and Robinson (1959), and Harnden (in press) using tissue cultures; and by Jacobs and Stewart (unpublished) using the bone marrow method. All found cells with 45 chromosomes and agree in giving the XO interpretation.

THE CONSEQUENCES OF NON-DISJUNCTION

How do these abnormalities arise? The obvious answer is by non-disjunction during the meiotic divisions, and this is implicit in the references to XXY and XO zygotes I have made. (I ignore the rather unlikely possibility of somatic non-disjunction having produced a gonadal mosaic in one of the parents). Non-disjunction of the daughter X chromosomes in the first mitosis of an XY zygote would give XXY and YO daughter cells and as the latter is likely to be inviable an XXY individual could result. On the other hand, non-disjunction of daughter X chromosomes in the first mitosis of an XX zygote would give XXX and XO cells, and since there is no reason to suppose that the triple-X cell would be inviable, a nearly equal, perhaps bilateral, mosaic would be expected. Simple loss of one daughter X or Y at the first mitosis, or non-disjunction at a mitosis later than the first, would inevitably yield mosaics containing normal XX or XY cells as a component. I have already given reasons for supposing that the normal cells would dominate such partnerships, if the unbalanced cells survived at all.

We are therefore brought back to non-disjunction during oogenesis or spermatogenesis as being by far the most likely source of the anomalous XXY and XO individuals.

So far as I am aware there is no direct evidence of non-disjunction during the maturation of the gametes in man. However, Hamerton and I (1956) observed that the X and Y chromosomes were not associated at metaphase in several primary spermatocytes. Random assortment at anaphase should then lead to the formation of spermatid nuclei with *both* X and Y, and with *neither*. This could, and should, be checked by observations at second spermatocyte metaphase.

The results of Nowakowski, Lenz and Parada (1959) who found (inter alia) two instances of a colour-blind chromatin-positive Klinefelter son with non-colour blind parents, has been interpreted by Stern as showing evidence of non-disjunction in the maturation of the ova, either at the second division or (with recessive homozygosis) at the first division (1959). However, the possibility of non-disjunction at the first zygotic mitosis with doubling of the X chromosome carrying the colour-blindness gene received from a carrier mother is not rigorously excluded.

A similar argument can be put forward to explain the case described by Stewart (1959) of the colour blind XO Turner patient with a colour blind brother, non-colour blind father, and mother whose presumed heterozygosity was supported by anomaloscopic evidence of a minor defect. This case strongly suggests non-disjunction during spermatogenesis and fertilization by an O sperm, but again it does not provide rigorous proof, since non-disjunctional loss of a paternal X from a normally constituted XX zygote would give an XO cell, and we cannot be sure that its XXX partner would die and not contribute to an adult XXX/XO mosaic.

Although they fall short of full rigour, the cases just quoted do provide evidence in favour of non-disjunction at both oogenesis and spermatogenesis. But it would be wrong to fall into the error of associating non-disjunction at spermatogenesis with Turner's Syndrome and non-disjunction at oogenesis with Klinefelter's Syndrome. There is not the slightest reason to suspect that the complementary O ova and XY sperm would be any less viable than the XX ova and O sperm, for which the evidence for functional competence has just been given. It is merely that the XXY state permits one type of argument, the XO state another.

At a first examination we would expect non-disjunction of X and Y chromosomes at spermatogenesis to yield XY and O sperm in equal numbers, and consequently a one-to-one ratio of XXY and XO zygotes arising from this cause. Similarly, non-disjunction of the X-chromosome pair during maturation of the oocytes would lead to the formation of XX and O ova, and hence to the appearance of XXX, XXY, XO and YO zygotes, again in equal numbers. There should therefore be a near equality in the overall frequency of XXY and XO zygotes. However, the general experience seems to be that patients with Turner's syndrome are much less frequent than cases of Klinefelter's Syndrome, (Prader *et al.*, 1958) and this is supported by the wide disparity between the frequencies of

newborn apparent females that were chromatin-negative (none among 1804), and of newborn apparent males that were chromatin-positive (5 among 1911), as determined by Moore (1959). It is premature to consider in detail reasons for this discrepancy when the frequencies themselves are very imperfectly known, but obvious possibilities are, differential mortality of the zygotes *in utero*; differential maturation or fertilizing capacity of the alternative sperm types (compare Braden 1958); and possibly an inequality in the frequency of XX and O ova as a consequence of the asymmetry of the maturation divisions in the oocyte.

I have said that in addition to the XXY and XO zygotes, XXX and YO zygotes were to be expected. The first of these (XXX) has very recently been identified (Jacobs et al. 1959). The patient is a mentally sub-normal woman whose most interesting feature is the presence of *two* sex chromatin bodies in most of the nuclei seen in a buccal smear preparation. Formally the case is equivalent to the 'superfemale' *Drosophila* (Morgan, Bridges and Sturtevant 1925) but there is no exaggeration of secondary sexual characters in this patient; on the contrary, they are rather underdeveloped. YO has not been identified. As in *Drosophila* it may well be lethal to the embryo.

Apart from the intrinsic interest and medical importance of the anomalies of sex development I have just discussed, the new findings provide vital information regarding the roles of the sex chromosomes in sex determination. In the *Drosophila* system the X chromosomes promote development in the female direction and the autosomes in the male direction, whereas the Y is inert developmentally, though necessary for fertility (Morgan, Bridges and Sturtevant 1925). This system has long been used as a model and it has often been tacitly assumed that it would apply to mammals and man. In the event, however, it appears that the human system shows closer formal ties with that in the plant *Melandrium* (Westergaard 1940). XXY is a sterile male in man; in *Drosophila* it is a fertile female. The human XO is a sterile female; in *Drosophila* it is a sterile male.

The new evidence shows that the human Y chromosome strongly promotes development in the direction of the masculine phenotype. This is at once apparent when we compare XX (normal female) with XXY (sterile male), and XO (sterile female) with XY (normal male): addition of a Y chromosome converts a potentially female type into one that is essentially male. In this connection it is of the greatest interest that XO mice have now been identified by Welshons and Russell (1959). They are females and, it would appear, normally fertile. Evidently in the mouse also the Y chromosome is necessary for male development. We may come to find that this is generally true of mammals, notwithstanding the few species in which XO males have been claimed to occur (see Matthey, 1949).

THE MECHANISM OF SEX DETERMINATION

The condition known as testicular feminization also requires mention since suggestions have been made that it may trace to a gross chromosomal defect (Petterson and Bonnier 1937, Danon and Sachs 1957, Taillard and Prader 1957). A number of pedigrees showing hereditary transmission of this condition have

been published (see Taillard and Prader 1957). The striking features are that transmission is solely through the female sex and that there is a deficiency of normal males in the affected sibships. The affected individuals are essentially female, with well-developed secondary sexual characters, but absence or deficiency of axillary and pubic hair. The external genitalia are female, but atrophic testes are present. These are sometimes retained within the abdominal cavity but are more usually present in bilateral inguinal hernias. Sex chromatin is absent. Chu and Grumbach (unpublished) have examined the chromosomes of one patient exhibiting this condition and found no evident difference from those of a normal male. The same result was obtained independently by Harnden (in press) using skin cultures from one of two affected sisters. We must therefore reject gross chromosomal abnormality as a possible cause of this condition. It could be determined by a genetic sex-limited autosomal recessive or by a sex-linked recessive (Grumbach and Barr 1958). It might be possible to discriminate between these possibilities by relating the appearance of the condition to the inheritance of colour blindness in the affected families.

Recently Hungerford (1959) has reported briefly his finding of chromosomes indistinguishable from those of a normal female in cultures established from peripheral blood leucocytes of a true hermaphrodite, a Negro aged 12. He concludes "Thus cases of intersexuality in humans may involve mechanisms other than aberrations in the number of sex chromosomes". If the first word were omitted this statement would be quite unexceptionable. So much is evident from the cases of testicular feminization I have just discussed. But it is not a necessary conclusion from the evidence in his case since the very real possibility of mosaicism is not excluded.

Harnden (unpublished) has also examined the chromosomes of a true hermaphrodite in conjunction with Dr. C. N. Armstrong. Accounts of this patient have been published (Armstrong 1955, Armstrong et al. 1957). Harnden established cultures from skin biopsies taken from both sides of the body and each was divided into two, so that there were four cultures in all. The vast majority of cells in all cultures were apparently normal XX cells with 46 chromosomes, but in one of the cultures (only) there were some 20% of cells in which an abnormal chromosome was present, suggesting a reciprocal translocation. The change, it would seem, must have arisen during culture. In this case also the possibility of chromosomal mosaicism involving the gonads cannot be excluded. To get an undisputable solution to such problems it would be necessary to establish cultures from the organs most directly concerned, the gonads themselves.

CONGENITAL ABNORMALITIES

News that Lejeune, Gautier, and Turpin (1959a) in Paris had discovered an extra small acrocentric chromosome in tissue cultures established from several mongoloid imbeciles reached us at Harwell just 4 days before we were able to examine bone marrow preparations (in conjunction with Professor L. S. Penrose and his colleagues) from a remarkable patient who exhibited the stigmata

both of mongolism *and* Klinefelter's Syndrome (chromatin positive). We found that this patient had 48 chromosomes regularly, including an extra small acrocentric as well as the expected two X chromosomes and a Y (Ford et al. 1959). Independent confirmation that an extra chromosome was present in mongoloids also came at the same time from Edinburgh (Jacobs et al. 1959). Subsequently the French group added a further 4 cases to their original 6 (Lejeune et al. 1959b). Fraccaro has informed me that the group at Uppsala have also found the extra chromosome to be present in the two examples they have studied. There is thus a total of 19 cases of mongolism that have been examined without exception to the rule that an extra small acrocentric is present. Evidently, mongolism is a primary trisomic condition, the first that is viable to be identified in mammals. (Frankhauser and Humphrey (1950, 1954) obtained some trisomic larvae in the diploid by triploid *Ambystoma* crosses, but few survived long and all were malformed.)

We must suppose that autosomal non-disjunction at spermatogenesis or oogenesis is the most likely source of the additional chromosome, with a weighting in favour of oogenesis in view of the well-known maternal age effect in mongolism (Penrose 1954). The simple explanation of this relationship would then be that ageing increases the likelihood of non-disjunction during maturation of the ova. It has been claimed that the mothers of mongols as a group can be discriminated from other mothers by certain physiological tests (Ingvar Ek and Jensen 1959), and the authors assert that a genetic hypothesis alone is insufficient. Their conclusion is that "a certain combination between the genotype of the foetus, the endocrine disposition of the mother, and exogenous stress-releasing factors could be the pre-requisite for mongolism". Accumulated experience of trisomy in plants and *Drosophila* (triplo-IV) shows that each individual trisomic has its own characteristic phenotype, and it would be quite contrary to this experience to suppose that in certain circumstances the phenotype might not be expressed. A more likely explanation of the influence of maternal factors in mongolism would be through an increase in the chance of non-disjunction at oogenesis, *not* through direct influence on the development of the foetus. The latter could be expected to influence the degree of expression of the condition, but hardly whether or not it was expressed at all.

After the discovery that mongolism was a primary trisomic condition speculation inevitably ran to the possibility of further examples. Twenty-two different types are of course theoretically possible and it is likely that zygotes of all 22 kinds are formed from time to time. However, the inviability of triplo-II and triplo-III in *Drosophila melanogaster*, the failure of most trisomic *Ambystoma* larvae to survive for very long, and the fact that, notwithstanding the millions of laboratory mammals that have been bred, no primary trisomic has ever been reported, or (so far as I am aware) even suspected, makes it prudent to assume that most of the human primary trisomic zygotes would be inviable. It is significant that the extra chromosome of mongolism is one of the two smallest members of the human set and represents a duplication only of about

TABLE 1. HEREDITARY CONDITIONS THAT HAVE BEEN EXAMINED CYTOLOGICALLY BUT IN WHICH NO EVIDENCE OF CHROMOSOMAL ABNORMALITY HAS BEEN FOUND

Condition	Authority
Acrocephalosyndactyly	1, 3
Arachnodactyly (Marfan's Syndrome)	1, 2, 4
Chondrodystrophy	1
Crouzon's disease	1
Epiloia	3, 4
Gargoylism	1
Gaucher's disease	2
Hypopituitary dwarfism	4
Juvenile amaurotic idiocy	1
Laurence-Moon-Biedl syndrome	1
Little's disease	4
Osteogenesis imperfecta	1
Phenylketonuria	2

(1) Böök, Fraccaro and Lindsten (personal communication). (2) Tjio, Puck and Robinson (1959). (3) Harnden (unpublished). (4) Ford (unpublished).

1/200th part of the whole. Trisomy of the longest autosome would represent duplication of about 1/25th part and would therefore be much more likely to cause a serious disturbance of gene balance.

Nevertheless some of the 22 types might be viable and result in live births; even survive into adult life and breed. For each a characteristic phenotype would be expected, with (if fertile), hereditary transmission in a manner mimicking a dominant gene. A number of possible conditions have now been examined, but in none has any evident departure from the normal set of 46 chromosomes been found. In table I a list is given of those at present known to me, together with some recessive conditions that have been examined and also found, as expected, to have apparently normal chromosomes.

In addition to these, Harnden, Briggs and Stewart (1959) have reported apparently normal chromosomes in cultures from 4 anencephalic foetuses, and Harnden, in conjunction with Penrose, has found no evidence of chromosome abnormality in cultures established from a hydatidiform mole.

Lejeune and Turpin (unpublished) however, have now found a second example of autosomal abnormality and the first of a new type. In tissue cultures established from a boy with multiple skeletal defects the cells contained only 45 chromosomes, one of which was clearly abnormal. The missing chromosome was one of the two smallest acrocentric chromosomes and it appeared that the greater part of this chromosome had been translocated on to the short arm of one of the three *longer* acrocentrics. Since precisely the same altered chromosome was identified in several independently established cultures there can be no question, in this instance, of origin during culture. Nevertheless the nature of this change suggests that it is a unique one and unlikely to be found again, except perhaps in other members of the same family. On the other hand there may be many more instances of multiple congenital abnormalities associated with different, but again unique, chromosome rearrangements awaiting discovery.

LEUKAEMIA

This is not the place to go into the problem of the relationship of chromosomal changes in neoplastic cells to the mechanism of carcinogenesis. However, the study of normal somatic and neoplastic cell populations is a legitimate field for cytogenetics and the bone marrow method was originally developed with the object of examining the chromosomes of human leukaemic cells (Ford et al. 1958). This was prompted by the discovery that a very high proportion of independently arising primary reticular neoplasms ("leukaemias") of the mouse consisted of mixed populations of cells differing both from the normal and from one another in respect of one or more of four cytogenetic features. 1) Variation in the chromosome count as opposed to virtual constancy in the normal reticular tissues. 2) Increase in the mode of the chromosome-count distribution from the normal 40 to a value in the range 41 to 50. 3) Presence of one or more morphologically altered 'marker' chromosomes as a constant, and sometimes highly individual, character. 4) Presence of primary structural changes in the chromosomes of some cells (Ford et al. 1958, Ford and Mole 1959).

In conjunction with Dr. L. G. Lajtha we have now examined the chromosomes in sternal marrow cells of ten leukaemic patients. Three of these cases were mentioned briefly in our original work on somatic chromosomes (Ford et al. 1959b). In one of them the modal count was 45 and included a minute fragment. Two of the remaining seven cases were clearly abnormal. In one of them the modal count was 48; in the other the modal count was 46 including a minute fragment. We have recently recorded instances of spontaneous tumours of the Chinese hamster in which the chromosome count was either always, or almost always 22 (the diploid number of the species), but in which one or more characteristic morphologically altered chromosomes were present (Unpublished work). It is therefore necessary to be alert to the possibility of similar instances appearing among the human leukaemias. Needless to say the definition of such changes will inevitably be much easier in the hamster with its much lower number of chromosomes. To identify similar changes in the chromosomes of human marrow cells will require preparations of the very highest technical standard.

SOME TASKS FOR THE FUTURE

One of the obvious requirements for the future is an accepted nomenclature for the individual human somatic chromosomes, and since there is already such good general agreement regarding the standard karyotype this should not take too long to achieve. Agreement, when it is reached, should aid, and perhaps stimulate, comparison between the chromosome sets of different ethnic groups. Since there is evidently no ban to the fertility of the offspring of mixed marriages, major changes which would be detectable in the somatic chromosomes, such as unequal reciprocal translocations and pericentric inversions, are not to be expected—except perhaps as isolated and sporadic occurrences that would be quickly eliminated in view of the consequent diminished fertility. But it is not inconceivable that some ethnic groups may be differentiated by duplication—deficiency changes involving heterochromatic regions, particularly of the X and Y

chromosomes, with an associated observable difference in overall chromosome length or arm ratio. In this connection the evidence of structural polymorphism of one of the chromosomes found by Rothfels and Siminowitch (1958) in cultures of Rhesus monkey tissue should be recalled.

The study of the chromosomes in human intersexual conditions has made a good beginning and it is probable that the main outlines are already complete. However, there is much detail to be filled in and the possible role of mosaicism in contributing to their rather bewildering variations of expression remains to be evaluated. Observations on the chromosomes of other types of congenital abnormalities should continue also, and undoubtedly will. In a matter like this it is quite impossible to peer into the future and foresee what it holds.

A quite different approach and one that has not received the attention it deserves is the study of meiotic chromosomes in testicular preparations. As I have already said, these could be of particular value in assessing the frequency of nondisjunction, particularly of the sex chromosomes and the small autosomes, with its obvious relevance to the sex anomalies and mongolism. Another aspect of such studies, of course, is the possibility of identifying a chromosomal basis for cases of infertility. Reciprocal translocations and both paracentric and pericentric inversions would be expected to reduce fertility through the production of gametes with unbalanced chromosome sets. It is well known that reciprocal translocations in the mouse reduce litter size to about 50%, the precise level being a property of the individual translocation (Carter et al. 1955). No undoubted instance of inversion has been recorded in experimental mammals but on the basis of the evidence in plants a varied diminution of fertility would be expected depending upon the length of the inverted segment and the frequency of chiasma formation within it (Darlington 1937). In human matings where one partner was heterozygous for a translocation or an inversion an erratic sequence of abortions and live births would be expected. From time to time I have made enquiries as to whether such instances were known, but without success. If the male were the heterozygous partner there would be no reason to suspect a lowered sperm count or altered sperm morphology. Snell was able to demonstrate many years ago in the mouse that chromosomally unbalanced gametes could be functionally efficient. His method was to set up a mating between two appropriately marked translocation heterozygotes, and then to recover exceptional progeny that could only have developed from chromosomally balanced zygotes arising from the fertilization of unbalanced ova by complementary unbalanced sperm (Snell 1946).

The maps of certain pachytene chromosomes that have been prepared by Schultz and St. Lawrence (1949) and Yerganian (1957) also require mention. Further development of their methods and extension of the work to include dominant congenital abnormalities would be welcome and might reveal deficiencies that would not be detectable in the somatic chromosomes. But it would have to be a labour of love and there would be no sure reward. All work on meiosis in the seminiferous tubules however suffers from the very severe disadvantage that

biopsy specimens can only be taken where there are independent clinical or surgical indications.

The study of human cytogenetics has now attained the stage that the Drosophilists had reached about 40 years ago. We can hardly expect an advance as rapid and dramatic as they achieved in the twenties and thirties, particularly after the rediscovery of the salivary gland chromosomes. Nevertheless there is now a great interest on the part of the medical profession and we can look forward to the screening of large numbers of individuals, at least in Western Europe and North America, and to a steady increase in our understanding of the relationship of chromosomal abnormalities to congenital disease, to neoplasia, and to general human biology.

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Note added in proof. The value of reviews such as this is largely bibliographical, and since the subject is developing so rapidly references are given below to a number of publications that were accidentally omitted from the main bibliography or appeared after the manuscript was submitted. Among them is a full report by Hungerford et al. on the true hermaphrodite discussed in page 110. The authors consider mosaicism to be unlikely, but on the evidence presented, XX/XXY mosaicism involving gonads but not bone marrow cannot yet be rigorously excluded.

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