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The Tubular System of Human Endometrium

J. J. Vázquez and P. Sesma

Departamento de Citología e Histología
Universidad de Navarra
Pamplona (España)

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The so-called «intranuclear» tubular system (TS) of human epithelial endometrial cells has been investigated in 50 specimens and has been found in some instances of secretory endometrium and in one case of hyperplastic endometrium with secretory change. The TS was found both in nucleus and cytoplasm. The intranuclear TS can be associated with the nucleolus, connected to the nuclear envelope or lying free in the karyoplasm. When it is connected with the nuclear envelope an intimately related cytoplasmic invagination containing many ribosomes is frequently found. The cytoplasmic TS is smaller than that found in the nucleus and is usually connected with rough endoplasmic reticulum profiles. These findings allow us to make the suggestion that the TS could have a cytoplasmic origin and subsequently migrate into the nucleus. The function of the TS is unknown.

Ultrastructural studies of the human endometrium have revealed an unusual tubular structure or tubular system (TS) which appears in the epithelial cells during the first week of the secretory phase (1-3, 6-9).

The purpose of this article is to describe the results of the study of a large number of electron micrographs which allowed us to discover this tubular structures not only in the nucleus, but also in the cytoplasm. These findings prompted us to suggest a cytoplasmic origin and a subsequent migration into the nucleus.

Materials and Methods

The study was carried out on 50 endometrial specimens obtained by curettage or hysterectomy. Five cases were in a normal proliferative and 20 in a normal secretory phase; and 25 belonged to glandular hyperplasia, one of which showed strong secretory changes.

Blocks of tissue 1 mm in diameter were fixed in 4 % cacodylate-buffered glutaraldehyde and post-fixed in 1 % phosphate-buffered osmiun tetroxide for 2 h, dehydrated in ethanol and embedded in

Epon 812. Ultrathin sections were double stained with uranyl acetate and lead hydroxide and examined with a Siemens Elmiskop 1A electron microscope.

Results

The TS was found in the normal secretory phase, more often in the first week, and also in a case of glandular hyperplasia with a strong secretory change, in which it was specially frequent and well-developed.

In the nuclei in which it is seen, only one TS is usually present, but occasionally two bodies have been found in the same nucleus. The intranuclear TS is made up of tubules, showing predominantly a parallel and concentric arrangement, embedded in a finely granular matrix (figs. 1, 2, 5). The tubules themselves measure 50-63 nm in diameter and are bounded by a membrane, which is difficult to identify due to the electrodensity of the matrix material. In some instances, a halo of fibrillar material is found around an intranuclear TS. For a more complete description see the paper by MORE (6), whose findings we agree with.

The TS has been found not only in the nucleus but also in the cytoplasm. The intranuclear TS are more frequently seen and have a size greater than those present in the cytoplasm. The intranuclear TS may be: related with the nucleolus, connected to the nuclear membrane or free in the karyoplasm. When it is in the nucleolus, there is a row of 150 Å dense granules at the periphery of the TS (fig. 2), as it was described by TERZAKIS (9).

When it is connected with the nuclear membrane the connection occurs very often in relation with cytoplasmic invaginations (fig. 5 *B*, *C*), which contain numerous ribosomes.

The cytoplasmic TS is normaly connected with the rough endoplasmic reticulum (RER) (fig. 3). Actually very often a TS lies agains a RER cisterna which is devoid of ribosomes in the contact area. These TS-RER complexes are also quite often connected with the nuclear membrane (fig. 4 *A*). Some of them are so closely connected with the nuclear enve-

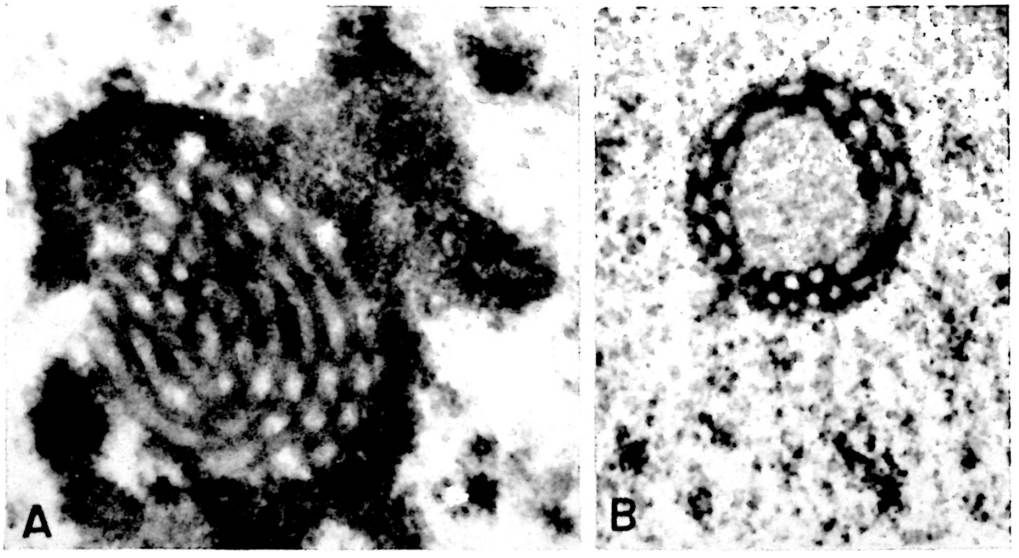

Fig. 1. *Intranuclear TS.*
A, TS located in the nucleolus. × 28,000. *B*, TS lying free in the karyoplasm. × 22,000.

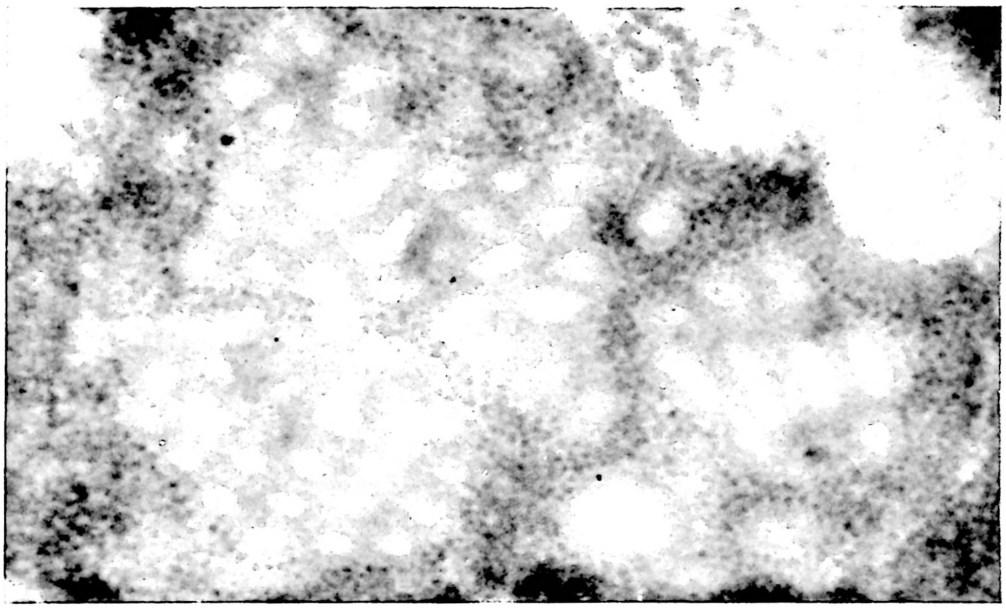

Fig. 2. *Intranuclear TS with a row of dense granules.* × *56,000.*

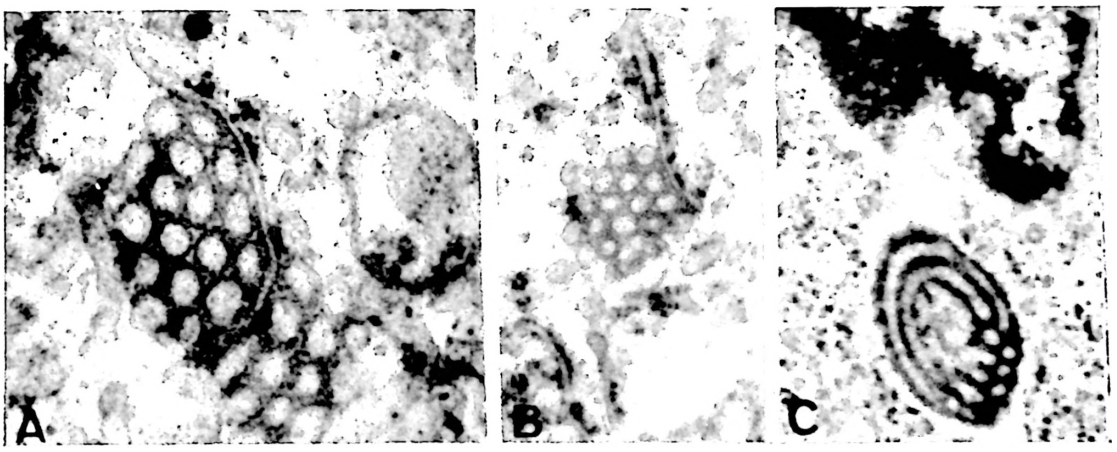

Fig. 3. *Three cytoplasmic TS. Two are connected with profiles of RER.* *A*, × 46,800; *B*, × 36,000; *C*, × 22,400.

lope that it is difficult to establish an intra- or extranuclear location. In some cases an intranuclear TS apparently pushes upon the nuclear envelope, causing the outline of the nucleous to bulge (figure 4 *B*, *C*). In such protruding areas the outer membrane is very often studded with ribosomes (fig. 4 *B*).

Discussion

The first description of the TS was made by DUBRANZSKY and POHLMANN (3), who in 1960 depicted a characteristic canalicular nucleolar structure, present in endometrial epithelial cells during the third week of the menstrual cycle and

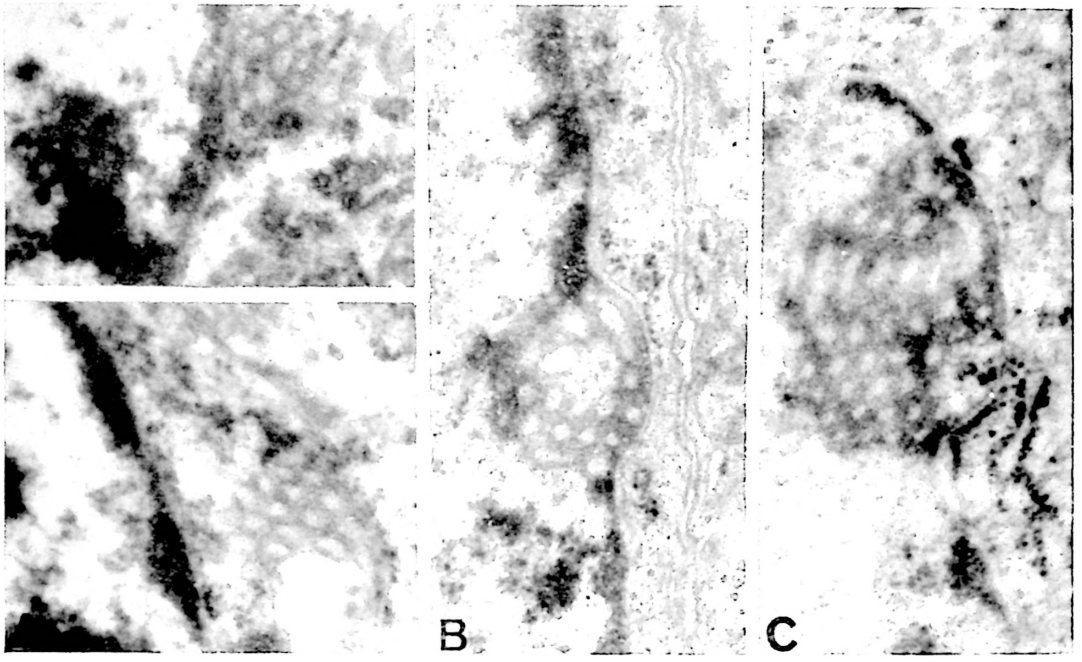

Fig. 4. *TS connected with the nuclear envelope.*
Two are in cytoplasm (on the left) and two inside the nucleus. × 36,000.

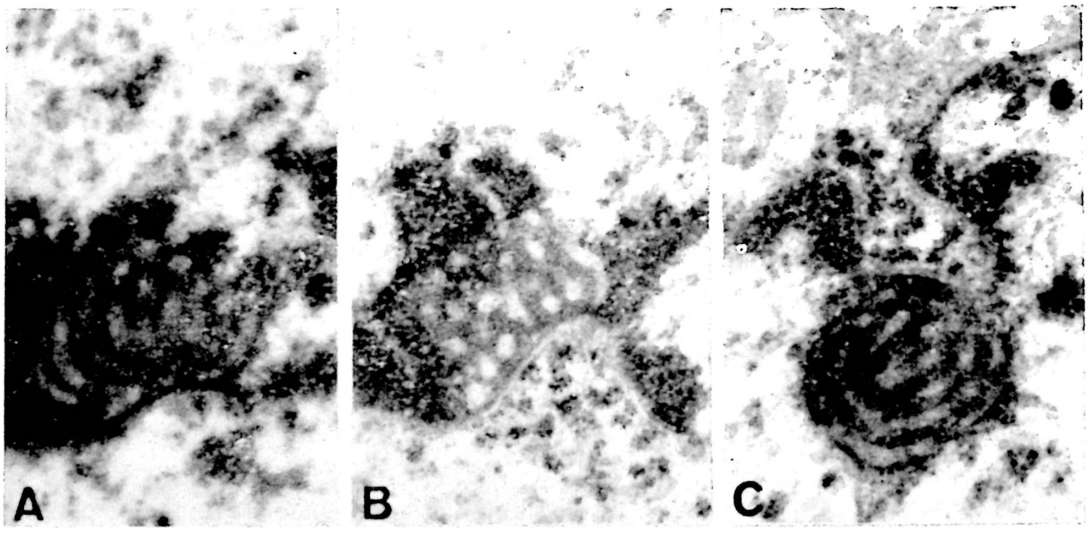

Fig. 5. *Intranuclear TS, connected with the nuclear envelope.*
In relation with the TS a cytoplasmic invagination is formed. In B and C it contains many ribosomes. × 36,000.

closely related to the nuclear membrane. They considered this structure to be a morphological basis of nucleolar cytoplasmic exchanges.

CLYMANN (2) in 1963 described again this canalicular structure, but since he was not familiar with the paper of DUBRANZSKY and POHLMANN (3), he considered his description as the first. Since then, some authors have inappropiately named these structures Clymann's bodies (1). In 1965 TERZAKYS (9) gave a quite complete description of the TS and showed the existence of continuity between the TS and the perinuclear space. He suggested the possibility that this structure could be a device for transport to the cytoplasm of materials, most probably RNA made in the nucleus or nucleolus. ANCLA and DE BRUX (1) remarked, as TERZAKIS (9) had suggested previously, that the TS may be independent from the nucleolus.

The present study shows that the TS is also found in the cytoplasm of normal and hyperplastic endometrial cells, such as was indicated by SIRTORI (8) in carcinoma cells. The observations allow moreover to suggest that the TS has a cytoplasmic origin and that it migrates from cytoplasm to the nucleus.

The sequence of events is illustrated diagrammatically in figure 6, which is a composite of the findings from many electron micrographs: at the beginning, a small TS containing a small number of tubules appears associated with a RER profile (fig. 6, I and III). Then, the TS RER-complex moves toward the nucleus (fig. 6, II) and makes contact with the nuclear envelope, with which the RER membrane fuses. The nuclear membrane seems to disappear in the contact area (fig. 6, III and IV, and fig. 4 *B*, *C*). In this way, the nuclear envelope is made partly by the ER membrane, which still supports ribosomes (fig. 6, IV, and fig. 4 *B*). Thereafter, the TS appears to sink into the nucleus, dragging down both the nuclear envelope and the neighbouring cytoplasm.

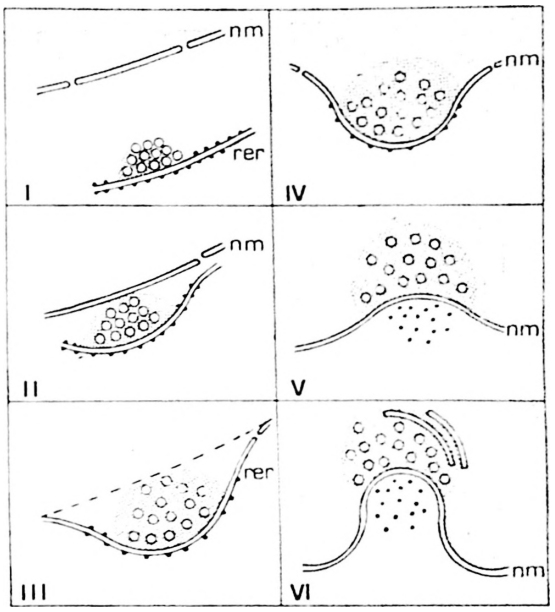

Fig. 6. *Diagram illustrating the origin and migration of the TS from the cytoplasm into the nucleus.*

This explains the frequent association of the TS with cytoplasmic invaginations into the nucleus (fig. 5) and the presence of the numerous free ribosomes seen in the invaginated cytoplasm and/or associated with the outer nuclear membrane at this level (fig. 6, V and VI, and fig. 5 *B*, *C*). Lastly the TS is detached from the nuclear envelope and lies free in the karioplasm.

Since the intranuclear TS is very frequently associated with the nucleolus, it was called a nucleolar channel system by TERZAKYS (9). The uncomitted name of tubular system seems more appropriate for it for several reasons: it is also found in the cytoplasm, its true functional significance is unknown and it is not really a true channel but rather a tubular system.

Its incidence is probably dependent on the progestagen stimulus acting in the first week of the secretory phase of the menstrual cycle and also in the secretory transformed hyperplastic endometrium; all authors agree on accepting the TS as typ-

ical of the secretory phase. Furthermore, several workers have considered the TS as specifically related to ovulation (4, 5). MORE *et al.* (6) were not able to find the TS before the 13 th or after the 26th day of the normal menstrual cycle. They saw the TS more commonly in biopsies taken on the 19th day than at any other time. KOHORN *et al.* (4) were able to provoke *in vivo* the appearance of the TS by the induction of secretory changes in the endometrial cells in control cultures.

Taking into account the finding of the TS only during the progestagen phase, it seems justified to think of it as a transient organelle of the endometrial epithelial cell.

The functions of the TS are unknown. Due to the frequent association with the nucleolus and the nuclear envelope, DUBRANSZKY and POHLMANN (3) and TERZAKIS (9) suggested the possibility that this structure may be a transport device for material made up in the nucleus or nucleolus.

If it is involved in a nucleolus to cytoplasm transport mechanism, the transported material might be RNAr, which is synthetized in the nucleolus.

Resumen

Se ha encontrado en varios casos de endometrios humanos en fase de secreción y en uno de hiperplasia secretora el llamado sistema tubular intranuclear (TS) de las células epiteliales.

Los TS han sido hallados tanto en el núcleo como en el citoplasma. Los situados en el núcleo aparecen asociados al nucleolo, conectados a la membrana nuclear o dispersos por el carioplasma. Con frecuencia, los TS nucleares asociados a la membrana están íntimamente relacionados con invaginaciones del citoplasma conteniendo ribosomas libres. Los TS del citoplasma son algo más pequeños que los nucleares y aparecen habitualmente conectados con perfiles de retículo endoplasmático rugoso.

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