THE GENESIS OF HUMAN BREAST CANCER

Histological, Histochemical and Cariometric Studies — Proposition on the Genesis of Cancer

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This paper is based on the analysis of 1.760 cases of breast pathology — interpretation of clinical and histological findings; histochemical and cariometric investigations. All of these studies have the purpose of determining the most characteristic features observed in pre-malignant and malignant cells and the phases of carcinogenesis, emphasizing the knowledge of the morphological precursors of cancer. Some implications of these investigations with the cause of cancer are mentioned.

THREE GROUPS OF FACTS IN CARCINOGENESIS RESEARCH

1. *Morphological Precursors of Cancer* — The essence of the problem lies in the answers we can give to a few questions. Is the cancer always preceeded by benign histological pictures which can be called morphological precursors or sometimes, may it arise from normal tissue? Do the morphological precursors always become malignant? Why do they become malignant?

It is our impression that, undoubtedly in the mouse breast cancer, the answer is" cancer is preceded by the appearance of "hperplastic nodules", as it has been demonstrated in the Cancer Research Genetics Laboratory at Berkeley (1) (3 to 24), by Foulds, in England (25) and, in some way, by Bonser, Jull and Josset at the Department of Experimental Pathology and Cancer Research of the University of Leeds (26). These experiments have been confirmed by Squartini e Severi at the Division of Cancer Research, Istituto di Anatomia e Istologia Patologica, in Perugia, 1958 — just some of the "hyperplastic alveolar nodules" ended in cancer; although the majority of the "plaques" of ductal origin described by Fould become malignant (57). According to Mühlbock, in the Het Nederlandsch Kankerinstitut (Antoni Leenwenhoek Huis) of Amsterdam, it has been proved that not all of the hyperplastic nodules — but just 1 out of 10 or 15 — may suffer malignant change (58) (the histological pic-

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tures of these two kinds of nodules have not been shown). Nevertheless, no one seems to admit that the experimental mammary cancer develops in a normal breast tissue.

On the other hand, as much as the human breast cancer was concerned, two points, that have not helped very much to make clear the problem, have been mentioned. The clinical data gathered during many years was not very much conclusive — it seems the interval between morphological precursors and cancer may be as large as the one between carcinoma in situ and invasive carcinoma which takes even 10 years. The post-mortem findings of Franz and all, ([27]) show a high incidence of chronic cystic disease in the so-called "normal breast" — these findings, however, are not quite corroborated by our experience of breast biopsy and histological studies ([28]) ([29]) ([30]). Although, not quite as frequent these histological pictures are not rare, and that is possibly the reason why breast cancer incidence is so high.

The term "Morphological Precusors of Cancer" has been used ah the International Conference held at Perugia, in 1961 ([1]). It seems more suggestive than "Preneoplastic Fields" proposed by Willis ([2]) and it corresponds to the experimental "hyperplastic nodules" of the mouse brests described in the Department of Zoology, Cancer Research Genetics Laboratory of the University of California, at Berkeley, and to ductal "plaques" mentioned by Foulds. Of course, it is employed instead of precancer — a significant but questionable expression.

2. *DNA-RNA increase the most important feature observed in pre-malignant and malignant cells* — The increase of the amount of DNA (Desoxyribonucleic Acid) and RNA (Ribonucleid Acid) seems to be the most important difference between malignant and normal cell noticed since Bisels, 1944 ([37]), Stowell, 1946 ([38]), Caspersson, 1950 ([39]), Leuchtenberger and all., 1954 ([40]), Mellors, 1955 ([41]) Atkins and Richards, 1956 ([42]), Harkness and all., 1957 ([43]), Long and Doko, 1959 ([44]), Ashworth and all., 1960 ([45]), Sandritter, 1952, 1958, 1960, 1961 ([46 to 50]), Grundmann, 1961 ([54]), Hopman, 1960 ([56]), Monteiro, 1962 ([30, 31]) Valeri e col., 1963 ([59]). From these studies the works of Caspersson determining the "dry weight" of the cells, of Atkins and Richards using the microspectrophotometry of Feulgen stain, and of Sandritter by quantitative ultraviolet photometry and plain cytophotometry which will have permitted to stablish a fairly accurate evaluation of the rate of the DNA-RNA of the cells must be emphasized.

Histochemical studies have also shown increase of DNA-RNA in carcinoma in situ of the cervix uteri by Valeri e col., 1963 ([59]) and in the so called morphological precursors of cancer by Mellors, 1955 ([41]), Harkness

and all, in experimental breast pathology, 1957 ([43]), in basal hyperactivity and squamous metaplasia in human uterine cervix by Monteiro, 1962 ([30]) and in human brest pathology by Monteiro, 1962 ([31]).

3. *Tetraploidism, Diploid reduction and Aneuploidism/Polyploidism phases of carcinogenesis* — In 1954 and 1960, Grundmann (Ludwig Ashof Haus, Freiburg) studying cytophotometrically the nuclei in intermitosis of the liver of rats submitted to a diet with dimetilaminoazabenzol (yellow butter) ([51]) ([52]) and dietilnotrosamine ([60]) observed the appearance of large nuclei, 90% tetraploids (premalignancy), followed by a diploid reduction (beginning of malignancy) originating an hepatoma either euploid (ex: diploidism) or aneuploid/polyploid. The same facts have been confirmed by Schmall, Preussmann and Hamperl, 1960 ([60]) and in human uterine cervix by Grundmann and all. 1960 ([53]), Oberling and Bernhard, 1961 ([61]), and Bayreuther, 1960 ([62]).

Cariometric determinations (measurements of the nuclei size) have also been mad in benign and malignant pathology os the breast by Monteiro, 1962 ([31]) as it is presented in the following pages.

OUR STUDIES ON THE DETERMINATION OF THE MORPHOLOGICAL PRECURSORS OF BREAST CANCER

1. *Clinical and Histological Evaluation of "Perilouness" (potencial danger)* — Out of 1760 cases of breast pathology we submitted to a combined clinical and histological evaluation of perilouness, there were 523 cases with the following histological diagnosis: Fibrosis, 139; Lobular hypertrophy, 37; Adenosis, 77 (63 blind duct adenosis and 14 sclerosing adenosis); Simple Cysts, 42; Apocrine epithelium, 25; Intraductal hyperplasia, 29; Intraductal adenomatosis, 10; Intraductal papillomatosis, 15; Fibroadenoma, 149.

Five factors were evaluated: A) Association to supposedly dangerous histological pictures. B) Agressive histology (hyperplasia and/or lose of differentiation). C) Histological association to cancer in the "surrounding coat". D) Histological transformation into cancer. E) Clinical evolution into cancer.

The findings observed are as follows (Table 1). The percentage presented has been calculated as the expected group ratio.

Summarizing these findings we may state that Fibrosis and Fibroadenomas present the lowest Index of Perilousness (only factors A and B positive) which means they just have an indirect perilousness as a result of a possible association of other histological pictures. The same cannot be said about the apocrine epithelium because it is in cause in the simple cysts (all factors positive) and in the papilliferous hyperplasia the precursor of papillomatosis. Lobular hypertrophy is the beginning of adenosis, which with ductal hyper-

TABLE 1

INCIDENCE OF PERILOUSNESS IN BREAST BENIGN PATHOLOGY (523 CASES)

Factors	A %	B %	C %	D %	E %
Fibrosis	5,38	0	9,2	0	0
Lobular Hypertrophy	29,7	0	5,5	3,7	0
Adenosis	10,4	42,8	11,1	11,1	0
Simple Cysts	69,04	69,04	18,5	9,2	1,5
Apocrine Epithelium	—	—	12,9	9,3	0
Ductal Hyperplasia	81,8	100	3,7	3,7	—
Ductal Adenosis	20	100	1,8	14,8	0
Ductal Papillomatosis	33,3	100	1,8	5,5	0
Fibroadenoma	—	5,5	1,8	0	0

plasia, adenomatosis and papillomatosis have factors A, B, C and D positive revealing a high Index of Perilousness. Although, we may assume that a long time — 10 to 20 years, — may elapse until an initial form of a morphological precursor become cancer. That is the reason we have not found a high incidence of malignant transformation in the follow-up of benign breast pathoolgy. Another reason is because many cases are submitted to surgical treatment.

Otherwise, we have observed in the so called "noncarcinomatous coat" of 54 cases of carcinoma of the breast the coexistente and, sometimes, the transformation of benign to malignant pathology. Findings are shown in Table 2.

In the analysis of these findings we emphasize, first of all that we have acquired the impression that malignancy does not arise from normal breast tissue. On the other hand, we may state that even the apparently less dangerous histological pictures as fibrosis and lobular hypertrophy, simple cysts and fibroadenomas cannot be considered completely innocent because of a possible association to other more agressive ones. Although we may consider the existence of two kinds of perilousness: direct and indirect.

According to this classification it should be estimated as directly dangerous: intraductal adenomatosis, intraductal papillomatosis, ductal hyperplasia and adenosis. The indirectly perilous

TABLE 2 :

INCIDENCE OF COEXISTENCE AND TRANSFORMATION IN CARCINOMA

Incidence in the "noncarcinomatous coat"				Transformation in carcinoma			
Apocrine epithelium ...	8,4 %	to	17,5%	Ductal adenomatosis	9,9%	to	19,6%
Adenosis	6,8 %	to	15,4%	Adenosis	6,8%	to	15,4%
Fibrosis	5,3 %	to	13,2%	Apocrine epithelium	5,2%	to	8,6%
Lobular hypertrophy ...	2,4 %	to	8,6%	Ductal papillomatosis ...	2,4%	to	8,6%
Ductal hyperplasia	1,1 %	to	6,3%	Ductal hyperplasia	1,1%	to	1,6%
Ductal papillomatosis ..	0,02%	to	3,6%	Lobular hypertrophy	1,1%	to	1,6%
Fibroadenoma	0,02%	to	3,6%	Fibrosis	0 %		
Ductal Adenomatosis ..	0,02%	to	3,6%	Fibroadenoma	0 %		

Percentage is represented by both the Maximum Inferior Value and the Maximum Superior Value.

picture would be represented by: apocrine epithelium hypertrophy, fibrosis and fibroadenoma.

2. *Histochemical Studies* — Three types of stains were emploeyd: Periodic Acid Schiff (PAS) for polysacarides, Feulgen's reaction for DNA, and Gomori's stain for collagenous. They were used in 122 cases — 53 breast dysplasias, 54 carcinomas, 14 fibroadenomas and 1 cystosarcoma phyllodes. A synthesis of the tresults is presented in Table 3.

To comment these findings we should say that the histochemical perilousness was expressed as follows: adenosis, Gomori (+); ductal hyperplasia (Feulgen B ++); ductal adenomatosis (Feulgen B ++ to B +++); ductal papillomatosis (Feulgen B +++).

According to the cariometric studies we consider dangerous the histological pictures in which we found large nuclei Feulgen B ++ to Feulgen B +++ that is a characteristic of tetraploidism of the morphological precusors of cancer, and its presence associated to micronucleated groups of cells in cases of early carcinomas. This happens in the ductal hyperplasia, ductal adenomatosis (comedoadenoma) or papillomatosis (papilloma) and in blind duct or sclerosing adenosis.

3. *Nuclei Measurements* — Cariometric studies were done in 82 cases: 21 normal breasts, dysplasias and be-

TABLE 3 :

HISTOCHEMICAL FINDINGS (122 CASES)

	PAS	Feulgen	Gomori
Normal lobules	positive	A +	
Normal ducts	positive	B +	
Basal membrane	positive		
Normal conective	positive		(++)
Lobular involution	positive		(++) to (+++)
Collagenosis	positive		(+++)
Lobular hypertrophy	negative	A ++	(++)
Blind duct adenosis	negative	A ++	(+)
Sclerosing adenosis	negative	A ++	(+)
Simple cysts	positive		(++)
Apocrine epithelium	positive	B ++	
Columnar metaplasia	negative		
Ductal hyperplasia	negative	B ++	(++)
Ductal adenomatosis	negative	B ++ to B +++	(++)
Ductal papillomatosis	negative	B ++ to B +++	(++)
Fibroadenoma (epithelium)	positive	A +++ to B ++	
Mixomatosis	negative		(+)
Cystosarcoma phyllodes ...	negative		(+)
Comedocarcinoma in situ .	positive (sec.) negative (epit.)		
Scirrous carcinoma	negative	A +++	(+)
Advanced carcinomas	negative		(+)

nign neoplasias; 50 invasive carcinomas; 10 fibroadenomas; 1 cystosarcoma phyllodes. To measure the nuclei a Leitz micrometric ocular was used and the measuments were taken during the intermitosis. Findings are in Table 4.

TABLE 4 :

CARIOMETRIC FINDINGS (82 CASES)

Type of cells	*Nuclei measurements in micra*
Normal lobules	2.96 to 4.44
Normal large ducts	5.92
Apocrine epithelium	4.44 to 6.66
Blind duct adenosis	4.44
Duct adenomatosis	4.44 to 6.66
Papilloma	6.66
Fibroadenoma	2.96 to 4.44
Cystosarcoma phyllodes	4.44

Of these measurements we emphasize the ones of papilloma and adenosis which may be considered increased to the cells from which they originate.

From 50 carcinomas, 29 which were iniating carcinogenesis have been of particular interest: 22 cases (79%) had nuclei from 4.44 to 8.88 micra. In all these 29 cases of initial stages of carcinoma formation there were areas of cells with smaller nuclei, most of them 2.96 to 4.44 micra. The localization of these areas of retracted nuclei varied: in connection with the surrounding dysplastic area 13; spreading through the whole tumor in 6 cases; as an invasive area in 10 cases.

From these measurements we may state that no micronucleated cells have been observed in intraductal forms of cancer but only in cases where the stroma is invaded. On the other hand, we did not find small nuclei in papillomas, adenomas or hyperplasias. In cases of comedocarcinoma the intraductal area of the tumor was macronucleated in contrast to the micronucleated invasive area with characteristics of scirrous carcinoma developped from area of adenosis (it is sometimes a very difficult differential diagnosis, as it has been noticed by Stewart (55). Another point that must be emphasized agair sis: the preinvasive anular form of comedocarcinoma must be considered carcinoma in situ and the solid intraductal adenoma (which may be called comedoadenoma) diagnosed as a morphological precursor of cancer, (see Table 5).

TABLE 5 :

HISTOCHEMICAL AND CARIOMETRIC PRECURSORS 0F CANCER
PRIMARY PHASE OF CARCINOGENESIS

	Comedocarcinoma	Apocrine Carcinoma	Papillary Carcinoma	Scirrous Carcinoma	
Histochemistry	PAS — Feulgen A +++ Gomori +	Not observed	Not observed	PAS — Feulgen A +++ Gomori +	Primary phase of Carcinogenesis
Cariometry	2.96 to 4.44 micra	Not observed	Not observed	2.96 to 4.44 micra	
Histochemistry	PAS — Ct + Feulgen B ++ Gomori ++	PAS + Feulgen B ++ Gomori ++	PAS — Axis + Feulgen B ++ Gomori +	PAS — Ct + Feulgen A ++ Gomori +	Histochemical and Cariometric precursors of cancer
Cariometry	8.88 micra	4.44 to 6.66 micra	6.66 micra	4.44 micra	
	Adenomatosis	Apocrine hyperplasia	Papillomatosis	Adenosis	

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Adenomatosis is preceded by ductal hyperplasia. Apocrine hyperplasia results from stimuli on apocrine metaplasia. Papillomatosis is a more advanced grade of papilliferous hyperplasia. Adenosis usually begins as a lobular hypertrophy.

All the carcinomas seem to originate either in situ (comedo, apocrine, papillary) or directly invasive (lobular), both acquiring the aspect of a scirrous carcinoma when invasion starts. The other types of breast carcinomas depend of the connective barrier.

According to our observations the type of carcinoma is the result of two opposing forces: DNA-RNA increase — the connective barrier. Most of the breast carcinomas seem to originate as *in situ* comedo —, apocrine — or papillary — and latter becoming invasive scirrous carcinomas: others start as a lobular directly invasive scirrous carcinomas. Either type may remains as a diploid carcinoma or becomes an aneuploid/polyploid carcinoma. If the surrounding stroma is densely collagenous the carcinoma stay as scirrous or as circumscribed (Haagensen's terminology) (70); if colloid it becomes a gelatinous carcinoma; if the connective tissue is loose by any reason (constitutional or hormonal as in pregnancy) it gives rise to a medullary carcinoma or to the so-called acute carcinoma with the aneuploid/polyploid type of nuclei. (see Table 6).

Regulating the growth and the type of the carcinoma two factors seem to be in cause: the increase of the DNA-RNA determining the rate of mitosis and the opposite barrier of the surrounding connective tissue.

Proposition on the Genesis of Cancer

The most important signification of these findings is related to the fact that is was possible to establish that the increase of DNA-RNA in the so called morphological precursors of cancer have the meaning of a *link between the normal and the malignant cells.* This link is another proof that the malignant cell cannot be considered as an autonomous cell which acts without obeying the biological laws. That this is not true is beeing suggested by the fact that in the malignant cell the same genetic code as it happens in normal cell is followed departing from the genetic order to the arrangement of the proteic molecule: DNA → RNA messager → RNA supernatant (genetic code) → RNA ribossomal → arrangement of the aminoacide in the proteic molecule according to the genetic code of triplets. This is the most important biological law, also followed by the malignant cell. Otherwise a malignant cell would not give rise to a malignant cell. The other point is that a carcinoma originated from an hormone dependant tissue will keep this dependance as long as they stay differentiated (50% in breat cancers). Finally, the malignant cells only integrated in the proteic molecule natural

TABLE 6:

PHASES OF BREAST CARCINOGENESIS

	Hormonal Hyperactivity	Morphological Precursors	Carcinoma in situ	Invasive carcinoma I — Initial phase	Invasive carcinoma II — Advanced phase (Dense connective or colloid barrier)	Invasive carcinoma III — Advanced phase (Loose or edematous connective tissue)	Sarcoma
1.	Ductal hyperplasia	Adenomatosis	Comedocarcinoma (intraductal)	Scirrous carcinoma	Scirrous carcinoma	Medullary carcinoma	
2.	Papilliferous hyperplasia	1. Apocrine hyperplasia 2. Papillomatosis	Apocrine carcinoma (intraductal) Papillary carcinoma (intraductal)	Scirrous carcinoma Scirrous carcinoma			
3.	Basal hyperactivity (rest of nipple pouch)	—	Paget's carcinoma (intraductal)	1. Neomammary carcinoma* 2. Paget's duct carcinoma	Circumscribed carcinoma **)	Acute carcinoma	
4.	Lobular Hypertrophy	Adenosis (blind duct or sclerosing)	Carcinoma starts invading lobular stroma	Intralobular scirrous carcinoma	Gelatinous carcinoma		
5.	Epithelial hyperplasia in fibroadenoma	Fibroadenoma with adenomatosis and/or papillomatosis	Carcinoma limited to fibroadenoma clefs	Carcinoma of the fibroadenoma			
6.	Stroma mixomatosis in fibroadenoma	Cystosarcoma phyllodes					Sarcoma

* Geschickter's terminology — ** Haagensen's terminology

L — aminoacids as happens in the normal cell, otherwise they would not survive.

Cancer must not be considered a "sui generis", mysterious disease, entirely different from either hyperplasias or bening neoplasias. It is the result of gradual transition from normal tissue to the so called morphological precursors. This biochemical and genetical link between normality and malignancy may be pointed out as an increase of DNA-RNA.

Qualitative differences, between normal and malignant cell have not been found, just quantitative ones. The most important, because it is the primary one, is the increase of DNA-RNA. All the other quantitative differences — enzymatics etc — result from the DNA-RNA increase.

Probably this DNA-RNA increase may result from different causes: virus, chemical carcinogenic agent, radiation.

In spontaneous cancers of mice the DNA-RNA increase may result from the presence of virus — which are always formed by DNA or RNA — in the cells, meanwhile it has been suggested that in human cancers it would be explained by the incorporation of the DNA virus to the DNA of the nucleus or the RNA virus to the RNA of the cytoplasm, as it happens with the polyoma virus and with the lisogenic bacteriophage. Even the increase of the DNA-RNA in the morphological precursors of cancer (hyperplastic nodules in mouse breast) get an explication if the works of Pitelka (18) and of Smoller (23) about a provirus and of Höllstrom (65) about a prophage of the lisogenic bacteriophagus are accepted.

The mechanism of the chemical carcinogenic agents could be interpreted, according to Karlson's (67) and Dannenberg's (64) experiments in the Max Planck Institute of Munich, by the inclusion of the carcinogenic agent with similar molecular formula and close staining properties (v. dibenzanthracen) in the DNA molecule between the vertical puric and pirimidic plaques, as it occurs in the "Chironomus tentana".

Nevertheless, in radiation as in most human cancers, the cause of the DNA-RNA increase seems to result — as far as it has been observed in whole body irradiation by Friedmann and all., 1964 (72), and in untreated leukaemia by Houston and all., 1964 (73) — from endoreduplication of the chromosomes (a form of polyploidisation characterized by diplochromosoms in prophase and metaphase resulting from anomalous spindle formation). The same phenomenon of endoreduplication of chromosomes, proved by idiograms, may explain the hyperdiploidism observed in hyperplastic nodules of the mouse breast by Banerjee and De Ome (10), at Berkeley.

Hormones seem to be carcinocinetic — accelerating mitosis in hormone dependent tumours — and may act in the production of morphological precursors originated from hormone dependent tissues, but they are not carcinogenic "sensu strictu".

As a matter of fact it seems that the evolution from normal to malignant tissue is gradual, and according to the following order: A — *Morphological precursors of cancer* — stage allways present. B — *Carcinoma in situ* — stage only present when there is a strong connective barrier * (more important than the basal membrane) as it happens in the uterine cervix and in intraductal breast pathology. C — *Invasive carcinoma* — when the connective tissue is beeing replaced by malignant cells which infiltrate — with no destruction or violence, except the subversion of the homeostasis — the interspaces and so reaching the lymphatics. Metastasis also seem to be a matter of simple cell replacement without cytolisis or necrosis (which are always a secondary phenomenon). Death results either from the substitution of mature cells of the essential organs by immature non functionning cells or by supervening complications determining the failure of vital systemic functions caused by compression. Not produced from special malignant cell property, but by the acceleration of mitosis resultant from the RNA increase.

Probably the reason why just some morphological precursors of cancer become malignant is the continous acting of a carcinogenic agent, radiation, virus etc. If you stop the cause of the DNA-RNA increase before occuring the transformation of the benign cells in malignant cells the cancer does not appear. This fact seems to have been proven experimentally.

The cause of cancer lays — as it is suggested by our studies — in the amount of DNA-RNA in the cell. This DNA-RNA increase explains pratically all the morphological and functional changes (coarse chromatin, basophilism, nucleolar proeminence, hyperactivity leading to immaturity) we observe in malignant cells. Nevertheless, some investigations must be done to prove — as we can assume from our work — that a morphological precursor of cancer has a lower amount of DNA-RNA than a carcinoma in situ and yet lower than an invasive carcinoma. Then we can tell that above some DNA-RNA level a benign cell becomes a malignant one, no matter which is the determining factor: virus, chemical carcinogenic agent, radiation.

* Possibly due to the ratio of colloidal Iron (Fe) in the stroma.

SUMMARY

1. Cancer arises gradually, preceded by histological, histochemical and cariometric (tetraploidism) or hyperdiploidism pictures which may be called morphological precursors of cancer.

2. Malignant cells are not autonomous, but obbey the principal biological laws — genetic code of triplets, hormone dependence etc. Then, cancer cannot be considered a "sui generis", mysterious disease.

3. Differences between normal and malignant cells are only quantitative. The most important feature in pre-malignant and malignant cells is the increase of DNA-RNA. All the other findings — enzymatics etc. — most be considered as secondary phenomena.

4. The increase of DNA-RNA in the cells of the morphological precursors of cancer — as stated by the author — has the meaning of a **link** between normal and malignant cells.

5. The increase of DNA-RNA explains all the morphological and functional changes observed in malignant cells, including accelerated growth, invasion, metastasis and death — malignant cells reaching the interspaces-vessels and impairing vital functions either through the substitution of functional cells by immature outsider cells or by compression of important organs.

6. The cause of this DNA-RNA increase may be diversified: virus (integration of the DNA-RNA of the virus in the DNA-RNA of the cell), chemical carcinogenic agent (inclusion of the molecule of the carcinogenic agent between the puric and pirimidic plaques of the DNA molecule), radiation (endoreduplication of the chromosoms).

7. Hormones act as a carcinocinetic agent (accelarating mitosis) in hormone dependent tumours and determining the appearance of the morphological precursors of cancer in hormone dependent tissues.

8. The growth of the malignant tissue — just a displacement of normal cells by malignant ones — depends of the amount of the DNA-RNA in the malignant cells and of the opposite force of the connective barrier.

9. Histological, histochemical and cariometric studies made by the author in cases of breast pathology lead to the conclusion that may be considered morphological precursors of breast cancer — apocrine hyperplasia, adenomatosis, papillomatosis and adenosis — which give rise to apocrine carcinoma, comedocarcinoma and papillary carcinoma, initially intraductal or intracystic, i.e., in situ. Adenosis gives rise to directly invasive lobular carcinoma (scirrous type).

Initiating invasion all the carcinomas in situ become scirrous carcinoma by diploid reduction, and acquire other patterns according to the connective barrier. If the connective is dense (possibly due to a high ratio of colloidal Iron) the carcinoma stay as scirrous or circumscribed. If there is a colloid degeneration of the stroma the carcinoma will be of gelatinous type. If the connective is loose or edematous the carcinoma will appear as medullary or acute.

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