A SYNOPSIS OF CANCER

GENESIS AND BIOLOGY

BY

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PREFACE

THE disciplines involved in research into the genesis and biology of cancer are growing ever wider, and the detail of study is becoming increasingly deep. It is not surprising that the practitioner of medicine finds it difficult to maintain an appreciation of advances, and to co-ordinate and apply the results of basic research to his own sphere of work. Not only does this imply the possibility of deficiencies in therapy, but it results in a serious and fundamental loss to the sum total of possible avenues of exploration of cancer. The lack of application and correlation of the results of investigation and experiment to the observation and management of patients suffering from cancer detracts from the practitioner's understanding of the disease and reduces his potential contribution to knowledge of the subject.

The very idiom and terminology of many branches of cancer investigation are evolving along specific and unique lines. The inability to understand the new language is creating a deep rift between the practitioner at the bedside and the scientist at the bench, and, in fact, between some of the workers in different spheres of research. To bridge this rift is, perhaps, the basic minimum for consolidation of efforts in different fields of work towards the comprehension and the cure of cancer.

It is patently important to co-ordinate the various disciplines of research, to correlate them where possible, and to compare and contrast their findings and deductions. It is equally important to apply the same idea of co-ordination to different branches of medical practice. The usual methods of teaching students and postgraduates militate against such co-ordination: the standard orientation of teaching is based upon organ classification, so as to fit into the divisions of specialist medical practice. The orthopaedic surgeon teaches bone and joint tumours, the thoracic surgeon instructs in lung cancers, the gynaecologist is restricted to his particular subject, the urologist to his, and so on. This leads to pigeon-holing of ideas and knowledge, with the attendant danger of losing sight of the composite subject of neoplastic disease. An essential requirement is a reorientation of teaching. The system of instruction in organ-compartmented form needs to be augmented by presentation of the whole subject as a broad and compound picture, at postgraduate as well as undergraduate levels. Co-ordination in medical practice in all its branches may then be practicable without the obstacles and difficulties that exist today.

The present work is designed to meet some of these problems. Its framework of a synopsis is intended to include a review and appreciation of current knowledge, to suggest the areas of correlation in different disciplines of research and practice, to serve as an introduction to more detailed works of reference, and to provide a book that will excite the interest of student and practitioner in the genesis and biology of cancer, and yet remain a book of manageable proportions.

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To Ora, Janet, and Barbara
for the help and happiness
brought by your enthusiasm

FOREWORD

By

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This quite extraordinary little book styles itself a 'Synopsis' and is subtitled 'Genesis and Biology'. These two wide aspects of cancer underline the predominant trends in an incredibly comprehensive description of this dire disease.

Synoptic in form the book may be, but it avoids the soul-destroying itemization of many similar volumes. It is essentially readable, well paragraphed, and well illustrated—largely by clear and intelligible diagrams.

The author's desire to find a common ground between clinician and research worker and to treat the subject as a whole rather than to divide it into systematic and apparently unrelated parts seems to have been more than fulfilled.

Brief historical references abound and are linked to the most modern concepts of cancer aetiology as is shown by such excellent chapters as those on Heredity, Genetic Factors, the Mutation Theory, and the relation of Immunology to Cancer. Regional consideration of various cancers is by no means neglected but is interestingly linked with an assessment of the part played in carcinogenesis by the viruses, by hormones, by ionizing radiation, and by other agents.

Several chapters on geographical pathology are evidence of the author's very wide experience and even wider reading—and yet, appreciating this is a synopsis, good but short reference lists are included to stimulate the search for further knowledge.

The book is essentially descriptive rather than clinical—but it can only be of the greatest use and greatest value to the practising doctor. It most certainly and efficiently links (as the author says) the bedside with the laboratory. It is a book both to read and to keep available for ready reference; it is a veritable mine of information, a classical *multum in parvo*.

I am sure it will prove to have a wide popularity and to be deservedly successful.

London, December 1965

CONTENTS

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CHAPTER I

THE NATURE OF CANCER

DEFINITIONS AND ATTRIBUTES

Neoplasm, or **New Growth**, implies the growth of newly formed cells derived from normal body cells or their preceding developmental cells of origin.

The new growth often, but not invariably, forms a lump or **tumour**, a term frequently used synonymously with neoplasm.

Benign Neoplasm, also referred to as 'simple tumour', indicates a tumour that does not of itself destroy the host. It may, however, cause such disturbance of function, e.g., bowel obstruction, as to be fatal. While growth in size of the benign tumour occurs, it does so by general expansion with fairly uniform enlargement of the whole tumour mass, maintaining its clear definition and remaining confined within a limiting capsule. It does not invade neighbouring tissue nor implant, i.e., metastasize, at distant sites. Its cells are mature in structure and arrangement.

Malignant Neoplasm, or **Cancer**, if left untreated, destroys the host. The tumour may be encapsulated for a limited period, but it ultimately infiltrates and grows through such confines to invade neighbouring tissues. Metastases (distant secondary sites) are characteristic. Its gross and histological characters are commonly irregular and degenerative changes are frequent. Malignant tumours arising from epithelial cells are called 'carcinomas'; those from connective tissues are called 'sarcomas'.

The attributes defining malignant neoplasms are elaborated in subsequent sections, but it is useful at this stage to tabulate them to indicate the main differences between benign and malignant tumours.

ORIGIN OF TUMOURS

All tissues in the body are liable to undergo malignant change, and all cells have an inherent potential for the development of cancer.

The origin of cancer may be unicentric or multicentric:—

1. Unicentric, or unifocal, origin implies that one cell or a localized group of cells becomes malignant and that all subsequent cancer cells are descendants from this focus. Neighbouring cells are not

Origin of Tumours, *continued.*

Table I.—Comparison of Properties of Benign and Malignant Tumours

Property	Benign	Malignant
Destruction of host	Absent	Present or potential
Gross form of tumour	Regular and defined	Irregular and without definition
Character of growth (i.e., increase in size)	Concentrically uniform	Lacks uniformity, and growth is from periphery
Rapidity of growth	Usually slow	Often rapid
Encapsulation	Characteristic	Absent or soon destroyed
Infiltration	Absent	Present
Dissemination	Absent	Present or potential
Cellular maturity	Mature and resembles tissue of origin	Varies: the more malignant, the more immature
Cellular morphology	Regularity of structure	Pleomorphism is common
Composite arrangement of cells	Adult type of organization	The more malignant, the less the resemblance to the adult arrangement
Cellular activity	Mitotic activity not increased	The more malignant, the higher the mitotic index
Mitotic pattern	That present is regular and resembles the normal	Often abnormal and irregular
Degenerative changes	Unusual	Common

themselves altered or added to the initial centre. This concept of the origin of tumours is subject to doubt. It certainly does not apply to all tumours: in virus tumours, there is evidence of affection of neighbouring cells, and in many parts of the body, e.g., in the tongue and colon, cells adjacent to clearly malignant sites often appear to be undergoing changes.

2. The multicentric, or multifocal, concept implies a simultaneous origin of cancer at a number of sites in one organ. There is a sound basis for this theory in regard to a number of cancers, but its universal application has not sufficient supporting evidence.

Malignant change appears to be more liable to occur in those cells which, in the normal course of activity, undergo repeated phasic and replacement alterations. Blood-cells which have a limited life and are constantly replaced by newly formed elements; epithelium which is constantly being cast off superficially and replaced from deeper layers;

endometrium and breast parenchyma, which have cycles of alternating quiescence and hyperactivity, are all examples of cells which carry a high potential danger of cancerous development.

The change from normal to malignant cell appears to be a sudden transformation, although a long period of induction may have preceded the change. Defined stages in such change have not been recognized.

GROWTH

Malignant tumours have the power of continuous growth. The cells increase in number, reproducing cells of a like character, whether in the primary site of origin or in secondary, metastatic sites.

Many tumours appear to grow without restriction or control, differing from normal cell growth which replaces effete cells, repairs injuries, or hypertrophies as a reaction to 'work demands'. Such normal cell increase is limited to the functional and morphological requirements of the particular tissue affected, whereas neoplastic cell growth is independent of such restraint and possesses a far greater degree of autonomy. However, this autonomy is not absolute, nor is it of uniform grade in different tumours. Some tumours, e.g., of the breast and of the generative organs of males and females, are known to be partially dependent upon hormone production by the host.

The rate of growth varies in different tumours from very slow to very rapid. Generally, the more rapid the growth, the more malignant is the tumour. Variation may also occur in a single tumour in that its rate of growth varies at different times.

The rate of growth is reflected in the increasing size of the tumour mass and also, microscopically, by:—

1. Active cell division, i.e., mitotic activity. This may be expressed as a mitotic index: a high proportion of dividing and multiplying cells giving a high index, and, by contrast, sparse mitoses are equivalent to a low mitotic index.
2. The maturity of the cells. Mature cells, i.e., resembling developed adult cells, are significant of benign tumours or relative benignance of a malignant tumour. By contrast, immature or primitive cells, also known as anaplastic cells, indicate malignancy of a grade directly proportional to the numbers of such cells. Broders's* classification of grades of malignancy is dependent upon this fact. The proportion of anaplastic cells is counted and the following grades are defined:—

Grade 1—Up to 25 per cent anaplastic cells (i.e., the least malignant).
Grade 2—25–50 per cent.
Grade 3—50–75 per cent.
Grade 4—Over 75 per cent (i.e., the most malignant).

DEGENERATIVE CHANGES

Such changes occur as a result of:—

1. A neoplasm outgrowing its own blood-supply.
2. Growth beyond effective lymphatic drainage so that metabolites collect.

* Broders, A. C. (1926), 'Carcinoma, Grading and Practical Application', *Archs Path.*, **2**, 376.

Degenerative Changes, *continued.*

3. Tumour invasion of vessels, leading to haemorrhage, infarction, and/or ischaemia.

Degenerative changes occur mainly in the centrum of the tumour, and consist of one or more of the following:—

1. Haemorrhage. Usually due to vascular damage by invading tumour cells, but sometimes also due to flimsy and defective vessel walls and support, e.g., in bone sarcoma.
2. Necrosis. From ischaemia due to deprivation of blood-supply, and/or secondary infection. Necrosis may become manifest by ulceration on the surface of a tumour, or by cavitation within the substance of a tumour mass.
3. Cystic vacuolation. From accumulation of tumour secretions, from absorption of haematomas, or from autolysis of necrotic areas.
4. Fatty degeneration. Found particularly when an immature tumour is associated with a poor blood-supply, e.g., carcinoma of the kidney.
5. Mucoid degeneration. Occurs especially in cancers of the stomach and gall-bladder. Mucus is normally secreted in these organs, but mucoid degeneration also occurs in organs not normally mucin-producing, e.g., the breast.
6. Hyaline degeneration. Affects especially the stroma of slowly growing tumours with marked fibrous tissue formation.
7. Calcareous deposition, calcification, and ossification. Tend to appear in unabsorbed necrosed tissue.
8. Amyloid degeneration. Occurs, but is rare.

HARMFUL EFFECTS OF CANCER

Cancer is a great menace to human life; it is second to cardio-vascular conditions as a lethal disease. Its ill-effects arise from:—

1. Growth at the expense of host requirements, drawing upon nutriment that is ordinarily used by normal tissues.
2. Peripheral invasive growth, destroying host tissues, affecting their functions partially or completely with consequent deprivation to the general body economy.
3. Toxic products of tumours directly, or secondarily, following decomposition of tumour cells.
4. Tumour cell products which may upset normal physiological processes, e.g., as in hormone-producing tumours.
5. Metastases which affect wider areas of the host's tissues and extend the ill-effects of invasive destruction and deprivation of nutriment.
6. Invasion affecting blood-vessels, causing haemorrhage of varying degree.
7. The tumour outgrowing its own blood-supply, or invading adjacent vessels, so as to give rise to necrosis and degenerative changes. Such changes are commonly subject to secondary infection, which adds to the general and local effects.
8. The extent and situation of the tumour which may interfere with essential function, e.g., obstruction of the bowel, the urinary

tract, or a bronchus, or interference with circulation of the cerebrospinal fluid.

STRUCTURE

Tumours consist of two elements, parenchyma and stroma, in varying proportions in different tumours and in different parts of the one tumour. The parenchyma carries the malignant properties; the stroma appears to be derived from the normal surrounding connective tissue as a host reaction to the tumour cells. The stroma may act as a support and medium of nourishment to the parenchyma elements. Sometimes, the stroma formation is so extensive and dense as to appear to isolate and deprive cancer cells of nourishment; often, the stroma itself is invaded and destroyed by cancer cells spreading to more extensive areas.

TUMOUR-CELL MICRO-ANATOMY

Differentiation of tumour cells to mature forms becomes manifest in their individual shape, size, and internal architecture, and also in the composite arrangement of groups of cells.

The morphology of differentiated cells depends upon the tissue of origin of the tumour. In general terms, the cells are uniform in shape, size, cell-membrane character, disposition and density of nucleus, distribution and pattern of cytoplasm, and relative proportions of cytoplasm and nuclear material. Cells of a well-differentiated tumour arising from a particular gland present micro-anatomical features very like those of the normal gland. Lack of differentiation, i.e., immaturity, manifests in cells of varying and irregular shapes, usually polyhedral or rounded, irregular hyperchromatic nuclei, many of which undergo irregular mitotic division, and with an inconstant cytoplasmic content and arrangement. The anaplastic, or immature, cells may all be of a similar character, or they may exhibit considerable variation in their size, shape, and internal arrangement. This type of variation is known as pleomorphism.

Adult differentiation of cells almost invariably affects their composite arrangement, bringing about a structure and pattern similar to that of the adult organ. Contiguous cells are arranged in appropriate positions and proper relationship to stroma elements to form glandular elements like acini, alveoli, ducts, lobules, etc. By contrast, undifferentiated cells lack such a pattern of arrangement. Mature cancer arising from glandular epithelium is known as 'adenocarcinoma'. Anaplastic cancer cells often grow in sheets or cords, or their cells are deranged into small clumps, and are designated 'carcinoma simplex'.

While cancer cells do not present pathognomonic morphological features, a sum of the cytological characters in a number of cells, taken together with their relationship to one another and to the surrounding tissues, usually provides a high degree of accuracy in diagnosis. Refinements of technique and electron microscopy have not yet produced any unequivocal or constant diagnostic criteria, but they have added information on the intimate architecture of different malignant cells. The following descriptions of cancer-cell micro-anatomy should be set against the background of the reservation that there are no specific malignant alterations.

NUCLEUS

Size.—The nucleus of cancer cells is often larger than that in the benign cells of origin of the tumour. The increase in size is more noticeable relatively than absolutely, i.e., when measured against the size of the cell. Cowdry and Paletta* express this as an increase in the nucleo-cytoplasmic ratio. The variability of absolute and relative sizes of the nucleus is perhaps more significant, especially as it becomes more marked with increased malignancy and anaplasia.

Jacobj† considers that the volume of the nucleus is largely dependent upon the volume and number of chromosomes. Shultz‡ reports the importance of the amount of protein in the nucleus as a determinant of size.

Shape.—Nuclear shape varies with the type, and state or phase of nuclear division. Mitosis, in which a cell divides into two daughter cells, each containing a replica of the chromosome number and pattern, is characteristic of normal somatic tissues. Meiosis, a form of division in which the chromosome number is halved, i.e., reduction division, occurs normally in ova and spermatozoa. Amitosis, a third type of division, consists of simple division of the nucleus without polar rearrangement of chromosome material. Of the three modes of division, mitosis is the important one in the consideration of nuclear shape in malignancy, and it requires further elaboration.

Mitosis occurs in stages which are named (*Fig.* 1). During *prophase*, the centriole divides into two, each of which shifts towards an opposite pole of the cell. The chromosomes become more dense and defined. The *metaphase* follows, starting by progressive dissolution of the nuclear membrane. The chromosomes become more contracted and come to occupy an equatorial plate across the cell. The centrioles become connected by a spindle of fibres to, and across, the equatorial plate where they are attached to the chromosomes. The metaphase ends with the replication of chromosomes into daughter pairs. This is succeeded by the *anaphase*, in which each partner of the chromosome pairs migrates towards a polar centrosome (surrounding a centriole). When chromosomal separation is complete, the *telophase* is signified by the development of nuclear and nucleolar substance from chromosomal swelling and changes in which definition and intense staining are lost. The nuclear membrane is re-formed around each nuclear clump at the poles of the cell. The cell itself becomes increasingly narrowed at its equator, progressing to complete division into two separate cells, which come to rest in an *interphase*.

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* Cowdry, E. V., and Paletta, F. X. (1941), 'Changes in Cellular, Nuclear, and Nucleolar Sizes during Methylcholanthrene Epidermal Carcinogenesis', *J. natn. Cancer Inst.*, **1**, 745.

† Jacobj, W. (1942), *Wilhelm Roux Arch. Entwmech. Org.*, **106**, 124. Quoted by Oberling, Ch., and Bernhard, W. (1961), 'The Morphology of Cancer Cells', in *The Cell*, Vol. V (Ed. Brachet, J., and Mirsky, A. E.). New York: Academic Press.

‡ Shultz, J. (1952), 'Interrelation between Nucleus and Cytoplasm: Problems at the Biological Level', *Expl Cell Res.*, Suppl. **2**, 17.

The shape of the nucleus of a cancer cell during interphase is usually irregular, its outline being indented by deep fissures and bulged by lobulations. Shape during mitosis is closely related to abnormalities of cell division which are noted in a later section.

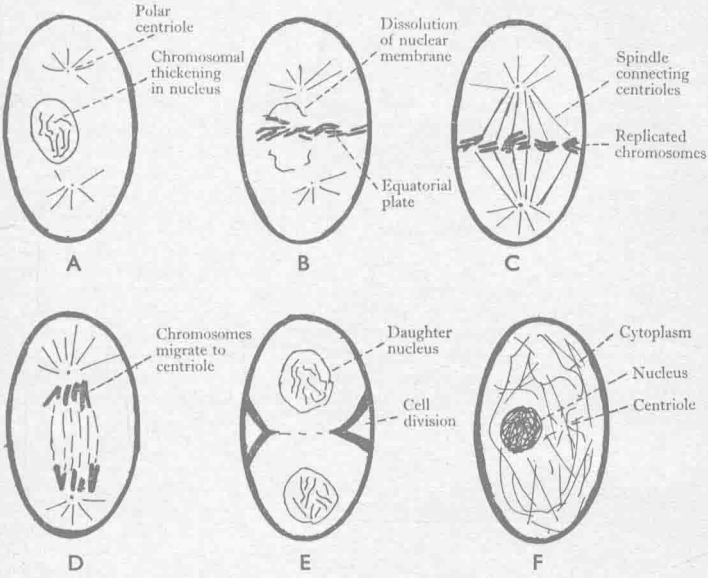

Fig. 1.—Diagram of phases of mitosis. A, Prophase; B, Metaphase I; C, Metaphase II; D, Anaphase; E, Telophase; F, Interphase.

Nuclear Membrane.—Details of irregularities of cancer cells have been recorded by Bernhard.* On electron microscopy, the deep indentations may present as thin canaliculi, limited by a double-walled nuclear membrane. Cytoplasmic structures within the invaginations may appear as inclusions within the nucleus. Often, nucleoli are situated at the bases of canaliculi, as if to provide a ready passage for nucleolar material into cytoplasm. A rich canalicular system is a marked feature in the large nuclei of Reed-Sternberg cells in Hodgkin's disease.

Nucleolus.—There may be one or several nucleoli, standing out as dark clumps of material within the nucleus. (*See Fig.* 2 which is a labelled diagram of the constituents of a cell.) They disappear during mitosis and reappear in the telophase. In some, but not all malignant cells, nucleoli are enlarged in relation to the nucleus

* Bernhard, W. (1963), 'Some Problems of Fine Structure in Tumor Cells', in *Progress in Experimental Tumor Research* (Ed. Homburger, F.). Basel: Karger.

Nucleolus, *continued.*

(Guttman and Halpern*). Page and others† remarked on the frequency of the nucleolar inclusions in malignant cells. These have been compared to inclusion bodies found in known viral neoplasms in experimental animals, e.g., the mouse polyoma, but proof of their viral nature in human and many animal tumours is lacking. The evidence is uncertain, as is well brought out in a report by Beaver.‡ He found comparable inclusion bodies in kidney-cell nuclei in lead poisoning. (However, lead is a carcinogen, and is discussed in Chapter XIII.) Viral inclusions have been suspected in cells of Hodgkin's disease, but Bernhard§ records their presence in only a few of a number of Hodgkin's affections examined by the electron microscope. This author emphasizes, 'the nucleolus of the cancer cell shows no specific characters associated with neoplastic transformation as such, and that all its changes and particularly its hypertrophy are merely a manifestation of metabolic disturbances to which the cell is subject'.

Heterochromatin.—This term is applied to the portion of chromosomal tissue which preserves its staining capacity during the interphase. Heterochromatin forms a part of the granular element of nucleoplasm. Its thread form is revealed on electron microscopy. It may undergo alteration in number, shape, and clumping, in malignancy, but there is, as yet, nothing that is peculiar to cancer.

Chromosomes.—Notes applicable to chromosomes are included in Chapter XXII. The discussion in the context of the present chapter relates to the possible bearing on characterization of the cancer cell.

The number of chromosomes in malignant tumours may be normal for the species, including man (Nowell and others‖); more rarely, the number is reduced (Koller¶). However, the common abnormality in cancer cells is an increase with aneuploidy, i.e., the increase is irregular and is not a multiple of the normal haploid number. This may occur in normal tissues, but is usually more marked and variegated in malignancy (Oberling and Bernhard**). The latter authors review the evidence for the concept that the seemingly complete irregularity of chromosomal number arises from the coincident presence of several stem lines, each producing a distinct chromosomal irregularity which is constant in that line, but when all the lines coexist in one tumour, marked diversity

* Guttman, P. H., and Halpern, S. (1935), 'Nuclear-nucleolar Volume Ratio in Rat Cancer', *Am. J. Cancer*, **25**, 802.

† Page, R. C., Reagan, J. F., and McCarty, W. C. (1938), 'Intranucleolar Bodies in Normal and Neoplastic Human Tissue', *Ibid.*, **32**, 383.

‡ Beaver, D. L. (1961), 'The Ultrastructure of the Kidney in Lead Intoxication with Particular Reference to Intranuclear Inclusions', *Am. J. Path.*, **39**, 195.

§ Bernhard, W. (1963), 'Some Problems of Fine Structure in Tumor Cells', in *Progress in Experimental Tumor Research* (Ed. Homburger, F.). Basel: Karger.

‖ Nowell, P. C., Hungerford, D. A., and Brooks, C. D. (1958), *Proc. Am. Ass. Cancer Res.*, **2**, 331. Quoted by Oberling, Ch., and Bernhard, W. (1961).

¶ Koller, P. C. (1947), 'Experimental Modification of Nucleic Acid System in Cells', *Symp. Soc. exp. Biol.*, No. 1.

** Oberling, Ch., and Bernhard, W. (1961), 'The Morphology of the Cancer Cells', in *The Cell*, Vol. V (Ed. Brachet, J., and Mirsky, A. E.). New York: Academic Press.

results. The different stem lines represent mutants and indicate the marked genetic instability of tumour cells; the mutations probably arise by reaction to altered environment, and may, during the course of tumour evolution, give rise to new lines with new properties.

The review by Oberling and Bernhard also includes descriptions of other changes found in cancer cells. Chromosomal morphology of neoplastic cells resembles other features of nuclear alteration, and presents in variable shapes and forms: from long filamentous threads to short, squat types. The anaphase may be disturbed by excessive cohesion between pairs, and striking irregularities are added to those affecting the form of the chromosomal material.

Mitotic aberrations are quite common in all the phases of cell division. Deviations may arise from abnormality of one or more intra- or extra-nuclear participating organelles. An example of abnormal chromosomal behaviour in anaphase has been mentioned above; during metaphase, formation of an equatorial plate may fail, i.e., the 'hollow metaphase', because the paired chromosomes congregate at the periphery; during telophase, more than two nuclei may form. Abnormalities may arise from irregular spindle development; absence of spindle fibres may result in failure of anaphase migration; and re-formation of the nucleus produces a cell with twice the normal chromosomal number, i.e., a form of polyploidy. Partial absence of spindle fibres leads to irregular aneuploidy. This may also arise from the formation of more than one spindle, giving rise to multipolar mitosis.

While deviations from normal mitotic division are common in malignant cells, none of them is characteristic and all of them may occur in non-cancerous conditions. Therefore, it is doubtful whether the abnormalities are part of the pathogenesis of malignancy; they may, in fact, be part of the effect upon the cell by some other agent.

CYTOPLASM

In the vast field of cancer research during the past 25 years, there has been little to alter the opinion by Bayne-Jones and others,* stated in a U.S. Public Health Report in 1938, to the effect that there are no fundamental differences and no striking variations in 'chemical make-up, enzyme content, metabolism or structure', between normal and malignant cells of the same tissue type. Nevertheless, the changes merit close study, for apart from significant quantitative alterations, hopeful anticipation of finding some crucial qualitative characteristic is justifiable. The structural features described in the text are included in *Fig.* 2.

As with malignant cell nuclei, so too with cytoplasm, the sum of the features in a field of cells is a valuable diagnostic element.

Size and Shape.—Normal cells maintain a fairly constant size and shape in a particular tissue or in the separate layers of one tissue;

* Bayne-Jones, S., Harrison, R. G., Little, C. C., Northrop, J., and Murphy, J. B. (1938), 'Fundamental Cancer Research', *Publ. Hlth Rep. Wash.*, 53, 2121.

Cytoplasm—Size and Shape, *continued.*

whereas the size and shape of malignant cells derived from one tissue show marked variations. Whilst this generalization holds good for malignant cells from *one tissue*, it is important to note that there is a wider range of variation between normal cells of *different tissues* than is the case with malignant cells from *different tissues*. In the course of the evolution of malignant cells, their functions are reduced or eliminated, their environment is altered, and they come to assume structural organizations and forms more common to the different neoplastic cells than they are in their cells of origin. The result is that over the whole field of malignancy, there is a general tendency towards de-differentiation of cells to a more uniform primitive basic pattern.

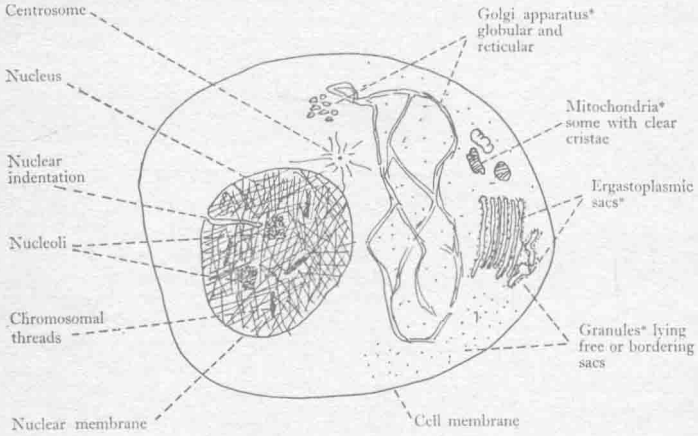

Fig. 2.—Diagram of cell constituents. * These constituents of cytoplasm are not confined to an area as suggested in the diagram.

In most cancers, the cells are larger than those of the normal tissues from which they develop. In some, as shown by Cowdry and Paletta* in squamous-cell epitheliomas, the cancer cells are smaller; yet others show no notable differences in size.

Cowdry† records correlations between physiological activity and cellular change. Normal cells of many tissues respond to functional demands by an increase in size, and then become smaller with disuse; but malignant cells do not respond in like manner. Increase in normal cell volume follows storage of metabolites and foreign matter, but malignant cells exhibit only slight changes of this character.

* Cowdry, E. V., and Paletta, F. X. (1941), 'Changes in Cellular, Nuclear, and Nucleolar Sizes during Methylcholanthrene Epidermal Carcinogenesis', *J. natn. Cancer Inst.*, 1, 745.

† Cowdry, E. V. (1955), *Cancer Cells.* Philadelphia: Saunders.