

# Ultrastructural Changes in Nucleus : Current Prospects

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## Abstract:

**Background:** Alterations in the architecture of cells and tissues and genetic instability are hallmarks of cancer. Electron microscopy has led to the visualization of the various components of the nucleus. Study of nucleus would illuminate mechanisms of malignancy and generate applications of value for clinical practice. Here in we discuss the current prospects of fulfilling this dream and identify barriers to further progress.

**Summary:** This review is an attempt to summarize the ultra-structural changes in components of nucleus in health and disease for future advances.

**Key Message:** The response of the nucleus to a particular insult, such as viral infection, may be unpredictable, leading to degeneration, lysis and cell death in one case and neoplastic transformation in another.

**Keywords:** Electron microscopy; malignancy; nuclear alterations; Ultra structural

## Introduction

The nucleus is the confluence of all biological form and functions of the cell. The study of the nucleus is at a tipping point and many new advances are at hand. In the last few decades, there have been significant developments in the knowledge of nuclear structural organization and various functions of nucleus.[1] Electron microscopy has led to the visualization of various components of the nucleus. The phase contrast microscopy had beautifully revealed the inter-phase nucleus and mitotic chromosomes. Histological assessment of nuclear morphology is a standard procedure in clinical practice. [2]

Alterations in the architecture of cells and tissues and genetic instability are hallmarks of cancer. Changes in nuclear structure are among the most universal of these and include increases in nuclear size, deformities in nuclear shape, and changes in the internal organization of the nucleus. These may all reflect changes in the nuclear matrix, a non-chromatin nuclear scaffolding determining nuclear form, higher order chromatin folding, and the spatial organization of nucleic acid metabolism.[3] Malignancy-induced changes in this structure may have profound effects on chromatin folding, on the fidelity of genome replication, and on gene expression. Some of the dreamers in the field of nuclear structure have over the years proposed that the study of nucleus would elucidate mechanisms of malignancy and spin off applications of value for clinical practice. [4] Here in we discuss the current prospects of fulfilling this dream and identify barriers to further progress. [5]

The four basic nuclear structural components, the nuclear envelope, consisting of the inner and outer nuclear membranes and the perinuclear cisterna; the chromatin, which are present as dense patches under the nuclear envelope, dispersed throughout the nucleus and in and around the nucleolus; the nucleolus itself and the nuclear matrix, including the nuclear pore-lamina complex.[6] Most of the knowledge of these structures and of their alterations in disease comes from electron microscopic observations.

Despite the underlying uniformity, different cell types can have distinctive nuclei, characterised by a combination of size, shape, chromatin disposition type, number and size of nucleoli and other features. Without an understanding of what is normal for the cell and tissue in question, no consideration can be embarked upon the altered morphology. [7]

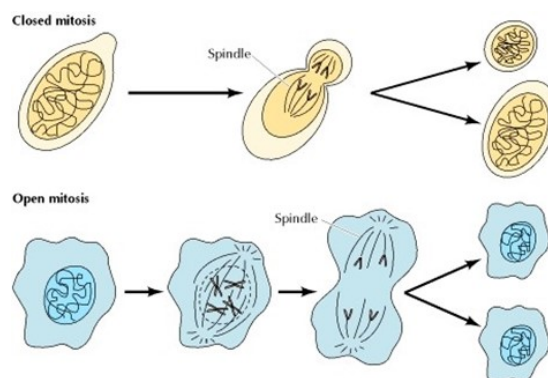
However, nuclear alterations cannot always be regarded as pathognomonic of any particular underlying condition. The following alterations can be observed in both physiological and pathological circumstances:

- Ultrastructural changes during cell division.
- Changes in nuclear Chromatin :An increased nuclear- cytoplasmic ratio
- Nuclear & nucleolar enlargement
- Segregation of nucleolar components
- Irregularities of the nuclear membrane
- Nuclear inclusions

### 1. The Nucleus in Mitosis

No other aspect of cell structure is subject to such radical morphological change as the nucleus in mitosis. Nuclei look different, in different cell types and when cells divide. During mitosis, a parent cell gives rise to two daughter cells, each with its own nucleus. [8]

Two main approaches have evolved to successfully carry out this task: open mitosis and closed mitosis (Figure.1). Open mitosis occurs in most eukaryotic cells, whereas closed mitosis occurs in certain species of fungi. In open mitosis, the NE disassembles early in mitosis, allowing microtubules that emanate from cytoplasmic centrosomes to contact the chromosomes and promote their segregation. At the end of open mitosis, the NE reassembles around the two segregated DNA masses to form the two daughter nuclei. In closed mitosis, the NE does not disassemble and chromosome segregation takes place entirely within the confines of the nucleus. This strategy works in cell types where the centrosome equivalents, known as spindle-pole bodies, are embedded in the NE, allowing microtubules to associate with chromosomes without the need for NE disassembly. [9]



**Figure 1:** Closed and open mitosis

A microscopist should be familiar with the fundamental cytological changes of the nucleus in mitosis. Centriolar division precedes nuclear division, resulting in the formation of the spindle poles. The four principal stages of nuclear division, prophase, metaphase, anaphase and telophase, are followed by cytokinesis, or cell division, which results in the separation of two distinct cytoplasmic territories around the reconstituted daughter nuclei. [10]

### 2. Changes in Nuclear Chromatin

1. Variation in Heterochromatin and Euchromatin Ratio (Table 1) The distribution and relative proportions of these two forms of chromatin in different cells show considerable normal biological variation.
2. Discrete dense aggregates known as perichromatin and interchromatin granules occur within the nuclear substances are observed.

3. Nuclear pockets represent localised invaginations of nuclear or cytoplasmic material into a saccular irregularity of the nuclear envelope, with an underlying rim of chromatin material. Ghadially et al. (1985b) pointed out that nuclear pockets are distinguished from nuclear pseudo inclusions by the 'presence of this chromatin band' beneath the nuclear envelope.

Nuclear pockets are classified into:

**Type 1** containing cytoplasmic material

**Type 2** containing nuclear material (the less common)

Current views suggest that nuclear pockets may reflect a state of chromosomal abnormality.

**Table 1:** Ultra structural changes in nuclear chromatin

CHANGE IN NUCLEAR CHROMATIN	CONDITIONS	EXAMPLE	REFERENCE
Increase in Heterochromatin: Euchromatin Ratio	<b>Physiological</b> :Resting cell Nuclei of resting cells or cells exposed to agents which inhibit RNA synthesis contain more heterochromatin. Heterochromatin stains more densely than euchromatin	Resting Fibroblast have a dark stained <b>closed nucleus</b>	Fawcett(1981)
Decrease in Heterochromatin: Euchromatin Ratio	Active cell Euchromatin, an essential component in active DNA and RNA synthesis, is abundant in functionally active and secreting cells, as well as in proliferating blast and stem cells	Active Fibroblast have a pale staining <b>open faced nucleus</b> and abundant cytoplasm	
Increased numbers of perichromatin granules	Protein synthesis inhibition or impairment After treatment with cycloheximide, actinomycin D . After thermic shock and hyperthermic treatment In several neoplastic conditions and in experimental animal tumours . The intranuclear spheroidal bodies seen	In cases of nasopharyngeal fibroma are said to represent giant perichromatin granules .	(Watson 1962) (Ghadially 1988) (Kamel et al. 1988), (Derenzini and Moyne 1978) (Daskal et al. 1975) (Heine et al. 1971) (Ghadially 1985)
Increased interchromatin granules	Nucleolar alterations due to toxic agents or virus infections various neoplastic conditions. Can also be derived from nuclear component other than nucleolar RNP.		(Monneron And Bernhard 1969)
Nuclear Pockets	Malignant tumour cells such as leukaemic and lymphoma cells. In the nuclei of Leydig cells in cases of After treatment by chemotherapeutic agents such as cytosine arabinoside, methotrexate and fluorouracil. In the granulocytes There was direct correlation between the occurrence of nuclear pockets and aneuploidy in leukaemic cells	Retinoblastoma  Klinefelter's syndrome  Pernicious anaemia	Ghadially et al. (1985b)  (Nistal et al. 1985).  Kamel 1985; Ghadially 1988 A.hearn et al. (1974)
Artefacts	Staining and distribution of chromatin can be affected due to factors Tissue preservation, fixative type, pH and storage temperature		

### 3. Changes in Nuclear Number

Multinucleation or polykaryocytosis, may often be distinguished from multilobation, with which it can be confused. Certain cytoplasmic features may accompany multi-nucleation (Table 2).

The occurrence of multiple centriole pairs, to be distinguished from multiple ciliary basal bodies, or of viral nucleocapsids, either intranuclear or intracytoplasmic, may provide useful confirmatory evidence of multi-nucleation in circumstances where the thin section appearances are equivocal.

**Table 2:** Change in Nuclear number

CHANGE IN NUCLEAR NUMBER	CONDITION	EXAMPLE	REFERENCE
<p><b>Multinucleation</b></p> <p>Binucleate plasma cells</p>	<p><b>Pathological Conditions</b></p> <p>Seen in neoplasms .</p> <p>The binucleate Reed-Sternberg cell sometimes displays further nuclear irregularity and segmentation, giving a complex multi lobated binucleated appearance .</p> <p>In several muscular disorders and in hypertrophic and regenerative conditions</p>	<p>Multiple and solitary myeloma, to reactive conditions such as chronic periodontitis, periapical granuloma, pemphigus vulgaris and other situations</p>	<p>(Jinn-Fei and El-Labban 1986; Yeo 1986).</p>
<p><b>Multinucleate Syncytia</b></p> <p>Multinucleation can result from nuclear division without accompanying cytokinesis, or alternatively, from the fusion of mononuclear cells</p>	<p>In Viral Infection and Neoplasia</p>	<p>In measles and herpes simplex</p> <p>Brain encephalopathy which accompanies the acquired immune deficiency syndrome (AIDS)</p>	<p>Kingsbury 1985; Dupuycoin et al. 1982; Wolinsky 1979)</p> <p>Sharer et al. 1985; Budka 1986).</p>

### 4. Changes in Nuclear Size

The nuclei of normal interphase cells vary greatly in size, this is characteristic of the cell type and its metabolic state. This dimensional variation occurs despite the fact that each somatic cell contains the same amount of DNA, corresponding to the full genomic complement. [11]

- When this DNA, together with its associated proteins, is condensed into the heterochromatic form, it takes up less space and therefore needs a smaller nucleus than if it were in its euchromatic form. Indeed there is often a roughly inverse relationship between the quantity of heterochromatin and nuclear volume.
- The size of a nucleus normally depends not only on the amount of heterochromatin but also to a large degree on the transcriptional activity of its euchromatin component. Transcriptionally inactive euchromatin is more condensed than active euchromatin, though not as tightly packed as heterochromatin.

In most cells only a small proportion of euchromatin is active at any one time, but this proportion may change with the functional state of the cell and hence the volume may change in parallel, even though the amount of heterochromatin remains the same. [12]

- An activated cell with a larger nucleus thus appears to have less heterochromatin because it is spread more thinly in the greater volume.
- Busy cells tend to have large nuclei and lots of euchromatin (since many of their genes are in use). If they are synthesizing much protein, they will usually exhibit a nucleolus (where ribosomes are made), and their cytoplasm will be bluish.

- Degeneration of cells is accompanied by shrinkage and increased condensation. A cessation of transcription is indicated by decrease in volume of euchromatin.

## 5. Changes in Nuclear Outline and Location

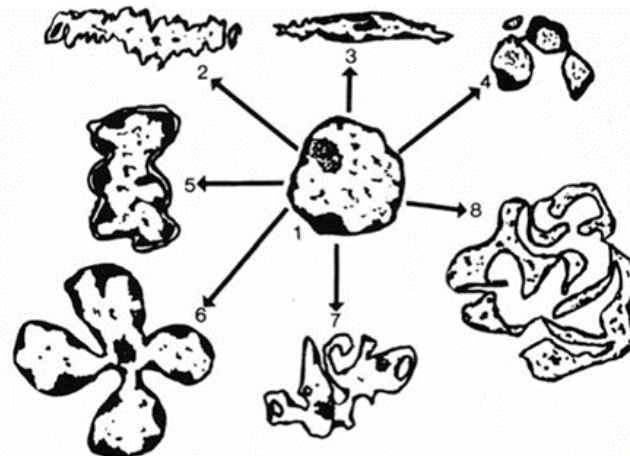
Electron microscopy provides higher magnification and greater resolution as compared to light microscopy in routine paraffin sections. [13] This results in many normal nuclei showing an unexpected degree of surface irregularity in ultrathin sections.

### (a) Normal Nuclear Irregularity

- The occurrence of irregularity of contour is a normal morphological characteristic of the nucleus in many cell types, such as smooth and striated muscle and endothelium.
- This can be seen as an adaptive mechanism in response to substantial changes in the overall size and contour of these cells, related to their mechanical functions and physical state.
- Inflammatory cells pass through very small apertures. As a result of the enforced narrowing and constriction which is required to enable them to cross vessel walls they often show extreme bi-lobing and bridge formation. [14]
- Nuclear irregularity is also a feature of the ageing process in liver, pituitary and adrenal gland cells.

### (b) Acquired Nuclear Irregularity

- In benign and malignant neoplasms and in secondary tumour deposits complex nuclear irregularity and segmentation, nuclear invagination and deep clefting of the nuclear envelope are frequently observed.
- Prominent in certain types of leukaemia and lymphoma and can be of diagnostic significance in cases of Sezary's and Reider's syndromes. The pattern of nuclear irregularity, as much as its mere presence, can be of diagnostic value.
- The radially segmented nuclei of Reider's cells characterise a range of lymphomas and leukaemias, including B-cell lymphomas, acute and chronic lymphoblastic leukaemia, acute myeloid leukaemia, chronic myelomonocytic leukaemia and lymphocytic leukaemia.
- The cerebriform nuclei display a peculiarly distinctive segmentation, with deep indentations. [16]
- Nuclear irregularity in most types of neoplasia does not have one characteristic pattern. It takes the form of apparently random surface disturbances, widely variable in nature and extent.



**Figure 2:** Heterochromatin is wound tight around nucleosomes. As genes are turned on, the chromatin structure is remodeled. Spectrum of nuclear irregularity: note that these diagrams assume that the nucleus in question has been sectioned through its major diameter. 1. Round or oval nucleus with minimal irregularity. 2. Crenated irregularity of spindle-shaped nucleus, as in smooth muscle cell. 3. Polar irregularity with spindle shape, as in fibrocytes. 4. Convoluted nucleus, as in polymorphonuclear leucocytes. 5. Shrunken irregularity with separation of nuclear envelope and peripherally condensed chromatin, as in degenerating cells. 6. Radially segmented nucleus, as in some leukemic cells. 7. Haphazard irregularity, as in some histiocytes and neoplastic cells. 8. Cerebriform . deeply convoluted nucleus (Courtesy: Pathology of Nucleus)

## 6. Ultrastructural Alterations of The Nuclear Envelope and Its Associated Structures

### (A) Nuclear Envelope Alterations

The common changes caused by various pathological conditions or injurious agents can be broadly, if rather arbitrarily categorised as either proliferative or non-proliferative. Either type of alteration can be produced by the same agent. The nature of the induced changes, however, will depend on the extent of the pathological event or the dose of the cytotoxic agent, as well as the effect on other cytoplasmic or nuclear structures.

Irradiation in non-lethal doses tends to produce largely proliferative changes, while damaged radiosensitive cells often show non-proliferative alterations. The changes can involve one membrane, often the inner, or both. Envelope changes are seen mainly in association with viral infections, in neoplasia and following exposure to irradiation and certain chemical agents.

#### (a) Non-proliferative Membrane Alterations

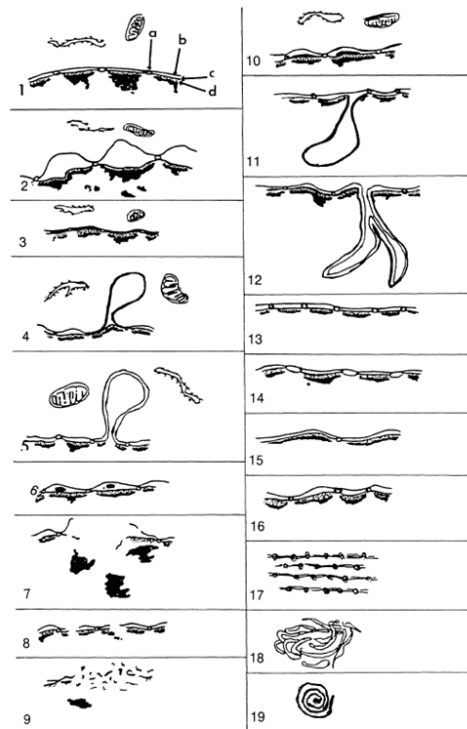
**Structure:** Non-proliferative membrane alterations include membrane separation or fusion, evaginations or blebbing, sloughing or fragmentation, with or without the formation of annulate lamellae, temporary defects and nuclear envelope rupture or lysis (Figure: 3).

#### **Occurrence:**

1. Nuclear membrane rupture "blebbing" occurs in necrotic cells.
2. Some nuclear inclusions which arise from the cytoplasm may gain access to the nucleus through these defects, which are later sealed by the endoplasmic reticulum.
3. Patchy or macular thickening of the inner nuclear membrane characteristically occurs in certain viral infections and is thought to be stimulated by viral antigens or replicative activity.
4. It is also sometimes seen in senile cells or cells with low metabolic activity.

#### (b) Proliferative Membrane Alterations

**Structure:** The nuclear envelope may form finger-like projections into the cytoplasm or the nucleus, or may produce elaborate tortuous branching invaginations with or without reduplication of the nuclear membranes (Fig. 3).



**Figure:3)** Diagrammatic presentation of various alterations of the nuclear envelope (NE) and pore-lamina complex (Courtesy: Pathology of Nucleus)

1. Normal NE and pore-lamina complex: nuclear pore; outer nuclear membrane; inner nuclear membrane; nuclear fibrous lamina.
2. Separation of component membranes of NE resulting in dilatation.
3. Fusion of membranes of NE.
4. Evagination of outer nuclear membrane.
5. Evagination of both nuclear membranes.
6. Dense inclusions in perinuclear cistern.
7. Rupture of NE. B. Temporary defects in NE.
8. Lysis and fragmentation of membranes.
9. Macular thickening of inner nuclear membrane.
10. Invagination of inner nuclear membrane.
11. Invagination and reduplication of both nuclear membranes.
12. Increased number of nuclear pores.
13. Enlargement of nuclear pores.
14. Decreased number of nuclear pores.
15. Thickening of fibrous lamina.
16. Formation of annulate lamellae.
17. Formation of tubular inclusions.
18. Formation of concentric laminated inclusions

### Occurrence:

These are described mainly in neoplasia and viral infections.

Also seen in less common pathological situations such as storage, genetic muscular dystrophy diseases and following exposure to certain chemical agents, irradiation or hypothermia. [17] Nuclear envelope proliferation may also result in the formation of concentric lamellar membranous arrays, nuclear pockets, annulate lamellae and tubular inclusions.

Intranuclear tubular formations derived from the inner nuclear membrane are seen in association with various pathological conditions, examples include idiopathic pulmonary fibrosis, various forms of fibrotic lung disease, sarcoidosis, collagen vascular disease.

### (B) The Nuclear Envelope in Viral Infections

Various virus-induced alterations in the nuclear envelope includes fusion, proliferation and reduplication of its two membranes, inner membrane macular thickening and the formation of dense inclusion bodies in the perinuclear space. [18] Infections by the adenovirus and the herpes-cytomegalic virus groups are associated with profound morphological alterations in the nuclear envelope (Grimley and Henson 1983). This association is attributed to the strategic location of the nuclear envelope and its contribution to virus assembly. [19] Sometimes the virus particles accumulate in vesicular structures derived from the proliferating inner nuclear membrane.

Virus-induced proliferation can cause NE invagination, the formation of small vesicles along the inner nuclear membrane. Formation of nuclear or cytoplasmic concentric lamellae may also be due to virus-induced nuclear membrane proliferation. These changes are thought to be induced by contact of the virus antigen with the nuclear envelope. [20]

### (C) The Nuclear Envelope in Neoplasia

Changes in the nuclear envelope in neoplasia are largely proliferative, involving either or both of the nuclear membranes, but mainly the inner one. Nuclear envelope proliferation may produce finger-like projections into either the nucleus or the cytoplasm. [21] Alternatively, it may result in the formation of concentric lamellar membranous arrays, tubular inclusions or intracytoplasmic and intranuclear lamellae and nuclear pockets.

### 7. The Nuclear Fibrous Lamina

The fibrous lamina is not a marker of particular active or rapidly proliferating cells, being seen rarely in malignant tumours. It is more described in slowly growing benign tumours, such as pleomorphic salivary adenoma, chondromyxoid fibroma, elasto-fibroma, nasopharyngeal angio-fibroma, chondroblastoma and granular cell myoblastoma. It has been described in the plasma cells of Hodgkin's disease, in myofibroblasts of repaired tissue and in the synovial cells of rheumatoid arthritis. [22] The significance of its prominence in pathological conditions remains largely obscure.

### 8. The Nuclear Pores

- The number and diameter of the nuclear pores correlate with DNA content, nuclear surface area, nuclear volume and in particular, transcriptional activity (Table 3). In order to compensate for any resulting decrease in the rate of nucleo-cytoplasmic exchange. [24]
- The increased frequency of nuclear pores in neoplastic cells is attributed either to increased synthetic activity or to the increased cell and nuclear surface areas.
- Some studies link increase or decrease in nuclear pore diameter to the metabolic state of the cell. Other studies, however, reported insignificant variation in pore size due to metabolic activity. [25]

**Table 3:** Changes in Nuclear Pore complex

CHANGE IN THE NPC	CONDITION	EXAMPLE	REFERENCE
Increase in size and number	increased RNA synthesis or heightened metabolic activity	neoplastic diseases, in regenerative or reparative activity.	(Maul 1977)
Decrease in size and number	Conditions associated with lowered transcriptional activity Decreased protein synthesis Increased nuclear activity.	starvation and in mature and aged cells  In neoplastic disorders, such as thyroid papillary carcinoma	(Lodin et al. 1978),
Enlargement of the nuclear pores.	Observed in yeast cells exposed to nitrogen starvation	Variation in metabolic state of cell	(Willison and Johnston 1978)

### 9. The Nuclear Matrix

The nuclear matrix participates in viral capsid assembly and also in its gene regulation and DNA replication. Actinomycin D-induced alterations in nucleolar shape were found to be associated with corresponding changes in the isolated nuclear matrix of the same cells. [26]

### 10. Intranuclear Inclusions

Intranuclear inclusions include most non-chromatin, non-histone, non-nucleolar, non-matrical bodies or substances contained within the nucleus and not in continuity with cytoplasm. Some structures such as perichromatin and interchromatin granules and normal nuclear bodies are traditionally not regarded as "inclusions". The term inclusion has sometimes been applied to altered chromatin, nucleoli or matrix, or to their component parts. [27]

#### (a) Inclusion or Pseudo-inclusion

Nuclear inclusions can be described and classified on the basis of their structure and perceived composition.



Nuclear inclusions can often be detected and identified using the light microscope. They appear as optically clear bodies, or as dense eosinophilic or basophilic structures of various shapes. The application of CTEM has allowed a more sensitive and specific identification and recognition of components. [28]

**i) Specified structural components** of inclusions include: glycogen, lipid, viruses and haemoglobin. They are often seen in ageing cells and after exposure to certain drugs and toxic compounds. They are described as characteristic of several neoplasms and can be incidental findings in almost any tumour. [29]

**ii) Unspecified descriptive components** include tubular, filamentous, crystalline and amorphous structures.

#### **b) Pseudo inclusions**

##### **Structure**

- Cytoplasmic inclusions are often designated pseudo-inclusions, because they represent invaginations which may be separated from the nuclear matrix by a double-membrane boundary derived from the nuclear envelope.
- Another rare form of pseudoinclusions can arise from pushing in of the inner membrane of the nuclear envelope into the nucleoplasm. [30]
- Single membrane bound pseudo inclusions can be formed with contents derived not from the cytoplasm but from the cistern of the nuclear envelope. Cytoplasmic invaginations can become pinched off to form true inclusions.

Terms such as intranuclear concentric laminated inclusions, intranuclear lamellae, tubules, vesicles and filaments were all introduced following the application of ultrastructural methods.

#### **(c) Intranuclear Glycogen**

**Structure:** Irregularly shaped compact masses of glycogen, either monoparticulate or aggregated,

##### **Occurrence**

- Have been described in hepatocytes in many diseases eg; diabetes mellitus, viral hepatitis, lupus erythematosus, Graves' disease, and Wilson's disease. [31]
- Several neoplastic disorders such as Hodgkin's disease, hepatocellular carcinoma and carcinomas of the stomach.
- Glycogen particles can sometimes be mistaken for viruses.
- CTEM appearance of glycogen depends upon the fixation and staining procedures involved.

#### **d) Intranuclear Lipid**

- In some normal cells such as the liver cells, lipid inclusions also occur in a spectrum of neoplastic and non-neoplastic conditions,
- From chromosomal disorders such as the Leydig cells in Klinefelter's syndrome reactive conditions such as the synovial cells in lipohaemarthrosis.
- Neoplastic disorders in different tissues. [32]

#### **e) Lead and Bismuth**

These two heavy metals can induce characteristic intranuclear dense elemental inclusions, with a distinctive ultrastructural morphology.

##### **i) Lead Inclusions**

**Structure:** Characterised by a markedly dense core surrounded by a less dense network of radiating fibrillar material.

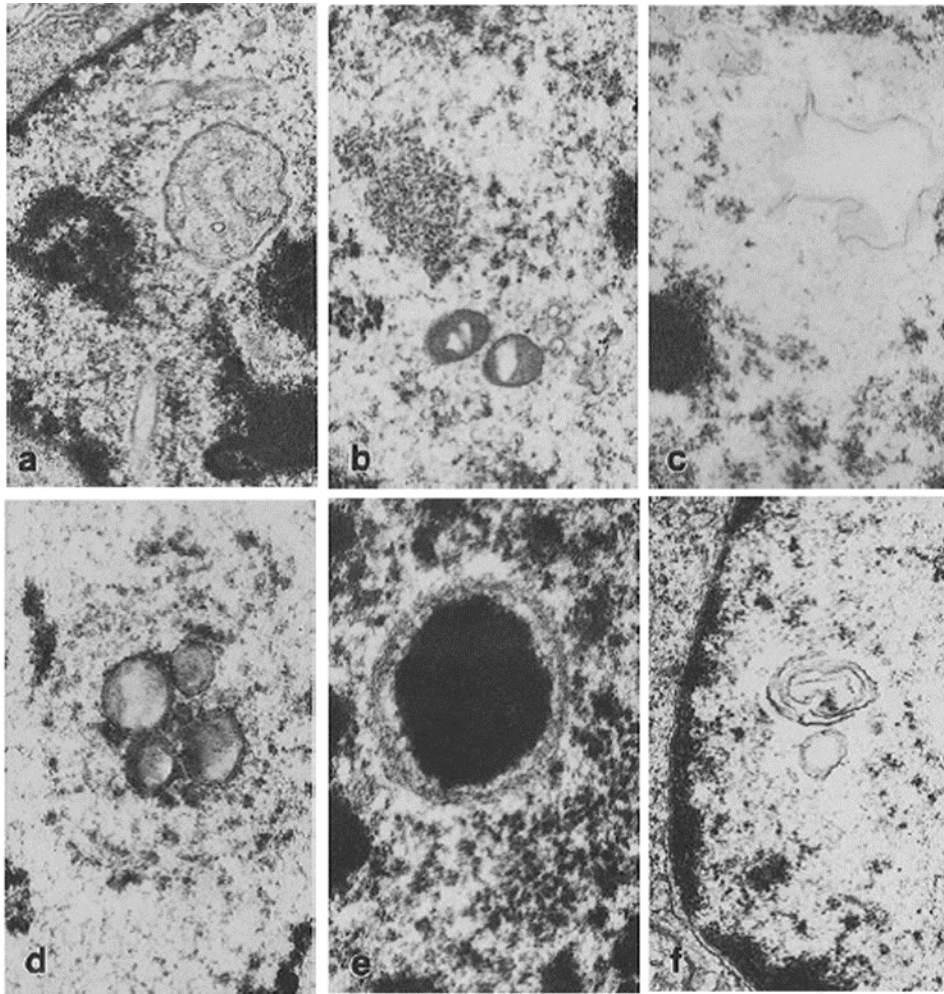
##### **ii) Bismuth inclusions**

**Structure:** Often well delineated, oval to rounded homogeneous dense structures, which sometimes show some granularity.

##### **Occurrence:**

- Both types of inclusion are typically detected in the renal tubular cells but lead inclusions can also be seen in hepatocytes.

- Electron-probe X-ray microranalysis offers a definitive means for their precise identification.
- The mere presence of these inclusions does not necessarily indicate acute intoxication, but can point to previous exposure to either of these elements (Figure 4).



**Figure: 4** Intranuclear inclusions. *a* Inclusion resembling a mitochondrion, apparently unenveloped within the nucleus in an experimental animal tumour.  $\times 14250$ . *b* Two inclusions resembling dense pyknotic mitochondria; note also the vesicular structures and the aggregation of interchromatin granules in a methotrexate-treated mouse sarcoma 180.  $\times 18800$ . *c* Membrane-bound intranuclear vacuolation of uncertain cause. Similar appearances can arise artefactually; actinomycin D-treated Ridgeway osteogenic sarcoma.  $\times 11\ 500$ . *d* Vesicular nuclear body with fibrillar exterior; astrocyte in multiple sclerosis autopsy tissue.  $\times 39000$ . *e* Nuclear body with fibrillar exterior and dense core; astrocyte in Alzheimer's disease biopsy tissue.  $\times 25500$ . *f* Concentric laminated inclusion in an experimental animal tumour.  $\times 14250$  (Courtesy: Pathology of Nucleus)

#### f) Unspecified Intranuclear Inclusions

Unspecified nuclear inclusions are seen in normal cells and in several pathological conditions. These include mainly viral infections and neoplastic disorders, but also some other miscellaneous conditions, including muscular and neuronal disorders and toxic or hormone-induced disturbances. In pathological situations they may be more numerous or more prominent than normal, or they may appear in cells which do not normally contain them.

#### Conclusion

Despite a voluminous literature on fine structural phenomena, which can only be touched upon in here, our understanding of the interrelationships between nuclear morphology and disease remains incomplete and largely circumstantial. There remain, however, some difficult barriers to future advances. The nucleus is a uniquely dynamic component, changing with time, most remarkably in the process of mitosis. In the consideration of agent effects, nuclear alterations and cellular consequences are materially influenced by such changes.

Moreover, the response of the nucleus to a particular insult, such as viral infection, may be unpredictable, leading to degeneration, lysis and cell death in one case and neoplastic transformation in another. The malignant nuclear phenotype itself, in ultrastructural terms, is probably a rather poor mirror for the many complex processes involved in oncogenesis. For this reason, for the foreseeable future, the ultrastructural study of nuclear morphology in health and disease is likely to prove considerably more challenging than most other investigations of cellular structure.

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