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The role of chromosomes in the characterisation of human neoplasms

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Abstract

Observations reported in the literature, since 1959, have been assessed and analysed for chromosome number per cell (ploidy levels) and karyotype (number of chromosomes per classification group, structure and DNA content of individual chromosomes).

Measurements of chromosome size are presented, to show how the genetical balance of chromosomal types within a karyotype can be determined in pseudodiploid and aneuploid cells.

These findings are discussed in relation to the role of chromosome anomalies in cell metabolism, malignant transformation and Boveri's theory that chromosome anomalies cause cancer. Objections to Boveri's Theory arise from the occurrence of (a) certain aneuploid pathological conditions and cell lines that are non-malignant, and (b) diploid primary and secondary malignant neoplasms with apparently normal karyotype. However, studies on families have indicated that syndromes due to chromosome anomalies may predispose cells for malignant transformation because of their metabolic instability; and the possibility remains that apparently diploid neoplasms may be pseudodiploid (and await further techniques for their detection).

Evidently, chromosome anomalies have a metabolic effect in neoplasms and are of considerable importance in aiding the progression of neoplasms towards greater malignancy. The selective advantage of cell variants results in the evolution of characteristic ploidy levels of tumours at different sites.

Chromosome studies may aid the diagnosis of malignancy in some neoplasms, where striking changes in the chromosome constitution is directly associated with their capacity for invasion.

Résumé

L'auteur fait une revue critique et analytique de la littérature, à partir de 1959, concernant le nombre de chromosomes par cellule (degré de ploïdie) et le caryotype (nombre de chromosomes par catégories, structure et contenu en ADN des chromosomes).

Des mensurations des chromosomes sont présentées, afin de montrer comment l'équilibre des types chromosomiques, dans le caryotype, peut être déterminé, pour les cellules pseudo-diploïdes et aneuploïdes.

Ces données sont discutées en fonction du rôle des anomalies chromosomiques dans le métabolisme cellulaire, la transformation maligne et la théorie de Boveri, selon laquelle ces anomalies sont la cause du cancer. Des objections à la théorie de Boveri proviennent des observations suivantes:

a. l'existence d'aneuploïdie dans certaines conditions pathologiques et dans des lignées de cellules non cancéreuses;

b. l'existence de tumeurs malignes, primitives et secondaires, avec un caryotype diploïde normal. Néanmoins, des études de certaines familles ont montré que des syndromes liés à des anomalies chromosomiques peuvent prédisposer les cellules à la transformation maligne, à cause de leur instabilité métabolique; la possibilité persiste que des cancers apparamment diploïdes pourraient être pseudodiploïdes (de nouvelles techniques seraient nécessaires pour leur détection).

Les anomalies chromosomiques ont, de toute évidence, un effet métabolique dans les néoplasies et participent, defaçon considérable, à la progression de celles-ci vers une plus grande malignité. L'avantage sélectif de ces mutations résulte en l'évolution des niveaux caractéristiques de ploïdie des tumeurs, en différentes localisations.

Les études cytogénétiques peuvent apporter une aide pour le diagnostic de malignité dans certaines tumeurs où des modifications marquées de la constitution chromosomique sont directemenst associées à leurs capacités invasives.

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Zusammenfassung

Der Verfasser hat die seit 1959 in der Litteratur mitgeteilten Beobachtungen kritisch ausgewertet in Bezug auf die Chromosomenzahl pro Zelle (Ploïde-Grad) und auf den Karyotyp (Zahl der Chromosomen pro Klassifikationsgruppe, Struktur derselben, ADN-Gehalt der einzelnen Chromosomen).

Die Chromosomengrösse wurde bestimmt, urn zu zeigen, wie das genetische Gleich-gewicht der Chromosomentypen innerhalb des Karyotyp erhalten wird und zwar sowohl in pseudodiploiden als auch in aneuploiden Zellen.

Diese Ergebnisse werden in Bezug auf die Rolle der chromosomalen Anomalieen bei Zellstoffwechselstörungen, bei bösartiger Entartung und in Bezug auf Boveri's Theorie über den Einfluss van chromosomalen Abweichungen auf die Krebsentstehung besprochen. Wiedersprüche gegen Boveri's Theorie ergeben sich aus der Existenz von (a) gewissen pathologischen aneuploiden Syndromen und Zellinien, welche nicht bösartig sind und (b) aus der Existenz van diploiden primären und sekundären bösartigen Tumoren mit anscheinend normalem Karyotyp. Trotzdem scheinen Untersuchungen von Familienstamm-bäumen zu zeigen, dass chromosomale Abweichungen Zellen zu bösartiger Entartung prädisponieren, wahrscheinlich auf Grund der Instabilität ihres Stofwechsels; die Möglichkeit bleibt aber offen, dass scheinbar diploide Neoplasmen in Wirklichkeit pseudodiploid sind und dass in Zukunft feinere Untersuchungsmethoden angewandt werden müssten.

Es erscheint wahrscheinlich, dass chromosomale Abweichungen den Stoffwechsel der Tumoren beeinflussen und von grosser Wichtigkeit fur die progressive Malignität der Geschwulste sind. Selektive Vorzüge von gewissen Zellvarianten führen zu der Entwicklung von charakteristischen Ploidiegraden in verschiedenen abschnitten desselben Tumors.

Die Untersuchung der Chromosomen kann der Diagnose der Bösartigkeit gewisser Tumoren zu Gute kommen und zwar insbesondere dort, wo auffallende Veränderungen der chromosomalen Zusammensetzung direkt mil der Invasionsfähigkeit in Zusammenhang zu stehen scheinen.Der Verfasser hat die seit 1959 in der Litteratur mitgeteilten Beobachtungen kritisch ausgewertet in Bezug auf die Chromosomenzahl pro Zelle (Ploïde-Grad) und auf den Karyotyp (Zahl der Chromosomen pro Klassifikationsgruppe, Struktur derselben, ADN-Gehalt der einzelnen Chromosomen).

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1. Introduction

The importance of chromosomes in the characterisation of neoplasms depends on the role that they play in malignant transformation and progression of tumours. The role of chromosomes in these processes is still not fully understood although many advances have been made since 1914, when Boveri first put forward his chromosome mutation theory for the cause of cancer, thereby stimulating many experimental investigations on tumour mitosis and chromosome patterns [1].

Knowledge of chromosome patterns has advanced with improvements in technique, notably the hypotonic treatment for spreading chromosomes [2] to allow accurate counting and analysis. With the exception of bone-marrow, actively dividing cells are not readily accessible for direct examination of chromosomes. For this reason, short term tissue culture techniques have also made a tremendous contribution to the study of human chromosomes by creating conditions conducive to cell division in tissues from foetuses, biopsies from surgical operations, skin [3,4] or blood [5].

Since the normal chromosome number of human cells ($2n = 46$) was not established before 1956 (Tjio and Levan [6] studied foetal lung cultures), all previous counts in normal and tumour cell populations are regarded as inaccurate, although they clearly showed general trends in ploidy level.

In order to assess the significance of chromosome anomalies in tumour cell populations it is necessary to make a comparison with the extent of chromosome variations in normal tissues of different persons.

2. Chromosome number

Variations deviating from the diploid number $2n = 46$, have been found in both normal and tumour tissues:

(i) *Differentiated tissues* – (Normal and non-malignant pathological conditions).

Levan [7] reviewed the literature for eighteen human tissues and found that the cells were predominantly diploid, ranging from 66% diploid (marrow) to 100% diploid (in lung). Aneuploid cells usually occur in most carefully examined tissues, due to errors in cell division which probably do not proliferate because abnormal clones are not normally found [8].

The incidence of aneuploidy in somatic cells may be related to age: Jacobs *et al.* [9] found a significant increase in aneuploidy of sex chromosomes with increasing age.

A variety of aneuploid individuals have been discovered in human populations. The first one to be found had 47 chromosomes [10]. Subsequently many aneuploid congenital deviants have been described, involving abnormal numbers of sex chromosomes, such as XO, XXX, XXXX and (or) other chromosomes [11,12]. The largest aneuploid number was first found in a boy with 49 chromosomes [13]. Other cases have been found to be mosaics of diploid and triploid [14] or diploid and aneuploid cells of different aneuploid numbers [15].

Evidence has accumulated to suggest that at least some forms of aneuploid congenital conditions may have a predisposition for the development of neoplasms that may be triggered off by some other factors. Stewart [16] found that acute leukaemia occurred nearly eighteen times more frequently in Down's syndrome (mongolism) than in the general population. In addition, it has been suggested that some genes may affect chromosome non-disjunction, causing the occurrence of several types of aneuploid individuals and leukaemia in the same families [17,18]. Hauschka *et al.* [19] found familial non-disjunction without leukaemia, possibly because offspring died too soon from other causes.

(ii) *Chromosome number in human neoplasms* – In cell populations, chromosomes are an indication of genetic stability or variability. Levan [7] tabulated 40 human cell lines, cultured *in vitro*, half derived from normal tissue and half from cancers. Both had a similar heteroploid chromosome distribution. The highest stemline for a cultured line was 133 whereas no human tumour *in vivo* was known to have a higher stemline than 92. Most human tumours had stemlines in the diploid-triploid range.

Hauschka [20] found that out of 73 malignant human ascites tumours, nine (12%) were diploid or pseudodiploid and 64 (88%) had aneuploid modes; on the other hand 13 benign effusions all had diploid or pseudodiploid modal chromosome numbers. A further analysis of 74 tumours (including 13 types) examined directly (without colchicine or culturing) indicated that 69 (93%) had aneuploid modes, while 5 tumours (7%) had a diploid modal chromosome number. Thirty-four cases of leukaemic bone marrow (63%) out of 56 also had aneuploid or pseudodiploid modes while 22 cases (37%) had apparently normal diploid modes. Hauschka [20] concluded that "Leukoses, on the whole exhibit a near diploid trend whereas the patterns of neoplasms from other tissues extend over the entire range of viable chromosome compliments".

Ishihara *et al.* [21] described 20 cancer effusions which all had abnormal modal chromosome numbers but these may not reflect those of the original tumour.

Makino *et al.* [22] found that many tumours from different sites had characteristic modal chromosome numbers. The majority of these tumours were primary tumours. Table 1 shows the ploidy levels of tumours at six sites, calculated from the data of Makino *et al.* It can be seen that the most frequent chromosome numbers are found at different ploidy levels in the various tumours e.g. the gastric carcinomas are mainly hypotriploid $(3n - x)$ whereas rectal carcinomas are mainly distributed in the hypo-to hyper-diploid range and also in the hypo-tetraploid level. There is considerable evidence to suggest that the different ranges of chromosome numbers found in the various neoplasms represent environmental selection of cell variants in the evolution, or progression, of the tumour cell populations towards greater malignancy at the various sites [23]. A general conclusion concerning a characteristic ploidy mode in mammary, ovarian and ascites hepatoma cannot be reached because too few cases were examined.

Very few studies have been made of very early cancer, or premalignant neoplasms, to obtain chromosome data more closely related to the nature of the mechanism of malignant transformation. Information with a bearing on this question has been obtained from studies on cervical lesions [24–27] and on primary tumours of the bladder [28]. Heteroploid chromosome numbers were found in the premalignant lesions of the cervix and premalignant bladder tumours; however, diploid modes were found at these sites. In the cervix the most striking difference in chromosome number was found between dysplasia (with a main range of 40–55) and carcinoma *in situ* (with a range of 40–100) so that considerable aneuploidy was found to occur some time before the onset of malignancy [26] and did not accompany the development of the capacity to invade. It is possible that genetic changes conferring the capacity to invade may remain latent until endocrine changes in the host at menopause enable the transformed cells to invade.

In the bladder the situation seems clearer. Lamb [28] found that extensive changes in chromosome number coincided with the capacity to invade. Nine benign bladder tumours were predominantly in the diploid range whereas 21 malignant bladder tumours had chromosome numbers ranging from 40 to more than 100 without any common modal ploidy level (see graph Fig. 1). It seems

Table 1
Ploidy levels (x = numbers 1–11)

	$(2n-x)$	$(2n)$	$(2n+x)$	$(3n-x)$	$(3n)$	$(3n+x)$	$(4n-x)$	$(4n)$	$(4n+x)$	Total cells
	%	%	%	%	%	%	%	%	%	
Gastric carcinoma (30 cases)	4.2	8.7	14.3	41.0	3.1	18.2	5.1	0.6	4.6	1282
Uterine carcinoma (13 cases)	6.1	1.3	35.8	23.6	2.2	17.9	4.4	0	8.7	229
Rectal carcinoma (4 cases)	20.0	20.0	18.7	11.2	0	3.7	20.0	0	6.2	80
Mammary carcinoma (2 cases)	0	0	8.0	44.0	0	40.0	4.0	0	8.0	25
Ovarian carcinoma (2 cases)	4.1	38.8	5.8	1.6	0	0.8	34.7	2.4	11.6	121
Ascites hepatoma (1 case)	0	0	0	5.0	5.0	85.0	5.0	0	0	20

Calculated from the data of Makino *et al.* [22].

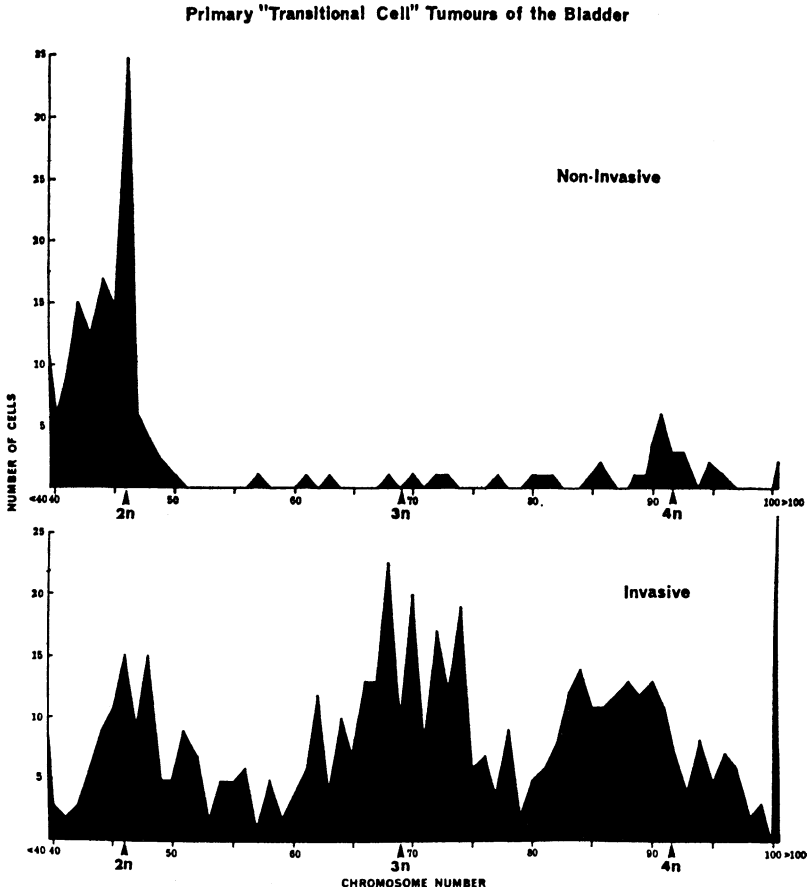

Fig. 1. Histogram of chromosome number distributions in primary 'transitional cell' tumours of the bladder, including total cells counted in nine non-invasive and 21 invasive tumours (by courtesy of D. Lamb).

possible to diagnose malignancy in terms of the chromosomes in this situation because over two thirds of the cells in the invasive tumours had chromosome numbers in excess of the diploid range (i.e. from $3n-x$ to $4n+x$). The wide spread in these numbers without a characteristic mode does not rule out the possibility that the primary transformation occurred in the diploid cells, the aneuploid cells being rapidly developing secondary variants in tumour progression. Note that the frequency of the diploid range is as great as the other types (Fig. 1).

The occurrence of primary malignant tumours with diploid modal chromosome numbers shows that aneuploidy is not an universal requirement for malignant transformation. In addition, many diploid stem lines have been reported in primary and even secondary tumours [20,23]. However, chromosome number is an inadequate criterion of the normality of a chromosome set. Until the chromosomes of cells with a diploid chromosome number have been analysed in detail it cannot be supposed that these cells do not have any chromosome anomaly. The distinction between normal and pseudodiploid karyotypes largely depends on our knowledge of the normal range of variation in chromosome structure (shape, size, cytochemistry), the size of the anomaly and the accuracy of the technique used.

3. Karyotype analysis and the recognition of chromosome mutations

The standard system for the identification of individual chromosomes on the basis of chromosome length and centromere position clearly distinguished seven groups of chromosomes [29,30]: denoted A, B, C, D, E, F and G. Some or all of the chromosome pairs in groups B, C, D, E, F and G could not be distinguished with certainty by the existing morphological criteria. In 1963, this situation remained largely the same except for identification of the Y chromosome, by its morphology and the X chromosome, by tritiated thymidine [31]. The human karyotype has been found to be a stable pattern consisting of the same number of groups (characterised by their chromosome number and morphology) in all normal cells of normal individuals (with 46 chromosomes). This forms the first level for the recognition of karyotype anomaly:

(i) *Chromosome groups* – Male and female cells contain the same number of chromosomes per group in groups A(6) B(4) D(6) E(6) F(6) but differ in groups C and G: Male C(15) G(5), female C(16) G(4), owing to the difference in sex chromosome pairs.

Table 2 shows chromosome group analysis of pseudodiploid cells in primary human neoplasms. The analysed cells in each neoplasm (except the Burkitt tumour) have different abnormal combinations of chromosomes, indicating that they were not directly derived from the same parent cell. It is not known whether they arose from diploid cells or indirectly by non-disjunction of tetraploid or aneuploid cells. However, cells with 46 chromosomes certainly have a selective advantage in these neoplasms because they form the mode. Structural chromosome abnormalities (especially 'marker' chromosomes) give clues concerning the origin of some of these cells.

(ii) *Morphological anomalies* (shape and size) Gross mutations in chromosome size and shape (according to centromere position), due to deletion, inversion or translocation, are readily distinguishable visually as marker chromosomes. Table 2 shows the frequency of marker chromosomes in chromosome groups of pseudodiploid tumour cells. The occurrence of the same marker chromosome in several cells strongly suggests that they originated from the same parent cell (i.e. belong to the same clone), even if these cells have different chromosome group combinations or have different chromosome numbers [25–27,32,33].

In the Burkitt primary tumour, 23 pseudodiploid cells (modal number) were found with the same chromosome group and marker anomalies indicating that they were derived from the same cell. Furthermore, the chromosome mutation involved, probably occurred in a diploid cell because it can be interpreted as an AC reciprocal translocation, forming two 'markers'.

Fig. 2 shows 'double-minute' fragment like chromosomes which may be small rings. They were found by Cox [34,35] in 78 per cent of the cells from a neuroblastoma, and 60 per cent of rhabdomyosarcoma cells. These marker chromosomes occurred in both diploid and aneuploid cells. The origin of the minute chromo-

Table 2
Pseudodiploidy

Material	No.cases examined	Number of chromosomes per group in individual cells							Refs.
		A	B	C	D	E	F	G	
Normal female cells		6	4	16	6	6	4	4	
Dysplasia	1 (H.182)	4	4	20	6	5	4	3	[26]
		6	5**	16	6	6	4	3	
		7	3	18	6	6	3	3	
Carcinoma *in situ*	1 (H.210)	6**	4[a]	16	6	6**	4	4	
		6[a]	5**	15	6	6	4	4	
		6	5[a]	13	6	7	4	5	
		7[a]	5[a]	15	6	5	5	3	
	1 (Case 1)	7	4	16	6	6	3	4	[25]
	1 (Case 7)	8	4	14	6	6	2	6	
Carcinoma of the cervix	1 (H.70)	6	2	16**	3[a]	6	4	7 (all[a])	[49]
Carcinoma of the corpus uteri	1 (H.96)	6[a]	4	16	6	6	4	4	
		6	4	16[a]	6	6[a]	4	4	
		7[a]	4	17	5	5	4	4	
Normal male		6	4	15	6	6	4	5	
♂Burkitt tumour (23 cells)	1	5	5[a]	15[a]	6	6	4	5	[33]

[a] Grossly abnormal chromosome.

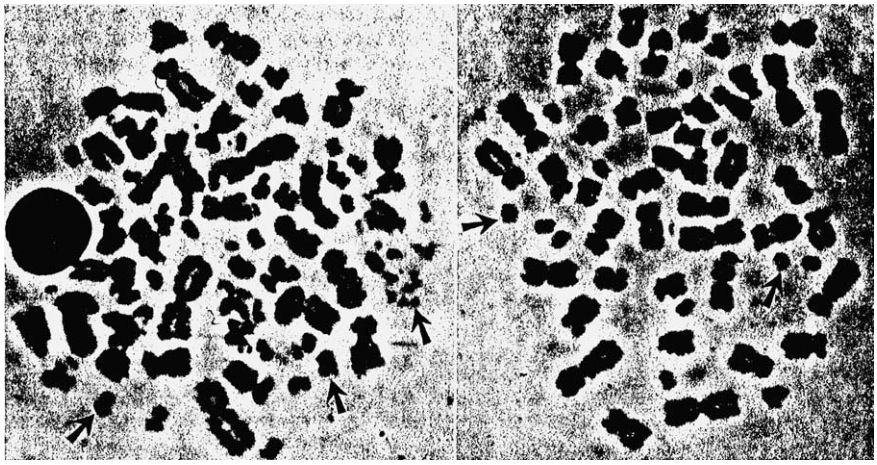

Fig. 2. Two cells from a neuroblastoma showing a range of 'double-minute' fragments (by courtesy of D. Cox).

somes is not known, nor their role in the progression of these tumours. Lubs [36] has also found similar marker chromosomes in a glioma.

Other chromosome anomalies may also occur in primary tumours but require the development of new techniques in order to distinguish them. New methods have been developed for the measurement of chromosome size including automatic planimetry of photographic areas [37]. HeLa cells and chronic myeloid leukaemia cells were used as test systems for measurements on abnormal karyotypes. The chromosomes of the HeLa cells examined were about half normal size, suggesting that they were composed of only half the usual number of strands, i.e. a mutation in the polynemy level of the chromosomes, yet retaining the same relative proportion of substance per chromosome.

Fig. 3 illustrates one such HeLa cell (with 51 chromosomes) which is compared with measurements of normal female cells in Table 3. Note the differences in the distribution of chromosomes per group. The comparative differences in percentage total karyotype, in terms of chromosome number, give a distorted representation of the distribution of chromosome material in

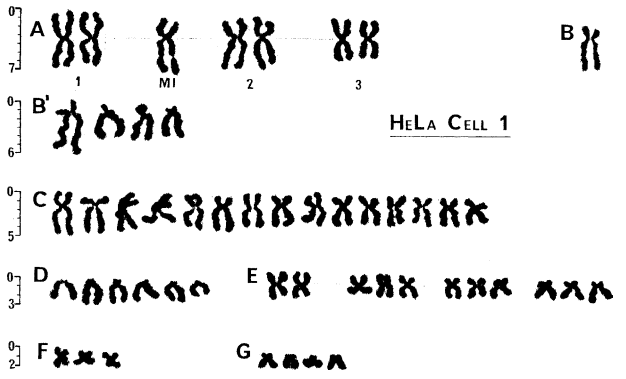

Fig. 3. Aneuploid karyotype of a HeLa cell with 51 chromosomes, showing an abnormal distribution of chromosomes per group and structurally altered 'marker' chromosomes (M′ and B′).

the abnormal cell, because of individual chromosome size differences between the groups. It was previously shown that chromosome area measurements are related to the distribution of DNA in a karyotype and hence the distribution of genes [37]. The genetic expression of an abnormal karyotype may well depend not only on what genes are present but in what amount and whether there is a balance of chromosomes of different types. Chromosome size measurements can indicate the proportional contributions of individual chromosomes and chromosome groups to the genome.

Large scale human population chromosome studies are needed in order to obtain valuable control data on the normal range of variation and to determine whether any anomalous karyotypes are associated with predisposition to cancer ontogeny. For this reason the normal tissues of cancer patients need to be examined in addition to the tumour. Thus Gunz *et al.* [38] found a deletion of the short arm of a chromosome 21 (designated Ch^1) in two families in which some of the carriers of this anomaly have lymphoid leukaemia.

Other examples are known that suggest the influence of recessive genes (i.e. on a sub-chromosomal level) on predisposition to neoplasia. Lele *et al.* [39] found a deleted chromosome No. 15 in a retinoblastoma and suggested that there is a recessive gene promoting this type of tumour on the long arm of a normal chromosome No. 15. Another possible example is a rare syndrome characterised by congenital erythema with an apparently recessive mode of inheritance [40]. Cultured cells had a high frequency of chromosome breakage; and three out of 19 cases developed neoplasms.

Although some chromosome anomalies may not be detectable by light microscopy, it is desirable to detect all possible anomalies to the utmost limitations of microscopy. These limitations have not yet been reached. Attempts have been made to obtain more accurate measurements of chromosome substance by determining their DNA content.

Table 3

Chr. groups	Normal female cells (46 Chrs)			HeLa cell (51 Chrs)		
	Number of Chrs	Percentage total karyotype		Number of chrs	Percentage total karyotype	
		Chr. number	Chr. area		Chr. number	Chr. area
A	6	13.0	22.7 ± 1.06	7[a]	13.0	22.7
B	4	8.7	12.6 ± 0.49	5**	10.9	13.3
C	16	34.8	38.2 ± 1.40	15	32.6	33.7
D	6	13.0	9.9 ± 0.39	6	13.0	8.5
E	6	13.0	8.5 ± 0.28	11**	23.9	15.7
F	4	8.7	4.1 ± 0.19	3	6.5	2.8
G	4	8.7	2.8 ± 0.34	4	8.7	3.4

[a] Grossly abnormal chromosome.

(iii) *DNA content per chromosome* – Direct methods of ultramicrospectophotometry and ultramicrointerferometry of individual Chinese hamster chromosomes have formed a basis for further studies on human chromosomes, when some preliminary problems have been overcome [41].

Rudkin *et al.* [42], using a photographic method, found that about 40% of the DNA of a chromosome No. 21, would have been lost in the formation of the Ph[1] chromosome of chronic myeloid leukaemia cells. More accurate methods are needed in order to determine whether the deleted portion of a chromosome 21 has been translocated to another part of the same karyotype.

In order to recognise the origin of translocations it is necessary not only to be able to distinguish the abnormal chromosome but also to determine the origin of its component parts, by developing techniques for linear differentiation of chromosome structure.

4. Discussion and conclusions

4.1. Chromosomes and metabolism

Since DNA is mainly responsible for the chemical basis of heredity and forms a major component of chromosome structure, chromosome anomalies are capable of modifying cell metabolism. Since some genes only express themselves in differentiated tissues, not all chromosomal anomalies may express themselves physiologically in undifferentiated cell proliferation. It is therefore important to determine which chromosome anomalies affect cell growth and reproduction. Some evidence on this question has been obtained by correlated studies on cytological, cytochemical and biochemical levels for the same population of cells. Cloned cell lines from Chang liver [43] and HeLa [44,45] have demonstrated the metabolic effect of different karyotypes on the activity of several enzymes. De Carli *et al.* [44] showed that short acrocentric chromosomes (Group G) had the greatest effect on alkaline phosphatase activity and probably carry the genes controlling this enzyme.

More studies of this kind are needed to determine the role of chromosome groups and individual chromosomes in cell metabolism.

4.2. Chromosome anomalies and malignant transformation

An anomalous chromosome pattern, common to all malignant tumours, has not been found; so that widely different patterns may result in malignant transformation (or are secondary products of the change.) Anomalous chromosome numbers of chromosomes per cell are not restricted to malignant cells. However, chromosome heteroploidy of cell populations has been found to be associated with malignancy in some primary tumours and in tissue culture, in some cases, and forms a basis for diagnosing malignancy [26]. More studies are needed on premalignant conditions and early neoplasms. The change from diploid chronic-leukaemia to acute leukaemia may be equivalent to malignant transformation and could contribute to this question.

Hayflick and Moorhead [46] showed that diploid cell strains have only a limited life in tissue culture conditions, malignant transformation being necessary in order to attain the capacity for indefinite growth *in vitro.* Further studies on chromosomal and biochemical changes involved in cell transformation *in vitro* can also make a valuable contribution. The malignancy of cultured hamster cells has been assessed by cultivation in Chinese hamster cheek pouches, chorioallantoic membrane of chick embryos and by injection into last stage cancer patients.

Evidence from late stages of primary tumours and in secondary tumours and heteroploid cell cultures with the characteristic stem lines, may not be related to the primary malignant transformation : only showing the selected secondary cell varients that arose during tumour progression towards greater malignancy.

Cells with a chromosome number of 46 are always found in primary tumours. However, since only a small number of tumours containing diploid cells have been

karyotyped in detail, it is not yet known whether pseudodiploidy is a general phenomenon in malignant transformation. Studies on nucleolar organising chromosomes [47] suggest that non-random changes in chromosome groups may be expected.

Further studies on the distribution of chromosomes per group and with new techniques for detecting structural anomalies of individual chromosomes are needed. Boveri's contention that abnormal chromosome constitution causes malignancy has not yet been disproved. It may yet be possible to diagnose further types of malignant cells by their karyotype.

4.3. Genetic predisposition

It is well known that the incidence of cancer is high in certain strains of experimental animals and certain human families [48]. Earlier, examples were described in which families seem to be predisposed to chromosome non-disjunction and chromosome structural changes. They may inherit genes that affect the stability of the chromosome mechanism. Genetically unbalanced individuals with abnormal karyotypes also have a greater tendency for cancer ontogeny, probably in response to environmental factors.

Karyotype analysis of families with a high cancer incidence may reveal structurally unbalanced karyotypes causing their predisposition to cancer.

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