NATURAL HISTORY OF THE CERVICAL PRECANCEROUS LESIONS AND THEIR EVOLUTIONS

J. DE BRUX

Institut de Pathologie et de Cytologie Appliquée
Paris (France)

SUMMARY

The numerous epidemiologic studies confirm that precancerous cervical lesions and C.I.S. are dependant on multiple mutagenic factors (chemical, virus and other nucleo-proteins, radiations and co-carcinogens, hormones, infections). These studies demonstrate that cervical cancer is a "sexually transmissible" disease.

The C.I.N. have a monomorphic mechanism. Their point of departure is the undifferentiated stem cells. Accord'ng to the number of mitosis, their epidermoïd differentiation and their capacity to mature, the morphology of these lesions will vary (C.I.N. 1, 2, 3, dysplasias: slight, moderate, severe, carcinoma *in situ*).

The prognosis of these lesions is still unknown. Some are easily healed, others progress more or less rapidly, still others dramatically invade the stroma. These variables depend on the gravity of the DNA lesion caused by mutagen: some rapidly repair, others have a blocking effect on the DNA-synthesis and the cell dies, others present a definitive mutation able to be replicated. The DNA lesions induce an increase of the DNA-synthesis, and the cellular differentiation will be absent or delayed.

The cytoplasmic protein-synthesis will also be modified (new glyco-proteins secretions: enzymes, globulins, angiogenesis factor, etc. ...) favoring new cellular differentiation and/or invasive factors.

So finally, the tumoral antigens induce a mediated cellular and humoral immunity of the host against his tumor.

All these facts permit a better understanding of the histogenesis and the different evolutions of the precancerous cervical lesions.

The progress during the 10 last years in virology and genetics have permitted a better approach to the understanding of the precancerous states in the cervix. Different elements seemingly without any relationship better explain some obscure facts. Among them: epidemiologic and etiologic factors. Moreover the histologic and cytologic morphology have a histogenetic value. The evolutive variants of these lesions are now more comprehensible.

EPIDEMIOLOGY

Since the beginning of the 19th century, Authors have known the role of the low socio-economic classes and of multiple pregnancies. Among them new knowledge was brought by Gagnon (1950) ([1]) and more recently by Rotkin ([2]), Beral ([3]), Pauli ([4]), etc. ... Now, the age of the first coïtus and the number of intimate partners and even the husbands' occupation have been extensively studied (tab. 1, 2, 3).

These facts are supported by the presence of very frequent severe cervical lesions and carcinomas *in situ* among teenagers having intercourses with many partners, sometimes before the menarche, and also by the forgotten hygienic cautions because of the wide use of contraception. So around the world, it's now admitted that cervix cancer is sexually transmissible (tab. 4).

ETIOLOGY

Since a long time, the chronic bacterial infections were admitted: gonorrhea, syphilis, inguinal granuloma, and more recently the Chlamidyae infections are considered as a favouring factor. But these bacterial infections maintain chronic inflammation, playing a role in the "transformation" of the cells.

The virus is every day, more and more, incriminated. HSV II and now Papilloma-virus of the sub-group No. 6 (Orth

Reprinted from "Eur. J. Gynaec. Oncol.", 3: 1, 1982.

Table 1. — *Relationship between social factors and carcinoma of the cervix (from H. K. Pauli).*

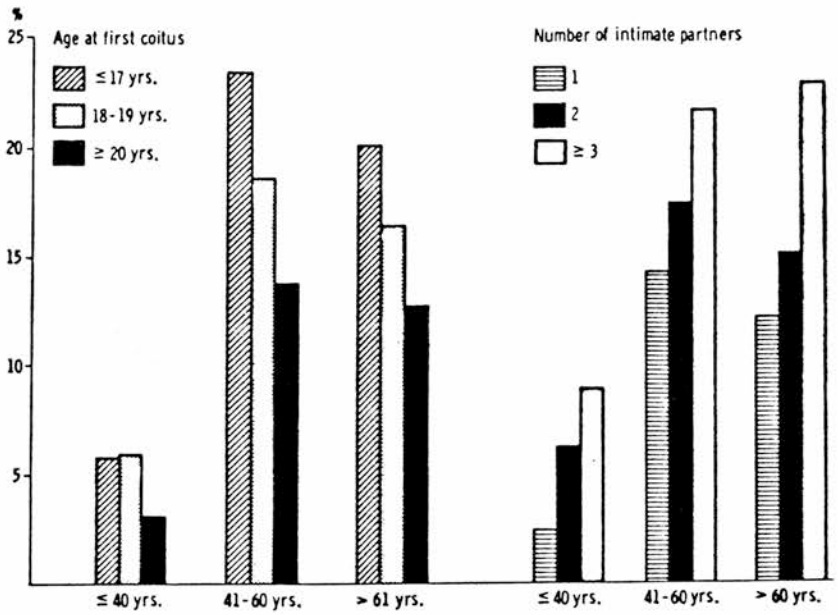

Table 2. — *Relationship between social factors and carcinoma of the cervix (from H. K. Pauli).*

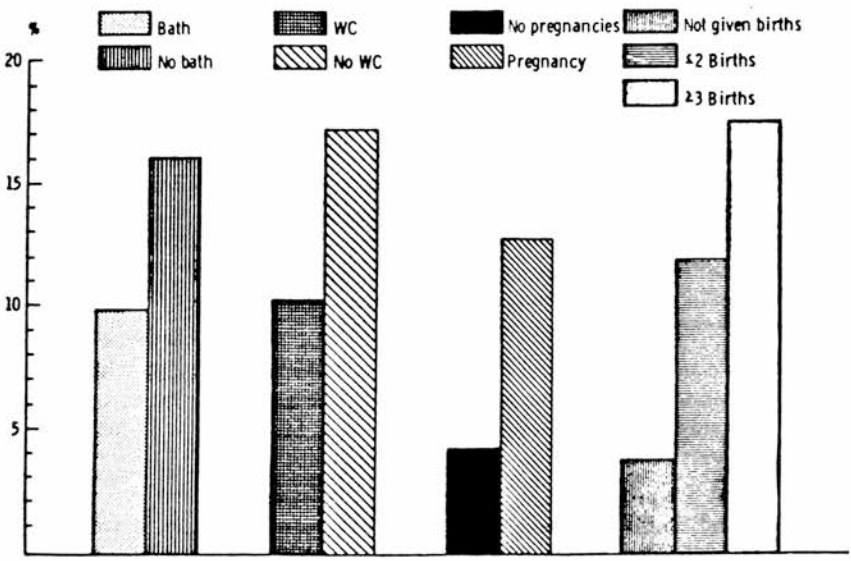

Table 3. — *Standardized mortality ratios for cervical cancer in married women by husband's occupation within social classes II and III (England and Wales, 1959 to 1963) (Adapted from Beral 1974).*

Social class	Husband's occupation	SMR
II	Clerks of works	40
	Clerks	64
	Crane and hoist operators	159
	Drivers of road goods vehicles	168
III	Shopkeepers and assistants	71
	Gardeners and groundsmen	98
	Fishermen	257
	Deck and engineroom ratings, bargemen and boatmen	263

and Jablonska) ([5]). The role of cytomegalovirus is aleatory.

Mutagenic factors, resulting from chemicals or radiations, are now accused. Cohen and Wherret ([6]) estimate the majority of spermatozoïds deteriorate in the vagina and on the cervix within a few minutes after their ejaculation. The spermatozoïds, heads present DNA molecular variations, even in the same ejaculate and even more in the ejaculate of different men. This DNA, called "de luxe" is an inactive heterochromatin. So some would be of "high risk" men.

Moreover, some women whose husbands have special occupations, such as farmers, fishersmanual workers, have a greater risk of developing a cervical cancer.

The rich-arginine histome from the degradate spermatozoïds would have a mutagenic action capable of differenciating and transforming the indifferent cells. Genetic predispositions, hormonal factors (pregnancy and E/P imbalance) would be co-carcinogenetic factors.

In fact, any of these factors seems specific of the cervical cell mutation.

The classic schema: iniziation→hyperplasia→promotion, and cancer may be quite variable. The evolution of the process may last months and years. Sometimes, the chromatin lesions have no histologic representation. In some cases the lesions remain stationary for many years, or disappear. A new mutation by reinfection or the chronic action of a powerful co-carcinogen is necessary to induce a histologic and cytologic lesion. However, the host reactions must be taken in account.

CLINICAL HISTOPATOLOGY

The simple ectropion, more marked during adolescence, in contact with the vaginal medium undergoes an epidermoïd metaplasia by slipping of the germinative cells of the normal epidermoïd epithelium, giving a true malpighian epithelium with glycogen. But, on the large ectropions, the epidermoïd epithelium arises from cells called "reserve cells" or from undifferentiated cells resulting from an extensive multiplication of the cylindrical cells which have no time to become differentiated, or from the cells of the naked superficial stroma. In some cases, an undifferentiated and immature epithelium formed by the piling of these cells is difficult to distinguish from a true carcinoma *in*

Table 4. — *Consolidated results of case-control studies in carcinoma of the cervix (from Rotkin, 1973).*

Variable	No. of studies	Mean ratio: Cases/ Controls
First marriage under age 20 or 21	13	1,4
Two or more marriages	7	1,8
Sexual initiation before age 20	5	1,5
Sexual initiation before age 17	4	2,4
Two or more sexual partners	3	1,7
Divorces and separations	6	2,3
Unstable sexual relationships	4	2,0
Coital frequency	6	1,1
Mean age menarche	3	1,0
Contraceptive practices	5	1,0
Partner not circumcised	7	1,1

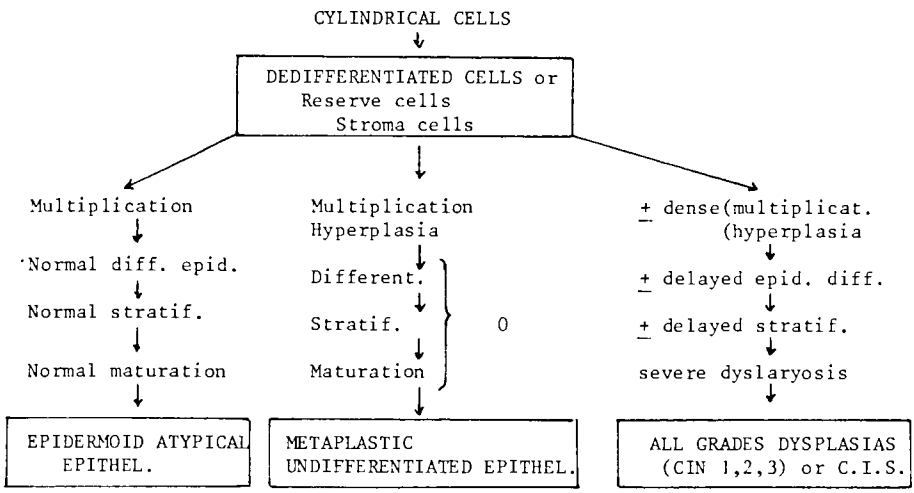

Fig. 1. — Histogenesis of intra-epithelial lesions.

situ. Anyway all the atypical cervical lesions depend on these germinative cells activity (cellular density, number of normal and abnormal mitosis).

The germinative cells pil up without epidermoïd differentiation. From the height of the epidermoïd differentiation of these germinative cells will depend the structural modifications of the epithelium. In this way, the epidermoïd cells secrete a special protein, a chalone, which limits the mitosis of the underlying layers. A precocious differentiation will give an almost normal epithelium with only some cell maturation (light dyskaryosis) corresponding to a light dysplasia. A great density of numerous mitosis of the germinative layers, a more delayed epidermoïd differentiation will induce troubles or absence of cellular maturation giving mo

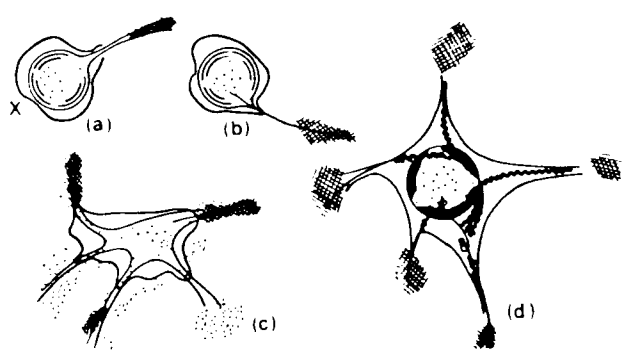

Fig. 2. — Surface of the mobile cells. a and b: Undifferentiated cell with extension of DNA nuclear filaments disaggregating outside the plasma membrane. c: Enlargement of DNA bundles forming a network able to catch extrinsec proteins. d: Reaggregation of the DNA filaments coming back to the nucleus, modifying and activating the genome. (From Reid and Coppleson, 1974).

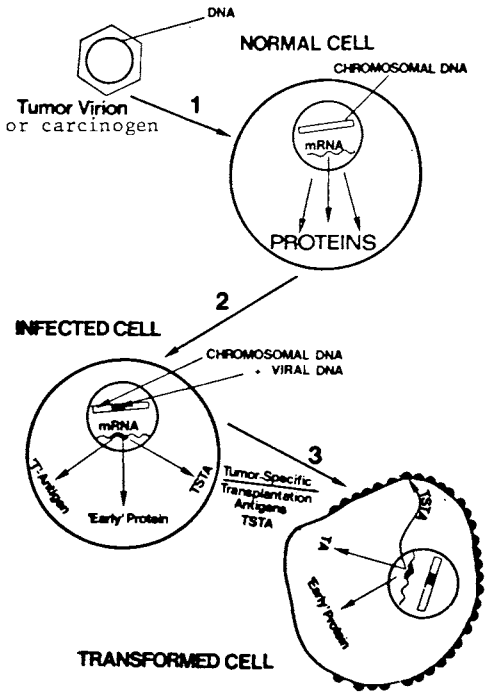

Fig. 3. — Cell transformation by tumor viruses. (From Chandra *et al.*, 1973).

derate/severe dysplasias or cancer *in situ* (CIN 2, 3) (fig. 1).

This conception would permit a quantification of the anomalias and to obtain a same pathological appreciation on the different cervical lesions.

PRECANCEROUS LESIONS EVOLUTION

It is difficult to distinguish between a severe dysplasia and a carcinoma *in situ*, and also to give a prognosis of these lesions which are capable of progression or regression within a few months and even within some weeks. In our statistical study now in progression on dysplasias and carcinoma *in situ* evolving side by side with flat condylomas, we have observed some complete regressions without treatment even in CIN 3 within a few months.

These evolutive differences are dependent on:

– the penetration of the mutagen,

– the lesions provoked by the action of cancerigen on the DNA, and its possibilities of reparation,

– the products secreted by the transformed cells,

– the host's immunitary reactions.

In a structural epithelium, the cells are potentially mobile, in spite of their "contact inhibition"; the "regeneration cells" and the young metaplastic cells have a "motion liberty", like cells in culture. So it is easy to understand the fa-

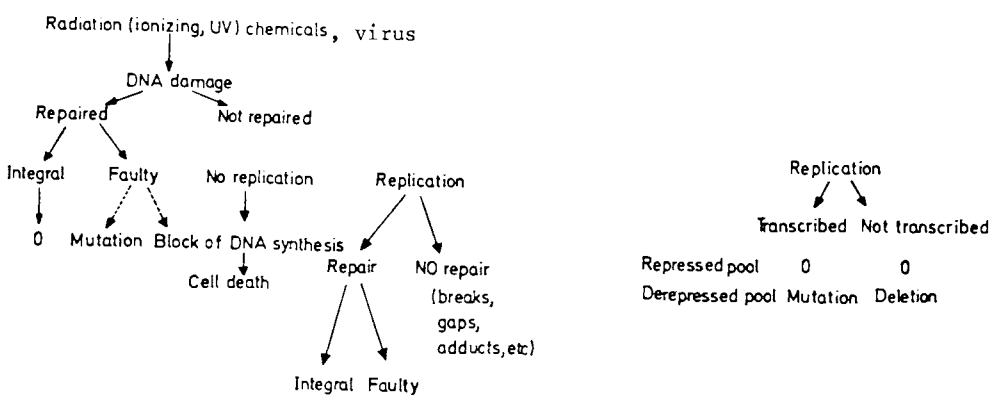

Fig. 4. — (From van Lancker J. L.).

voring role of undifferentiated cells (reserve cells, regeneration cells) having no cohesion, in the histogenesis of the severe cervical lesions, and the role of the cervical chronic infections.

Coppleson ([7]) seems to have demonstrated that nuclear DNA filaments are capable of spraying outside the cytoplasmic membrane into the extracellular space. They form the "glycocalix" and the DNA is demonstrated by tritiated thymidine. These filaments after crossing and aggregating with those of neighbouring cells come back into the nucleus. But they have incorporated protein-molecules, as spermatic histones or viral nucleo-proteins (fig. 2).

In the nucleus, the chromosomes are modified by adjunction of this new DNA (viral or histone). In this matter, the synthesis of the DNA will be accelerated and the mitosis are more frequent and more or less atypical. Moreover, the protein synthesis will be modified: loss of the chalones, new enzymes (glyco- and proteolytic, transcriptase, etc. ...), new tumoral secretions and tumoral antigen globulins (fig. 3).

So, these factors may induce the invasion of the tumoral cells by disappearance of the basal membrane by powerful lytic enzymes and by the angiogenesis tumoral factor, increasing the number and volume of the stroma capillaries penetrating to the dysplastic epithelium.

In some cases, the histologic lesions may be more or less quickly healed. Even, in few cases, the DNA lesion may be completely repared with no visible cellular modifications. In other cases, the DNA lesions persists giving a cellular mutation. If the chromosomal lesion is very severe, the cell dies by DNA-blocking (Van Lancker) ([8]).

If the cell is capable replicating, the same process is cellular healing, cellular death, according to the severity of the DNA lesions; but also the cell undergoes a transformation (break, deletion or adjunction on the chromosomes, etc. ...) followed by the perpetuation of the cellular and histologic lesion (fig. 4).

Sometimes, if the chromosome modifications have an only slight or moderate histologic exteriorisation, a new carcinogen or a reinfection will modify and enhance the evolution: dramatic and rapid apparition of a histologic lesion, fast progression of an old and quiescent dysplasia, or brutal invasion of a carcinoma *in situ*. So it seems necessary to destroy all the cervical dysplasias, even if they appear evolutively benign.

The part of the host in the defence against the tumor is still progressing. But we know some of the globulins induced by the carcinogen: the T antigen and the T.S.T.A. (tumor specific transplantation antigen). The antigens induce two varieties of immunity:

– The mediate cellular immunity: by action of the T lymphocyts acting directly on the tumoral cells by mean of the complement and the killer-macrophages activated by the lymphokins secreted by the T lymphocyts. The histologic pictures of the lymph-nodes permit to give an approximation of the grade of this type of cellular mediated immunity in the invasive cancer.

– The actions of the mediated humoral immunity is not yet well known because its complexity.

REFERENCES

1) Gagnon E.: *Contribution to the study of the etiology and prevention of cancer of the cervix of the uterus.* Am. J. Obst. Gyn., *60*, 516, 1950.

2) Rotkin J. D.: *A comparison review of key epidemiological studies in cervical cancer related to current searches for transmissible agents.* Cancer Research, *33*, 1353, 1973.

3) Beral V.: *Cancer of the cervix: a sexually transmissible infection?* Lancet, *1*, 1037, 1974.

4) Pauli H. K.: *Some aspects of the prevention of cervical cancer.* In: "Cervical Pathology and Colposcopy" ed. by E. Burghardt, E. Holzer, J. A. Jordan, George Thieme Pub., Stuttgart, 111, 1978.
5) Orth G., Jablonska S. *et al.*: *The human papilloma viruses.* Bull. Cancer (Paris), *65*, 151, 1978.
6) Cohen J., Werret D. J.: *Antibodies and sperm survival in the female tract of the mouse and rabbit.* J. of Reproduction and Fertility, *42*, 301, 1975.
7) Coppleson M., Reid B.: *Natural history and diagnosis of malignant and premalignant cervical disease.* In: "The Cervix", ed. Jordan and Singer, S. W. Saunders Co., 1978.
8) Van Lanker J. L.: *DNA injuries: their repair an carcinogenesis.* In: "Current Topics in Pathology", Springer Verlag, Berlin, 1977.