

## **The Structure of Adenocarcinoma and the Structural Differentiation**

While making microscopic diagnosis of tumor, pathologists encounter a wide variety of pictures. There are malignant and benign tumors, carcinomas and sarcomas, tumor cells showing various features, functions, grades of differentiation or ways to aggregate into different patterns. The variety reminds us of the structure of organs, where different pictures are presented from one organ to another. In fact, microscopically, the tumor is an organ. It comprises parenchymal cells (tumor cells), interstitial tissue and the vessels running in the latter, all arranged according to a certain principle. A tumor only differs from usual organs in that it keeps changing its structure incessantly and at a speed because of the continuous proliferation of tumor cells. Thus, what structure a tumor presents, and in what aspect the structure is proper to the tumor, is a subject to be studied from an organ structure point of view. And this viewpoint provides us with a clue to strengthen our microscopic diagnosis of tumor by refining the concept of “structural atypia.” This has long been considered to be of profound significance in diagnosis but so far, no clear definition has been given. In the following, we attempt to visually analyze the microstructure of gastric adenocarcinoma as an organ. It will make us realize that the concept of differentiation applies, not only to cellular constituents of tumor, but to the structure of adenocarcinoma which is more or less deviated from the glandular tree of ordinary stomach.

### **The structural pattern of normal gastric glands (Fig. 5-1)**

In Japan, carcinoma of the stomach has been and still is the malignancy that claims the largest number of lives. In histopathological terms, most of the gastric carcinoma belongs to adenocarcinoma. This type of carcinoma is so called because it is considered to originate from glandular epithelia of the stomach and more or less retains features of glandular cells even after they are transformed into carcinoma cells. Figure 5-1 is a schema illustrating normal gastric glands which open at the mucosal surface. They belong to the tubular type gland, dividing a few times downward within the mucosa and forming a small tree, with the secretory cells situated at the bottom. Gastric juice secreted by these cells is led upward to the gastric cavity through the duct. On account of this structure, the gastric gland, when sectioned in longitudinal direction, emerges in a section as a gland of “reversed Y” shape.

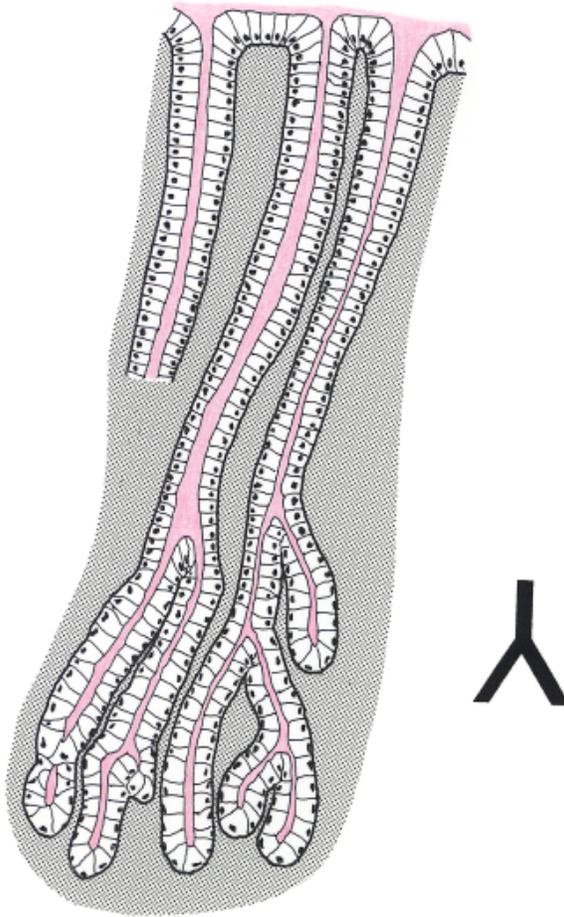


Fig. 5-1. A schema illustrating the normal gastric gland. The upper margin corresponds to the mucosal surface where the glandular duct opens and secretes the glandular product. The duct is tubular, runs vertically in the mucosa and divides a few times toward the mucosal bottom, creating on section a reversed Y-pattern. The ductal lumen (red) is continuous and its inner surface is lined with a monolayer of epithelial cells that are sitting on basal membrane.

### Cellular atypia of adenocarcinoma (Fig. 5-2)

As well known, pathologists make a diagnosis of carcinoma recognizing the feature of carcinoma cells that is expressed generally as cellular “atypia.” In the microphotograph in the left half of Fig. 5-2, one can see cross-sectioned glandular tubes (gastric pits) of normal gastric mucosa, and in the right half, an adenocarcinoma growing in gastric mucosa. The difference may be clear: the carcinoma is presenting as tubular glands lined with cells that are markedly “atypical” compared with the normal glands. The atypia is a concept comprising a series of morphological features of form, including enlarged nuclei and nucleoli, nuclear pleomorphism, coarse texture of nuclear chromatin, elevated nucleo-cytoplasmic (N/C) ratio and thickened nuclear membrane,

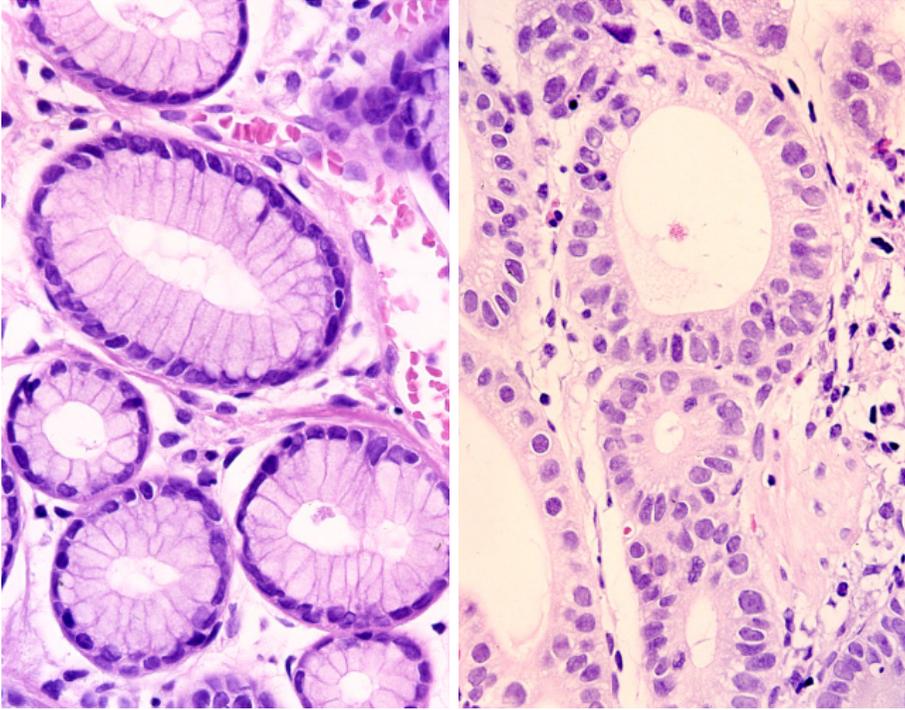


Fig. 5-2. Microscopic appearance of adenocarcinoma of the stomach (right). In the left, normal ducts of gastric gland (the foveolae), cross-sectioned, are exhibited for comparison. In carcinoma, the cells retain the basic feature of glandular epithelia by lining along the inner surface of tubes, but differ from the non-carcinoma cells in the presence of what is generally called “cellular atypia,” a feature most characteristically expressed in the form of nuclei. Hematoxylin-eosin stain.

all confirmable in the carcinoma cells exhibited in the figure. These features will be visited again in Chapter 8 dealing with the computer-assisted morphological classification of carcinoma and carcinoma-related cells.

### **Structural atypia in adenocarcinoma: Y-pattern (Fig. 5-3)**

However, there does exist another morphological aspect of carcinoma which is of equally basic diagnostic significance as the cellular atypia. That is, an abnormality in the structure of cellular assembly forming either a gland or something like gland. Look at Fig. 5-3, an early adenocarcinoma of stomach which has just begun growing in the mucosa. The tumor belongs to the well differentiated (tubular) type, and there is slight if any atypia of individual cells lining the tubular glands. However one can find here that even in the absence of severe cellular abnormalities, the glandular structure appears strikingly deviated from the norm. There are glands of non-reversed Y, in addition to X or H-pattern. If, in a mucosal biopsy, a pathologist fails to take notice of this, carcinoma may escape detection and remain in the patient where it will keep growing.

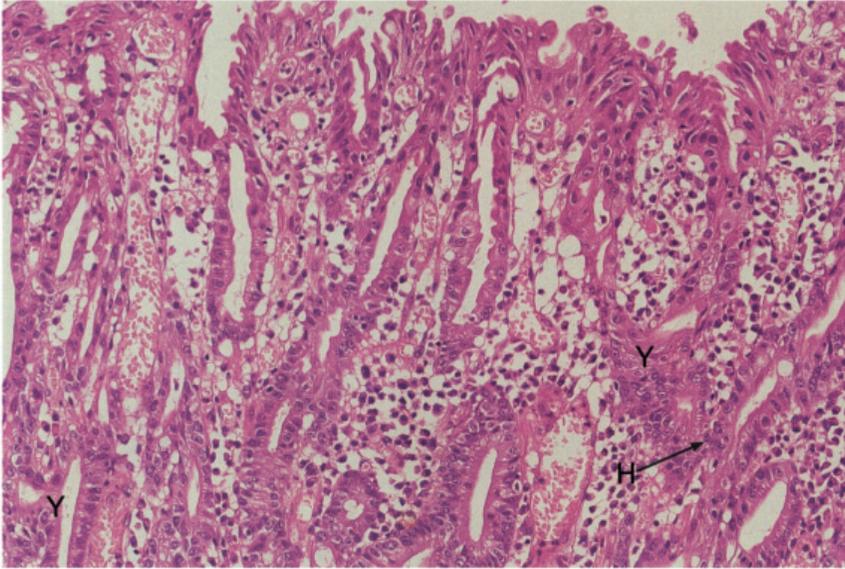


Fig. 5-3. Abnormality in the glandular pattern in a well differentiated adenocarcinoma of stomach. Several glandular tubes are arranged in the mucosa, but their structural pattern is markedly abnormal, with Y-pattern, not reversed but upright, at the places denoted by Y. Since in this case the cellular atypia is minimum, microscopic diagnosis of carcinoma solely depends on the recognition of abnormal gland pattern. Hematoxylin-eosin stain.

This structural feature of adenocarcinoma has been pointed out by some Western pathologists (Grundmann, 1975; Morson *et al.*, 1980). However, its importance in diagnosing early gastric carcinoma had been emphasized in the pioneer studies of Japanese pathologists (Ota, 1964; Nagayo, 1966) who established diagnostic basis for distinguishing carcinoma from various non-carcinomatous changes of mucosal gland. Japanese Research Society for Gastric Cancer (1974) expressed this feature as “structural atypia” (SAT) of adenocarcinoma, contrasting with “cellular atypia” (CAT), the abnormalities of individual cells. Of these, CAT has been the subject of a large number of studies with the information now accumulated and systematized in the form of exfoliative cytology. However, SAT still remains a matter of ambiguity, leaving us uninformed about how to establish a criterion for diagnosing adenocarcinoma on an architectural basis. Retardation in this aspect of study is understandable if we notice that SAT belongs to a feature that can only be definable in terms of 3-D structure of carcinoma.

Apart from its diagnostic significance, SAT poses another question: how, from a biological viewpoint, one can explain the morphogenesis of carcinoma that can assume such a variety of structures as will be shown. In view of this, 3-D structural analysis of adenocarcinoma and adenoma was undertaken, using surgical material of gastric tumors (Takahashi and Iwama, 1984a,b,c, 1985).

### Three-D structure of well differentiated adenocarcinoma (Figs. 5-4, 5-5)

Exhibited in Fig. 5-4 is a manually performed 3-D reconstruction of well differ-



Fig. 5-4. Manually performed 3-D reconstruction of carcinomatous glands in the well differentiated adenocarcinoma shown in Fig. 5-3. This presents an exterior view of carcinomatous glands, a picture to be called a reconstruction of "nests," in order to discriminate from that of the glandular lumina. Note that the carcinomatous tubes are forming a 3-D network with loops, a structure different from the branching tree of normal gastric glands. Reproduced from Takahashi and Iwama (1984): *Virchows Arch A Path Anat Histol* 403, pp. 129.

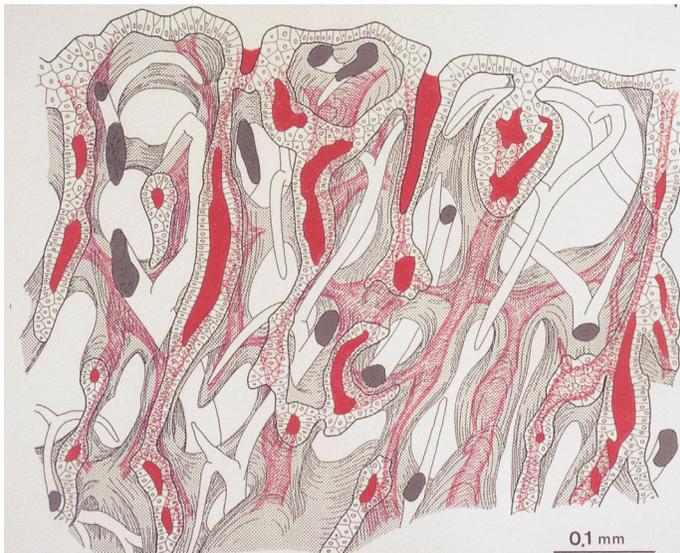


Fig. 5-5. Manually performed 3-D reconstruction reproducing the tubular lumina (red) in the well differentiated adenocarcinoma shown in Fig. 5-4. Note that the lumina are continuous over the whole reconstructed region, nowhere leaving a separate part of lumen. Reproduced from Takahashi and Iwama (1984): *Virchows Arch A Path Anat Histol* 403, pp. 129.

entiated tubular adenocarcinoma shown in the foregoing picture (Fig. 5-3). What one can find here is a network of glandular tubes connected with the neighboring ones, instead of the trees of normal glands branching downward. Clearly this explains how in this carcinoma, glands of non-reversed Y, X or H pattern appear in a 2-D section instead of reversed Y. The network, having a number of meshes (or loops), is intertwining with small arteries (red) and veins (blue). However, the picture presents only an external appearance of the tubular tumor. Whether and to what degree the luminal tunnels are open and continuous cannot be visualized with this sort of expression.

The foregoing 3-D picture is reproduced in Fig. 5-5 to show the glandular lumina in red. This is necessary because in adenocarcinoma, usually the connectivity of lumina does not coincide with that of the cell masses, or cell nests, the latter reconstructed in Fig. 5-4. In fact, by closely comparing the two figures, one may detect discrepancy between the lumina and cell nests at several places. However in this tumor, one can say at least, the larger part of the luminal tunnels retain continuity. Since this is an early mucosal carcinoma, where the tumor is confined to the upper 2/3 of the mucosa, the proper gastric glands (fundic glands) in the lower 1/3 are left uninvolved by growth of carcinoma. They are continuous with the carcinomatous glands, and this brings about a situation where gastric juice secreted by the fundic glands is led through the carcinomatous canals to the mucosal surface.

### **Moderately differentiated adenocarcinoma: 2-D and 3-D (Figs. 5-6, 5-7, 5-8)**

The second type is the moderately differentiated (tubular) adenocarcinoma. An example is shown in Fig. 5-6, an area from a deep layer of gastric wall where carcinoma is infiltrating. Apparently, the cells look sufficiently atypical to make a pathologist instantly give a diagnosis of carcinoma. However, there are also structural abnormalities. At several places, one can find carcinoma cell masses (or cell nests) containing not a single lumen but several round lumina, a pattern widely expressed as either cribriform pattern or "back to back pattern without intervening stroma." Also, most of the glandular lumina appear rounded, suggesting that they are all spread due to accumulation of mucus that is secreted by carcinoma cells.

Often one can find carcinoma cell nest appearing in section as a gland ruptured and gaping, as in Fig. 5-7. This too may be the result of overextended carcinomatous gland and contributes to giving an impression of structural atypia.

Three-dimensionally, the moderately differentiated tumor of Fig. 5-6 is again forming a network with fine meshes (Fig. 5-8). However, there is a difference from the well differentiated tumor of Figs. 5-4 and 5-5. As painted in red, the lumina are no longer continuous, but are split into many small vesicles that are dispersed in the cell nests. Therefore 3-dimensionally, the cell nests containing separate lumina is not a tube but is a structure that may properly be expressed as porosity. Although microscopically classified as *tubular* adenocarcinoma, this may be a misnomer. Thus, strictly speaking, one cannot determine until 3-D reconstruction has been performed whether a pattern resembling a tube in a microscopic section is really a continuous tube. At the same time, reconstruction makes us understand that the cribriform pattern, which has been regarded as a typical SAT of adenocarcinoma, corresponds to nothing but a sectional picture of porous nests. Also in the intraductal tumors of the breast, Ohuchi *et al.* (1985) demonstrated by 3-D reconstruction that porous nests are the clearest mor-

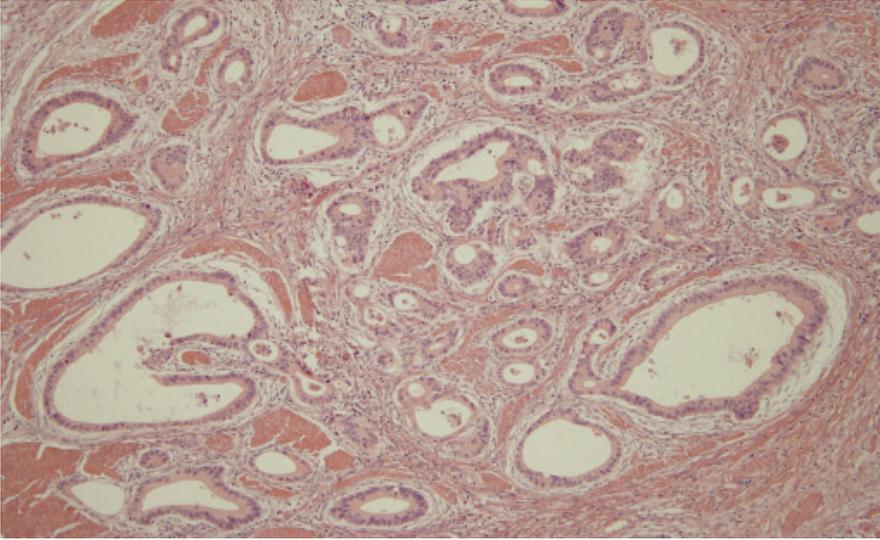


Fig. 5-6. Moderately differentiated adenocarcinoma of the stomach. From the portion of stomach where carcinoma is invading in the wall. Not only are the cells markedly atypical, but the glandular structure is also abnormal, with masses of carcinoma cells having multiple round lumina, a pattern expressed as "back-to-back without intervening stroma." Hematoxylin-eosin stain.

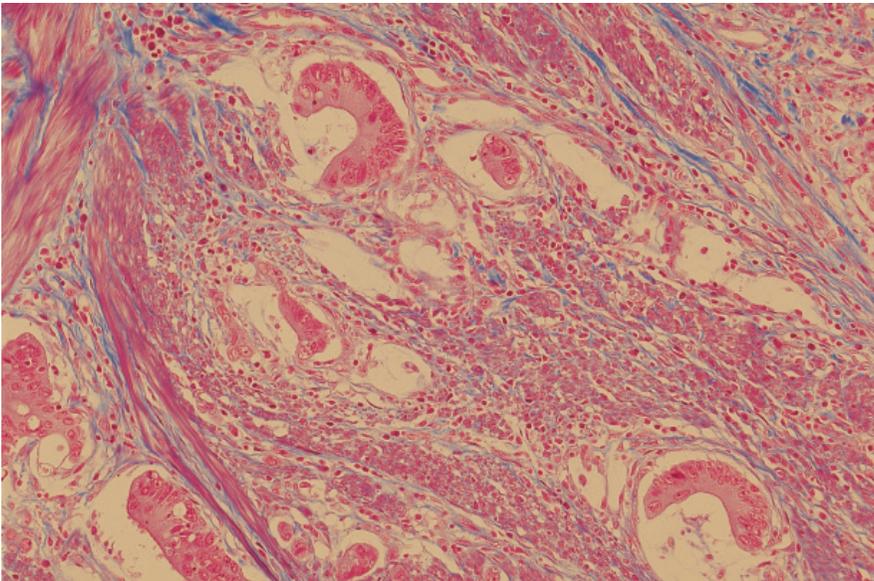


Fig. 5-7. Ruptured glands found in the moderately differentiated adenocarcinoma of Fig. 5-6. The glandular structure was broken because the lumina are separate, having no draining route for the products secreted by the carcinoma cells. Azan-Mallory stain.

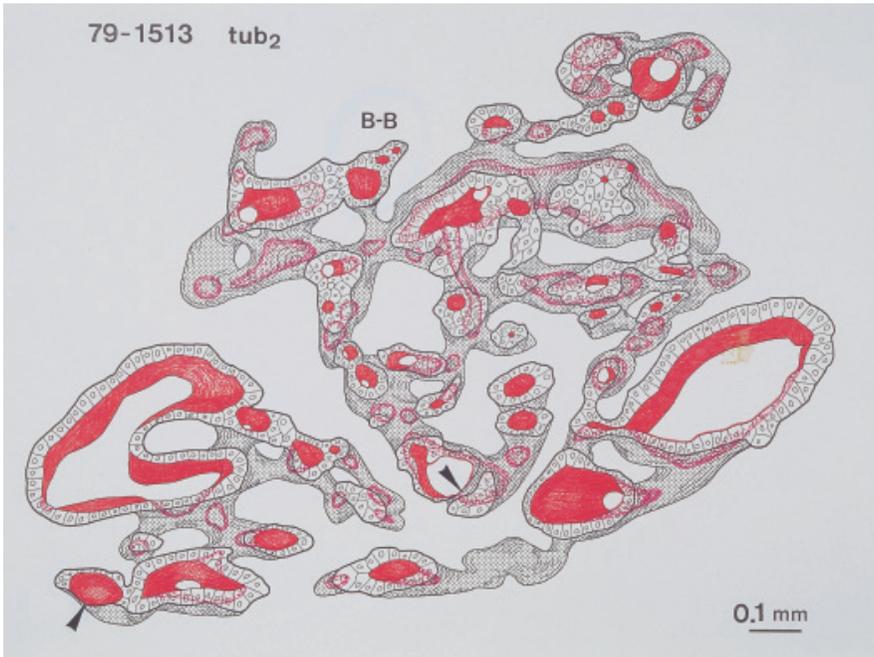


Fig. 5-8. Manually performed reconstruction of moderately differentiated adenocarcinoma of the stomach shown in Fig. 5-6. The glandular lumina are shown in red. Note that the carcinoma cell nests are forming a continuous 3-D network with loops, whereas the lumina are entirely split into solitary vesicles, a state of “porous nests” presenting on a 2-D section as “back-to-back” (B-B) pattern. Ruptured glands are also seen (arrowheads). Reproduced from Takahashi and Iwama (1984): *Virchows Arch A Path Anat Histol* 403, pp. 131.

phological sign of malignancy. Since cells of gastric adenocarcinoma secrete mucus more or less, the produced mucus comes to accumulate in the minute spaces. They are separate vesicles that continue to nowhere, creating in section the round-shaped, spread lumina that are often ruptured.

### Poorly differentiated adenocarcinoma: 2-D and 3-D (Figs. 5-9, 5-10)

The third type of the present series is the poorly differentiated adenocarcinoma. In a 2-D section, as in Fig. 5-9, this type of tumor presents as separate small clusters of carcinoma cells diffusely infiltrating in the connective tissue stroma (arrows). Glandular structure is retained in some of the clusters, but only rudimentarily.

In 2-D section, most of the cell nests seemed separated one from another. But three-dimensionally, there still remain carcinoma cells assembled in the form of continuous 3-D network with porosity (Fig. 5-10). It is shown however that from the network, clumps of a few carcinoma cells have begun separating, with some of them having a tiny, porous lumen. Thus, this type corresponds to the stage of dedifferentiation in which not only the lumina but the cell nests are losing connectivity.

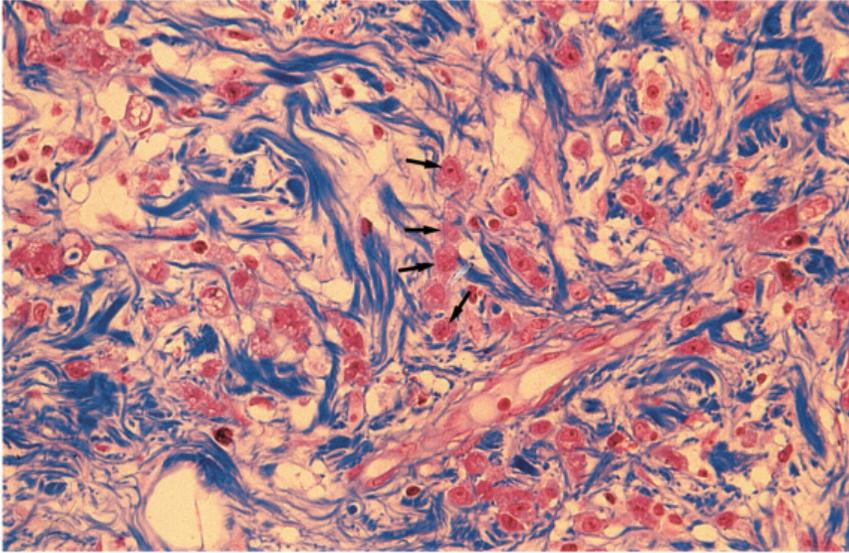


Fig. 5-9. Poorly differentiated adenocarcinoma of stomach: Carcinoma cells (arrows), solitary or forming small clumps, are dispersed in the stromal connective tissue. Tubular structure is not obvious. Azan-Mallory stain.

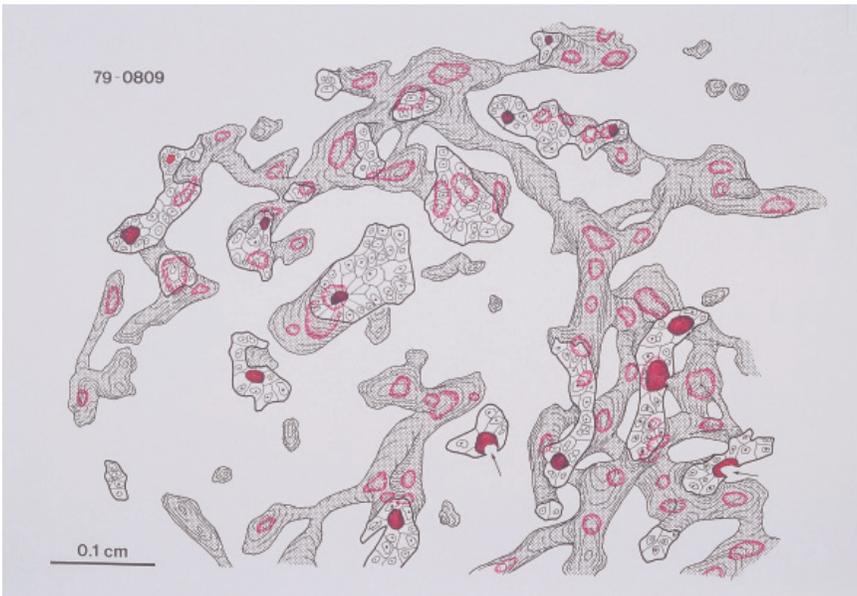


Fig. 5-10. Manual 3-D reconstruction of poorly differentiated adenocarcinoma. Although network made of porous nests remains in the right half of the figure, fragmental nests have begun leaving the network. This may be a state of disintegrating glandular structure. Reproduced from Takahashi and Iwama (1984): *Virchows Arch A Path Anat Histol* 403, pp. 132.

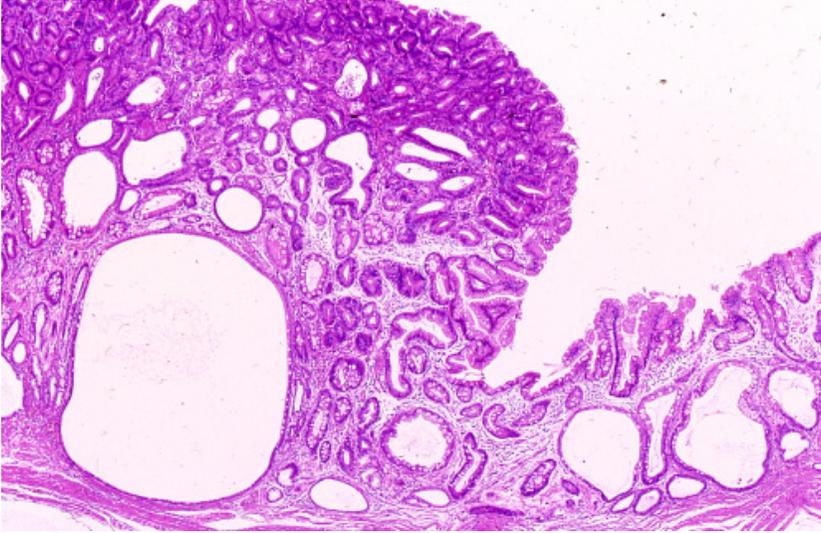
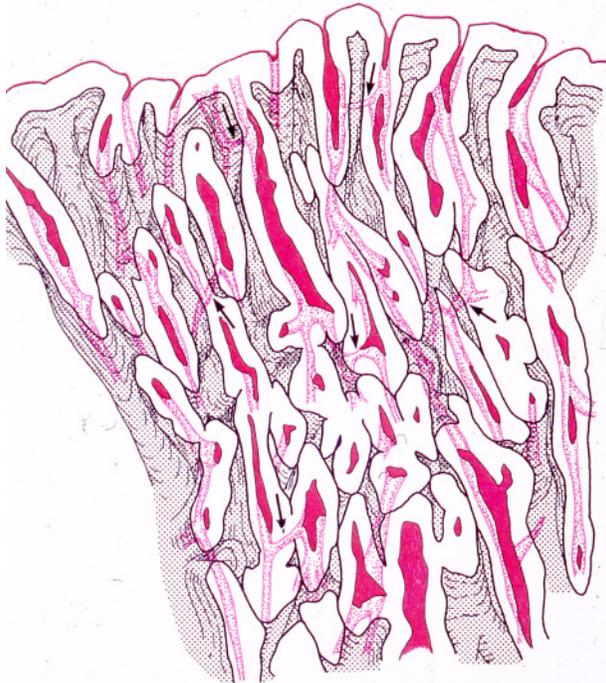


Fig. 5-11. Adenoma of the stomach, presenting a flat mucosal elevation comprising glandular tubules with moderately atypical cells, a picture reminiscent of an adenoma of the large bowel. Hematoxylin-eosin stain.



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Fig. 5-12. Manual 3-D reconstruction of gastric adenoma. Tubular glands, all penetrated with a continuous lumen, are packed in the elevated mucosa. At several places one can find connection, of both nests and lumina, between a pair of neighboring tubules (arrows), showing that network formation has already begun. Reproduced from Takahashi and Iwama (1984): *Virchows Arch A Path Anat Histol* 403, pp. 139.

### Gastric adenoma: 2-D and 3-D (Figs. 5-11, 5-12)

In the large intestine, adenomas are found very often. Though less common, it also arises in the stomach and sometimes carcinoma develops within adenoma. Fig. 5-11 is an example of gastric adenoma where one can find atypical glands bearing some resemblance to adenoma of large intestine. They gather in the superficial layer of mucosa, but the degree of cellular atypia is milder than overt adenocarcinoma.

Figure 5-12 presents a 3-D reconstruction of gastric adenoma. Atypical glands are closely packed in the mucosa, and though infrequently, there are places where a pair of neighboring glands are connected, as denoted by arrows. There, the lumen too is continuous as in the well differentiated adenocarcinoma. Thus, as a whole, the basic skeleton of adenoma is already a coarse 3-D network. In other words, the gastric adenoma can be expressed as a miniature of adenocarcinoma.

### Tree and network: what is connectivity? (Fig. 5-13)

As above, among the various types of adenocarcinoma and adenoma, there is a difference in the skeleton. This can be translated as difference in *connectivity*, or in other words, difference in the topological properties of structure, either among the cell nests, or among the lumina. We will have to recur several times to topological way of thinking in the problems that follow, and therefore it seems pertinent to give a small comment about the concept.

Figure 5-13 is a schema explaining the meaning of connectivity. In the left, one can see a pattern consisting of several nodes and branches. It includes a loop,

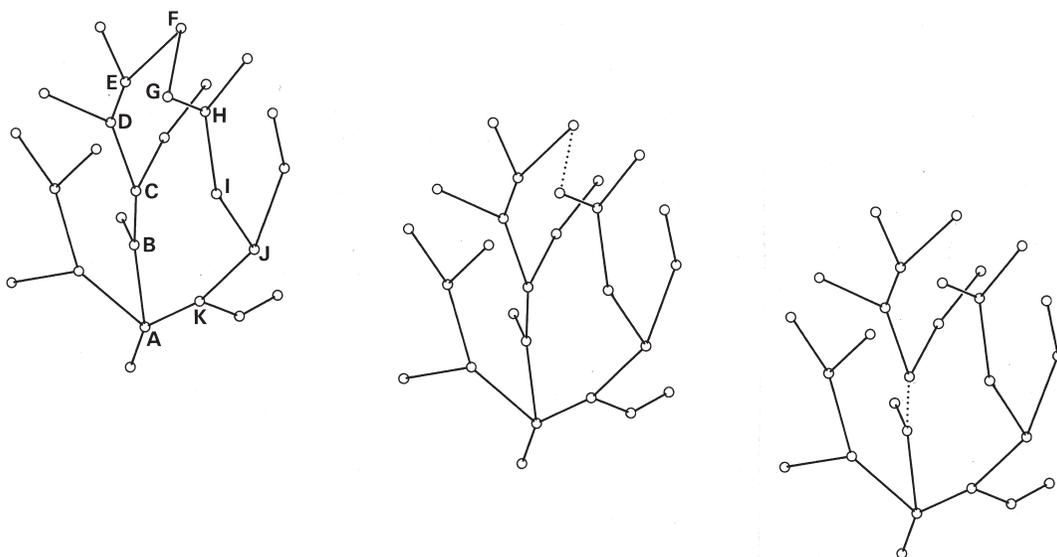


Fig. 5-13. A schema of small tree and network, explaining the meaning of connectivity. Presented in the left is a figure made of nodes and branches, all united in the form of small network with a hole (in other words, a cycle). In the figure in the center, one of the branches forming the loop has been taken away. The figure, still united as a whole but having no hole, corresponds to the state of tree. If, from this tree, any branch is taken away as in the right figure, the tree is inevitably split into two parts. This implies that the tree is definable as a pattern having no inner redundant connection.

ABCDEFGHIJKA, which can also be expressed as a hole, or a cycle. In the central figure, one of the branches forming the loop (FG) has been removed, and this causes the loop to disappear and the whole pattern is reduced to a simple tree having no hole. This means that if there is a loop, the node-branch system contains redundant connectivity, because even after one of the loop-forming branches is removed, the system still retains unity without breaking up into separate parts. If, from this tree, any branch is taken away as in the right figure (BC), then inevitably the tree is separated into two parts. This occurs because the tree is a pattern that is definable as having no inner redundant connection.

As shown, the structure of adenocarcinoma can be reduced to a skeleton that varies according to the degree of differentiation and dedifferentiation. There, the basic pattern of skeleton can be either a tree, or a united network having several loops, or a network that is partially disconnected. Then, how can we describe in quantitative terms the skeleton difference in this sense?

**Topological expression for the skeleton of carcinomatous glands (Fig. 5-14)**

For adenocarcinoma of stomach, we talk about “cell nest,” or simply “nest,” with which to express the whole cell mass wrapped in basement membrane. This is to distinguish the connecting relation of cell mass from that of luminal tunnel. For example, a normal gastric gland forms a miniature tree that is united as a whole, with regard to either the whole gland (the cell mass) or the lumen. However, in the well differentiated adenocarcinoma, both the cell masses (nests) and the lumina are forming a network with multiple holes (loops), meaning that they both are redundantly

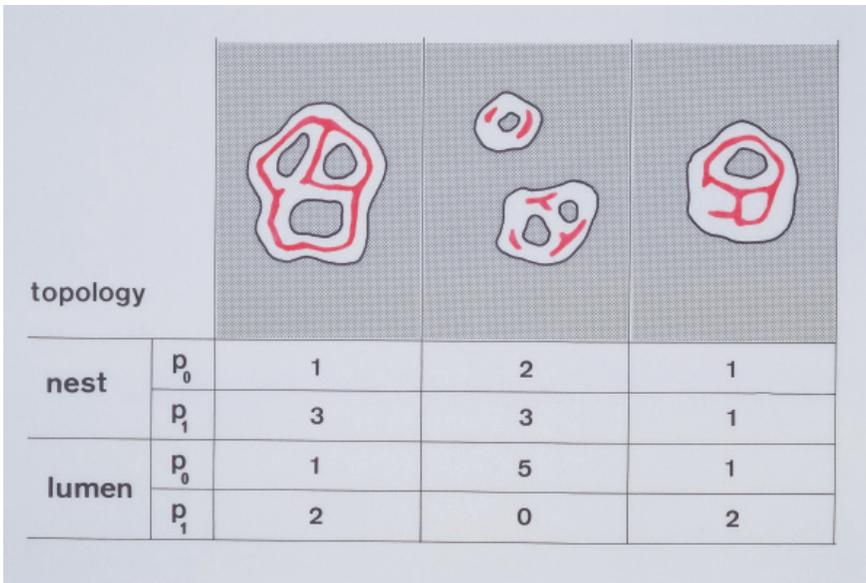


Fig. 5-14. Quantification of various structural skeleton for adenocarcinoma and adenoma with topological parameters. Illustrated using simple forms having nests and lumina (red).  $p_0$ : the number of separate parts.  $p_1$ : the number of holes.

connected. In the moderately differentiated tumor, the nests remain as a network with loops, whereas the lumina are split into many separate parts, showing loss of luminal connectivity. Thus, what we are dealing with is a difference in the connectivity of skeletons, which can pertinently be described if we use topological parameters.

Figure 5-14 illustrates the principle, taking as examples three simplified patterns. The lumina contained in the nests are shown red. In adenocarcinomas, usually the network of nests and that of lumina have different number of loops. Moreover, nests and lumina are often split into different number of separate parts. Therefore, each of them has to be quantified as an independent network. To quantify the connectivity, we introduce two parameters,  $p_1$  and  $p_0$ . Of these,  $p_1$  denotes the number of holes contained in a network.  $p_0$  is the number of separate parts of network. Here it should be taken for granted that there can be a network having no holes, since we make it a rule that even if the object is a small part consisting only of a segment of nest, this should be considered a network, so long as it remains as an independent pattern; in this case  $p_1 = 0$ , but  $p_0 = 1$ . In topology, the quantity denoted by  $p_1$  is called the genus.

Let us see the examples. In the left pattern, the nest is entirely connected and therefore  $p_0$  is 1 for the nest, while it contains three holes and therefore  $p_1$  is 3. On the other hand, the lumen (red) is united and forming two holes. Therefore for the lumen  $p_0$  is 1 and  $p_1$  is 2. In the middle pattern, the nests are separated into two parts and have three holes, and therefore  $p_0$  for the nest is 2 and  $p_1$  is 3, whereas the lumina are separated into five parts and there are no holes, and therefore  $p_0 = 5$  and  $p_1 = 0$ . In the right pattern the nest is united and has one hole, so  $p_0 = 1$  and  $p_1 = 1$ . The lumen is united and has two holes, so  $p_0 = 1$ , and  $p_1 = 2$ .

Both  $p_0$  and  $p_1$  are 3-D quantities that have to be counted directly on serial sections. This is because stereology does not work in estimating the topological parameter values (the connectivity of features: See Table 2-2). As one may see in the above discussion, if a pattern has a hole, the value of  $p_1$  is 1, no matter how the pattern is transformed. For example, from a topological viewpoint, the alphabetical letter B is equal to the Arabic numeral of 8 since  $p_1 = 2$  in both. Stereology is a methodology to estimate length, area, volume or angle, all in the scope of metric analysis. The connectivity of network as we have seen in the skeleton of adenocarcinoma belongs not to geometry but to topology. In this sort of problem, we can rely only on direct analysis of the space by scanning with serial sections.

### **Structural skeleton of carcinoma with various differentiation (Fig. 5-15)**

The above rule of quantification was applied to six gastric tumors. In Fig. 5-15, the pattern of glandular skeleton is compared among different tumor types with the topological parameter values. Values of  $p_0$  as well as  $p_1$  are expressed as the number contained in 1 mm<sup>3</sup> of tissue. The normal gastric gland is a tree with small number of ramifications. Since there is no hole,  $p_1 = 0$ . Three adenomas of the stomach were studied, in each of which small number of connections proved to exist between neighboring glands, thus showing that the network skeleton was beginning to form. Still, the number of holes remains small, with the  $p_1$  value for the lumina remaining only 24, 29 and 48 per 1mm<sup>3</sup>. In the well differentiated adenocarcinoma, the tree pattern is completely lost and replaced with a dense network. The  $p_1$  value for lumina is as large as 384/mm<sup>3</sup>. Here, the lumina are all connected with no separated cavity as shown by

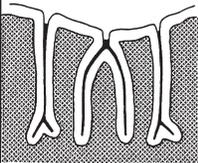
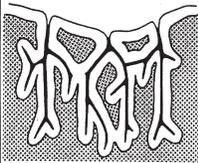
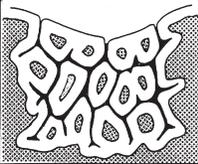
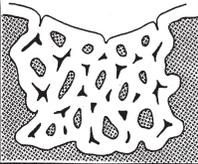
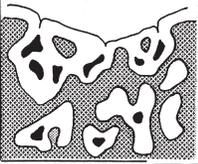
		$p_0$ (separate parts / $\text{mm}^3$ )		$p_1$ (loops / $\text{mm}^3$ )	
		Nests	Lumen	Nests	Lumen
	Normal	-	-	0	0
	Adenoma				
	Case 1	1	1	103	24
	Case 2	1	1	129	29
	Case 3	1	1	192	48
	Adeno- carcinoma Well diff	1	1	1640	384
	Adeno- carcinoma Mod diff	1	439	287	0
	Adeno- carcinoma Poorly diff	871	1133	653	0

Fig. 5-15. The skeleton difference among variously differentiated tumors of the stomach. All the parameter values were counted on serial sections. From the uppermost row downward: normal gastric gland, gastric adenoma, well, moderately and poorly differentiated adenocarcinomas.  $p_0$ : the number of separate parts in  $\text{mm}^3$ .  $p_1$ : the number of holes in  $\text{mm}^3$ . How the structure changes from fully differentiated normal glands to poorly differentiated tumor is described by the combination of  $p_0$  and  $p_1$ . From the top downward: tree pattern, formation of coarse network, fine network with continuous lumina, fine network with porosity, and network beginning to disintegrate. Reproduced from Takahashi and Iwama (1985): Science on Form I, pp. 548.

the  $p_0$  value of 1. In this combination of parameter values, one can see that although the tree pattern of ordinary gland is lost, the tumor still retains its glandular character. In the moderately differentiated tumor, the luminal connectivity is entirely lost as shown by the  $p_0$  value of 439, and this expresses that the tumor is now entirely porous. But the nests themselves, with a  $p_0$  value of 1, are still entirely united and remain forming a dense network, with a  $p_1$  value of 287. In the poorly differentiated tumor, not only the lumina but also the cell nests have begun separating into parts, as reflected by the

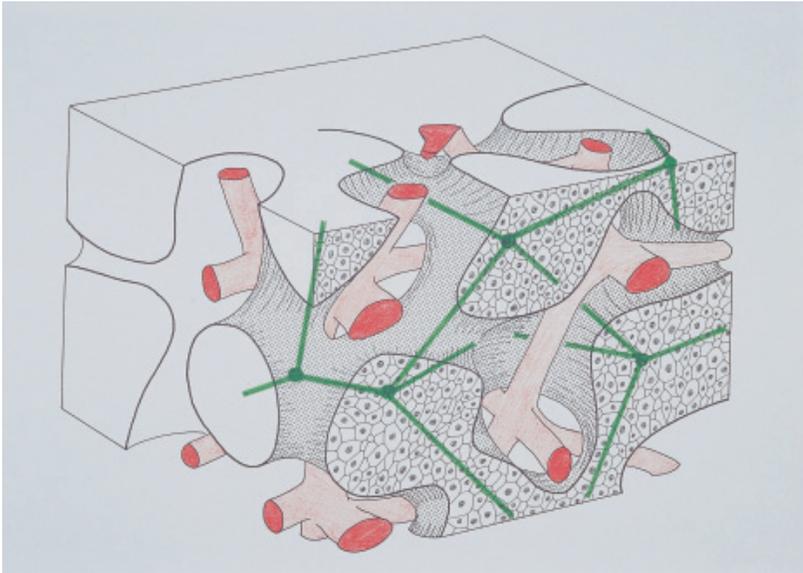


Fig. 5-16. A schema showing why gastric carcinoma has a network skeleton (green). The mass of carcinoma cells is intertwined in the space with capillaries (red) which form another network. Reproduced from Takahashi and Iwama (1984): *Tohoku J Exp Med* 143, pp. 463.

$p_0$  value that is as large as 871 per  $1 \text{ mm}^3$  tissue.

Thus, we find a transition of glandular skeleton from the normal to adenoma to well, moderately and to poorly differentiated adenocarcinoma. In the first step of changes, the tree pattern is lost and replaced with a network, still retaining the whole connectivity. Then the lumina lose unity, suggesting that the cells have begun stopping to form a canal and forming instead a simple trabecular mass containing vesicles filled with mucus. Finally, the cell nests begin to lose unity, and this means that the whole structure has started to disintegrate. Here one can see a chain of events where, the lower the differentiation of cells, the further does the glandular structure deviate from the normal tree.

In pathology, the usage of the term “differentiation” is usually confined to that of cells. However, based on what has been found, it seems that we can also define differentiation and dedifferentiation for the structure of cell assembly; in the case of stomach, the most differentiated structure is the tree of normal gastric gland. As dedifferentiation advances, the skeleton goes further and further away from the tree. Besides, visualization of the 3-D structure of carcinoma has been a lesson showing us what features in a microscopic 2-D picture should be counted as important signs of structural atypia (SAT) in making diagnosis. About this, however, the details are to be referred to the original papers (Takahashi and Iwama, 1984c, 1985).

### How does the network skeleton form? (Fig. 5-16)

Why do carcinomas form a network? We think that this may be explainable from the relation of carcinoma cell nests with the stromal tissue, as schematized in Fig 5-16.

In the stroma, capillaries form another network. Carcinoma cells will grow so as to fill the space as a continuous mass, but there is a limitation to this. As carcinoma continues spreading, at least it has to spare capillaries on which it depends for blood supply. Otherwise, the subsistence of carcinoma itself will be endangered. Since capillaries form a network in the space, carcinoma that has to co-exist with them must automatically be molded into another network which is topologically “conjugate” with capillaries.

In addition, it is to be pointed out that the capillaries, forming a 3-D network in various organs, are another object of topological research. An example will be found in the studies of Shimizu *et al.* (1993, 1996), who analyzed 3-dimensionally the topological difference in the structure of hepatic sinusoids in normal and cirrhotic livers and in hepatocellular carcinoma, relating the results with possible hemodynamical changes.

### The origin of various tumor skeleton (Fig. 5-17)

Finally, we propose a model of morphogenesis for different types of adenocarcinoma as in Fig. 5-17. The cells of adenocarcinoma express various degrees of differentiation into secretory cells. A normal glandular cell sits on a sheet of basement membrane and secretes its product upward from its top, or apex. Thus a secreting cell, when normally differentiated, is polarized into the basal and apical poles, and morphologically, the polarization is the very expression of differentiation for glandular cells. When a tumor arises, it comprises cells in which, in this sense, differentiation is more or less reduced. There can emerge cells half polarized or non-polarized, and these

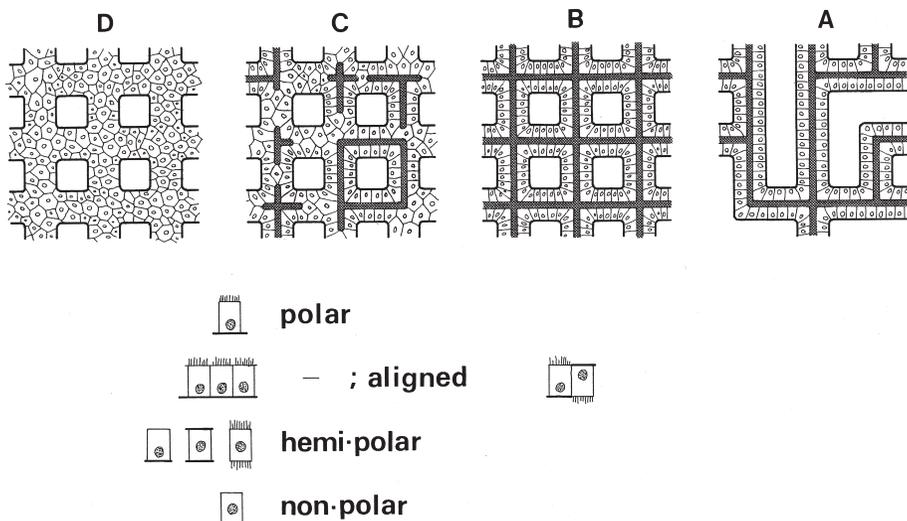


Fig. 5-17. The development of various skeleton in variously differentiated gastric tumors is schematized. A well differentiated tumor (B) has a network skeleton where the lumen is continuous throughout because the tumor comprises well differentiated cells that are sufficiently polarized into apical and basal direction. As less differentiated or undifferentiated cells come to join and have a larger share of cellular population (C), the lumina lose continuity, creating porous nests. Reproduced from Takahashi and Iwama (1984): *Tohoku J Exp Med* 143, pp. 464.

come to participate in forming the nests, taking various share of cell population. Assume, for example, that a certain percentage of non-polarized cells are mixed in the nests, as in Fig. 5-17-C. Then it would be conceivable that the non-polarized cells come to block the lumina here and there, resulting in the formation of porosity. When the nests consist exclusively of non-polarized cells as in Fig. 5-17-D, luminal canal no longer forms, and this is a state equivalent to the undifferentiated carcinoma. In this way, we can correlate various stages of structural differentiation with the differentiation of the individual cells that constitute the nests.