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CONTENTS

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Alpha-1-Antitrypsin Deficiency in Cirrhosis of the Liver

S. Gürsel, M.D.* / Ş. Karacadağ, M.D.**

Alpha-1-antitrypsin and its association with pulmonary and liver disease has been well documented. Recently more studies have been reported in different types of liver disease with alpha-1-antitrypsin deficiency.

The present study was undertaken to determine the alpha-1-antitrypsin deficiency in patients with cirrhosis of the liver.

Materials and Methods

Thirty-six patients with cirrhosis of the liver were studied at Hacettepe Medical Center. Diagnosis is based on history, physical examination, liver function tests and the liver biopsy.

There were 36 normal healthy controls with no history of previous liver or pulmonary disease. Serum alpha-1-antitrypsin (α_1-AT) were determined with M-Partigen immunodiffusion plates from Behringwerke A.G. Co. All patients had routine serum protein electrophoresis prior to serum α_1-AT determination.

Results

Controls: Alpha-1-antitrypsin values were found within normal limits in all controls. Values ranged from 2.10 to 3.88 mg/ml, the average being 2.97 mg/ml.

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Cirrhosis: Values ranged from 1.10 mg/ml. to 3.71 mg/ml., the average being 2.88 mg/ml. Only two patients were found to have low alpha-1-antitrypsin. The first patient had 1.10 mg/ml and the second 1.60 mg/ml. Routine serum protein electrophoresis of these two patients showed decreased α_1 fraction of the globulin (Figure 1).

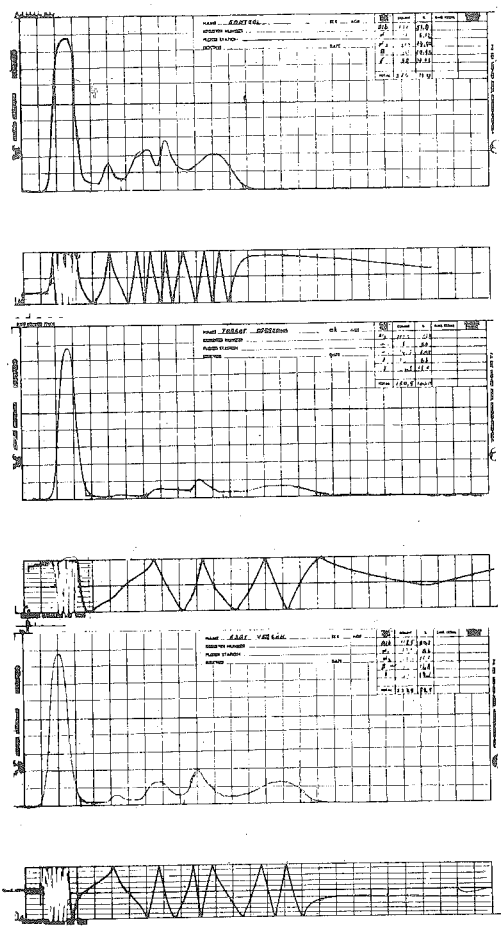

Figure 1
A normal protein electrophoresis (above).
A low α_1 globulin patient with low α_1-AT (below).

Discussion

α_1-AT, a glycoprotein with a molecular weight of about 45.000, comprises approximately 90 % of the α_1 globulin fraction,[2] determined by routine serum electrophoresis. Although its physiologic role is still uncertain, it has been shown to inhibit many enzymes, including trypsin, plasmin, thrombin, collagenase, elastase and leucocyte proteases.[1]

Several genetic variants of α1-AT have been identified on the basis of electrophoretic mobility, electroimmunodiffusion, acid starch gel electrophoresis with crossed antigen-antibody electrophoresis and immunofixation electrophoresis. At least 13 genes occurring at an autosomal locus, control the production of α_1-AT.[2] Approximately 2.3 mg/ml comprises the vast majority of healthy populations. The phenotype P_iZZ is associated with low serum levels of 5 to 15 % of normal values and with most cases of pulmonary or liver disease. Intermediate levels are seen with phenotypes P_iSZ (31 %), P_iSS (63 %), P_iM (61 %), P_iMS (83 %). However, wide and overlapping ranges of α_1-AT concentration can occur, so that the screening tests based on quantitative methods do not give a reliable indication of phenotype.[3] Other allotypes are F, I, V, X and W. The incidence of homozyguos (P_iZZ)α_1-AT deficiency in the general population is 0.1 to 0.2 % and the incidence of the heterozygous deficiency is estimated to be 5 to 14 %.[4]

The diseases which have been associated with a deficiency of α_1-AT are principally pulmonary emphysema of early onset[5] and juvenile hepatic cirrhosis.[6] It has been estimated that two-thirds of individuals homozygous for the deficiency will develop emphysema, but the reason why the remaining third do not develop it is obscure.

Cirrhosis occuring in adult homozygous individuals has been described with[7] and without[8] emphysema. Cirrhosis[9, 10] has also been described in heterozygous individuals. Ishak, et al[11] considers the light microscopic and ultrastructural features to be highly characteristic if not pathognomonic of α_1-AT deficiency and recommends PAS staining after diastase digestion on liver tissue from all patients with the deficiency. Light microscopy shows the accumulation of PAS positive inclusion bodies in the hepatocytes and periportal areas, especially in the areas of more severe liver damage. With electronmicroscopy. amorphous material antigenically related to α_1-AT was seen by immunoflourescence within the rough endoplasmic reticulum of liver cells.

The pathogenic mechanism of liver disease associated with antitrypsin deficiency is not yet understood. The theory advanced by Eriksson[5] to explain the development of lung disease seems logical and may apply to a certain extent to liver disease as well. It is based on the concept that a deficiency of the antienzyme renders tissue more vulnerable to damage. Lieberman, et al[12] propose an alternative hypothesis to explain liver injury, in which the increased vulnerability results from the abnormal deposit of clumps of α_1-AT within the hepatocyte. Either concept is applicable to individuals with severe or partial deficiency of α_1-AT.

This protein seems to have a protective role against a multiplicity of potentially noxious factors. The activity of several enzymes such as Trypsin, thrombin, plasmin, human skin collagenase, pancreatic elastase and leukocyte proteases has been shown to be inhibited by α_1-AT. A severe dificiency gives minimal protection and mere vulnerability, making it possible for advanced liver or lung disease to occur early in life. A partial deficiency may result in a precarious state of incomplete protection, which may be enough in some circumstances and inadequate in others.

In our study 36 patients with cirrhosis of the liver were studied and only 2 patients with low α_1-AT values were found. Unfortunately we were unable to check the families and to determine the type of α_1-AT deficiency. Also we were unable to perform the immunoflourescent studies on the liver biopsy. From this study we can say that there is α_1-AT deficiency in few patients with cirrhosis in Turkey, and further detailed studies should be done in this field.

Summary

In thirty-six normal healthy controls and 36 patients with cirrhosis of the liver serum α_1-AT levels were determined with M-Partigen immunodiffusion plates and only 2 patients showed low values. All controls had normal values. The literature is also reviewed.

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Hacettepe Bulletin of Medicine / Surgery
Volume 9 / Numbers 1-2 / January-April 1976 / pp. 6 – 9

A Case of Scrotal Hemangioma

Doğan Remzi, M.D.* / Demokan Erol, M.D.**

It has long been an established custom to include under the more or less exact term of hemangioma all the congenital lesions of the vascular system. A tumor consisting of capillaries of normal caliber microscopically is termed "capillary hemangioma". Cavernous hemangioma is characterized microscopically by the large, cavernous. vascular channels. Sclerosing hemangiomas (dermatofibroma) are believed by some to be capillary hemangiomas that become transformed from a highly vascularized lesion to a solidly cellular tumor by the progressive proliferation of endothelial cells and connective tissue stroma.[1]

Cavernous hemangioma of the scrotum is a rare tumor. In literature only 36 cases were reported. We think it will be interesting to report a case of hemangioma we have seen in our clinic and to review the literature on the subject.

Case Report

M. B., 22-year-old unmarried student was admitted to our service with the complaints of a feeling of heaviness and progressively growing tumor on the left side of his scrotum. From his past history it was learned that the tumor was present since his birth, and it had rapidly grown during the past year. He had experienced no operations, trauma or accidents. Occasionally blood was oozing from the tumor and it was painless. On examinations of the scrotum, it was seen that there was a painless, red-purple tumor over the left hemiscrotum growing towards radix penis and perineum. The tumor was rich of dilated vessels and on palpation it was separate and continuous with the testis (Figure 1).

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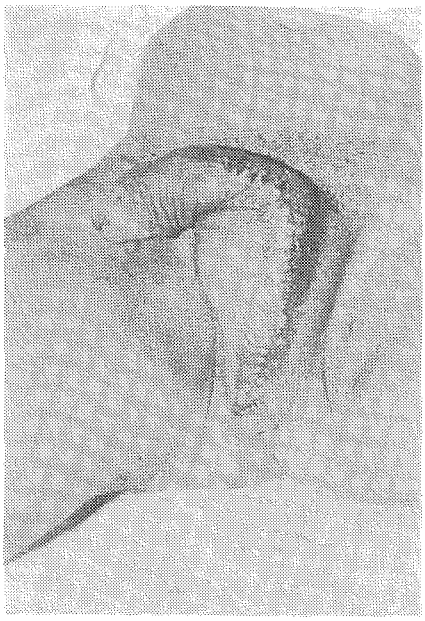

Figure 1
Preoperative appearance.

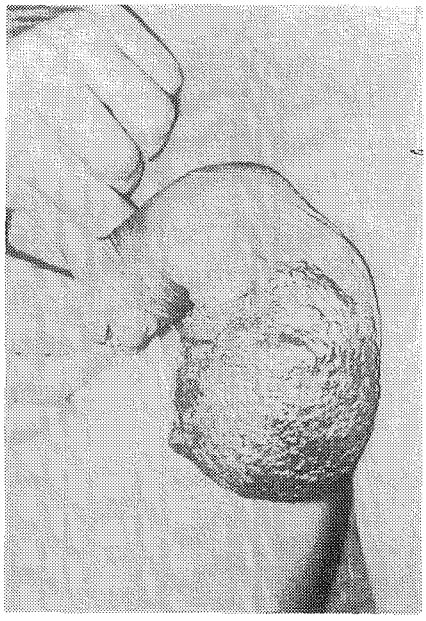

Figure 2
Postoperative appearance.

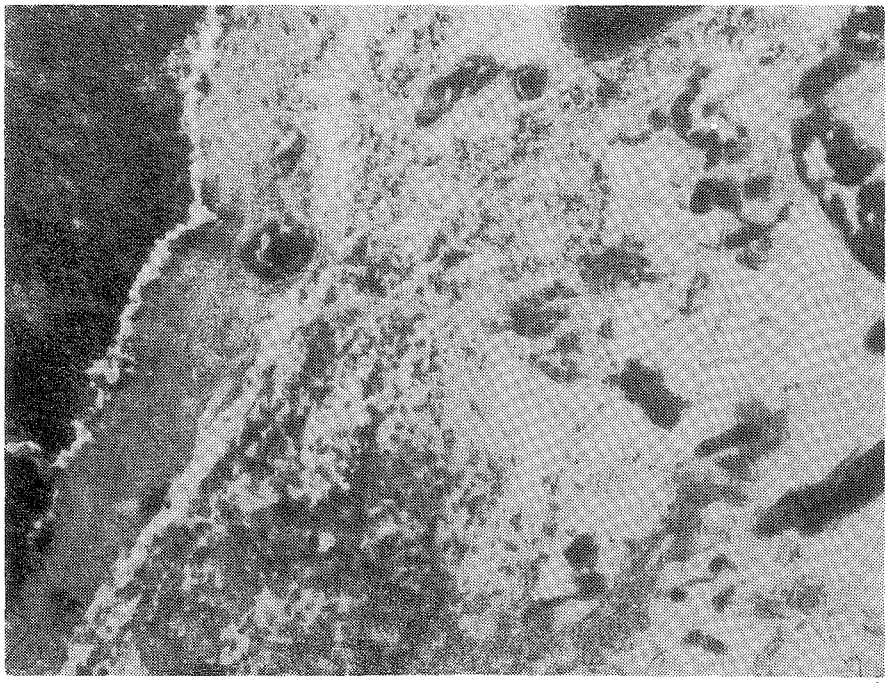

Figure 3
Microscopic section.

Routine blood and urine analyses and chest X-rays were normal. Urine culture was negative. On 2/12/1975 total hemiscrotectomy was performed under general anesthesia. The gross pathologic appearance of the tumor was; a tissue 10x5x4,5 cm in dimensions and purple colored containing 10x5,5 cm of curinckled skin. In different localisations there were sausage like vessels and multiple papillary growths, the largest being 0,5 cm, which were seen on scrotal skin. Microscopically, enlarged vessels with thick walls and lumens full of erytrocytes were seen. (Figures 2,3).

Discussion

The cavernous hemangioma of the scrotum was first described by Robert[2] in 1851. In 1937 with Gibsons[3] case only 19 cases were present in literature. Today, however the total number of cases reported is 36.

Although the hemangiomas of skin are seen frequently, the genital lesions are only 1/100 of the total hemangiomas.

Scrotal hemangioma is congenital. Therefore it is seen very early in life time. But because of social restrictions and since it does not have any negative effect on sexual activity, the patients with such genital lesions come very late to see the doctor.

The youngest case in literature, reported by Mahoney[6] is a two months infant with cavernous hemangioma of scrotal septum. Another case is a one year old infant reported by Mininberg[7] with a cavernous hemangioma of the scrotal wall.

Gulienetti[5] reviewing more than 2,000 cases of hemangioma, pointed out that only 21 cases were located in genital area and incidence in men were higher than women.

Cooper and associates[4] compared hemangioma with varicocele. Their findings could be summarized as follows:

a) While hemangiomas are congenital, varicoceles are seen in puberty when the vascularity of testes is very high.

b) While hemangiomas are seen either on the right or left side of the scrotum and sometime bilateral, varicoceles are always seen on the left side.

c) And their diagnostic criteria was; the tumor being firmer in hemangioma and when the patient is lying down, or the veins would not drain empty; with the manipulation of the scrotum upwards.

Gibson, in differentiating between the hemangioma of the scrotal skin and the hemangioma of the scrotal wall, pointed out that only in the first case one could see the change of color.

To differentiate between the tissues attached by the lesion, Mason[8] employed angiography. With this method he was able to demonstrate the internal and external Pudental arteries and ligate them for treatment of hemangiomas.

Treatment

Even though Pais in 1954, Laborde in 1956, Roselli in 1956 employed irradiation in the treatment of hemangiomas, today this method is not being used because of the hormonal imbalances and impairment in growth seen in patients receiving such therapy.

Hot and cold sclerozing agents have been used by many authors including Ward[9] with some successful results. But today many authors have the same opinion that surgical treatment is the best in use.[6, 7, 8] Simple excision is the most often used method and provides the best results.

Suturing percutaneously and impairment of the arterial supply are not as reliable.

Electrofulguration is applied in some cases. If the need be, hemiscrotectomy or orchiectomy could be performed.

The "chess-board" technique modified by Gabarro[10] is the method that gives the best results.

Summary

A case of cavernous hemangioma in a 22 year-old male on whom hemiscrotectomy is performed was reported and the literature on hemangiomas was reviewed.

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Hacettepe Bulletin of Medicine / Surgery
Volume 9 / Numbers 1-2 / January-April 1976 / pp. 10 – 34

Light Microscopy in Hyperplastic Endometrium

Presentation of new findings with an overall review

Yaman Örs, M.D.* / Özden Tulunay, M.D.**

Functional or *dysfunctional bleeding*, in contrast to the *organic* one, is the term applied to those cases of uterine hemorrhage in which there is no clinical evidence of any cause and whose origin is believed to be hormonal. In many cases of this sort of uterine hemorrhage bleeding is attributed to a drop of blood estrogen level that has been high and/or prolonged under the influence of different factors. It is natural to find in these cases, exaggerated poliferative, or hyperplastic, changes in the endometrium, and then pathologists speak of an *endometrial hypeplasia*, which is one of the commonest lesions leading to gynecological complaints.[1-3] However, bleeding is not the main symptom or sign in every case, although it is the most frequent one.

Observations[4-23] and animal experiments[5,24-26] have revealed the role of estrogen in the pathogenesis of the lesion, a fact one would theoretically expect. It may thus be called, from the physiological standpoint, *hyperestrinism*.[5]

What we call endometrial hyperplasia, factors in its pathogenesis being several, is not a "clinical entity" but, as the name implies, a histopathological term. It will be clear then that the lesion should be called *hyperplastic endometrium* rather than endometrial hyperplasia.

A much less frequent lesion of the endometrium is the exaggerated secretory phase brought about by the activity of large *corpora lutea* or an excess of lutein tissue in the ovaries.[5]

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Material and Method

This paper is based on the data of a previous retrospective study that had been done by one of the authors.[27] He had then re-investigated the hematoxylin-eosin slides of 347 cases, diagnosed previously as "endometrial hyperplasia" with different qualifying subtitles, among the gynecological material sent to the Department of Pathology of the Medical Faculty of A. U during a ten-year period between 1954 and 1964. We have re-evaluated the earlier findings and reviewed the recent literature.

In some cases new sections had been obtained and stained with Weigert's fibrin stain for the differentiation of this material from necrosis.

Of the 347 cases, 155 were re-diagnosed as "hyperplastic endometrium," five as "endometrial changes due to *corpus luteum* hyperactivity," and one as "adenocarcinoma". A great majority of the remaining slides were diagnosed as "chronic endometritis," the others as "transitional or senile endometrium" or "endometrial polyp". Two of the latter showed hyperplasia. Lastly, some of the slides were accepted as normal endometrium showing one of the phases.

The material in 147 out of 155 cases of hyperplastic endometrium had been obtained by curettage, in four by biopsy, in one by biopsy together with curettage, in another by hysterectomy; in one case part of the uterus, and in another a slide had been sent. Two of the materials obtained by curettage belonged to the same patient.

Concise clinical data. The oldest of the patients in reproductive activity among 155 cases of hyperplasia was fifty-four and the youngest eighteen years old. There were three cases beyond menopause, the oldest one being eighty years of age. The patient with carcinoma was fourty-eight years old. The youngest of the cases with endometrial changes due to *corpus luteum* hyperactivity was twenty-seven and the oldest forty-five years of age.

In the great majority of cases the complaint had been bleeding, its duration, type and intensity differing greatly from patient to patient. In a few it was sterility or pain in the groin, with an additional clinical finding such as an enlarged uterus. Three patients had had the complaint of hypomenorrhea and two showed the symptoms of the Stein-Leventhal syndrome. Some had given no history of pregnancy, while its incidence was as high as nineteen among the rest.

Results and Discussion

We shall first consider the changes in the epithelium and those of the stroma, other important findings and finally the less frequent characteristics of the lesion and additional relevant points.

Changes in the Epithelium: The surface epithelium was observed to be high in most cases, revealing in different areas a true or false stratification which was as a rule associated with that of the glandular epithelium. It covered almost the total circumference of some endometrial islands in curettage or biopsy specimens, a finding which can also be seen in cases of chronic endometritis or normal endometrium, less frequently though. Some areas showed numerous glands, others few or none. Although a true increase in the number of glands may not be present or apparent in many fields,[22] it suffices to see an increase in the number of epithelial cells, the ultimate criterion for the lesion to be called a "hyperplasia".

The glands revealed, in most cases, what is known as a "classical" finding - a marked disparity of size and shape. We observed this, together with other findings, in all the layers including the *basalis* in the single case of hysterectomy.[1] The difference in size, caused by the cystic dilatation of some glands, was less marked or almost non-existent in some cases or areas, so that the appearance was more uniform. It must be articularly in such cases that the lesion may be overlooked on a superficial examination. A more careful study would reveal the proliferation of the epithelium, the frequent enlargement and darkness of nuclei in the absence of regressive changes, and a dilatation, however slight, of the glands.

By means of serial sections Ratzenhofer and Schmid have found that dilatation and cyst formation of the glands are brought about by those which cannot reach the surface.[28] The irregularity of shape is attributed to the unproportional proliferation of the epithelium. Contours of the glands were either regular or slightly tortuous. We did not regard the double contour as a remarkable finding. Gögl and Lang believe that this is artificial in some glands;[29] it may well be that it is so in all.

The epithelial nuclei occupy a greater part of the cells than normally observed, and a true or false stratification seems to be the rule (Figure 1). Authors in general believe that the more enlarged the glands

[1] The term "Swiss-cheese pattern", used for this appearance, has been widely accepted since 1924 when it was first suggested by Novak.[18] However, as we do not find it serious and scientific to compare any microscopic (or macroscopic) lesion to food and call it accordingly, we shall not use the term here.

are, the more flattened the epithelium becomes. We have observed that, while this was usually so, it was not so constant as is generally held, and a stratification could be seen even in the enlarged and cystic glands. Unless degenerative changes, which will be referred to later, or evidence of bleeding were present, mitoses were frequent in the epithelial cells (Figure 1). Such instances must be taken as "active" cases. (The presence of mitoses is also observed in the proliferative (and secretory) phase and in the non-functioning and proliferative types of senile endometrium, and therefore can be of no definite diagnostic value.)

The cells called "hypertrophic" by Saphir[30] may represent a specific characteristic of adenomatous type of hyperplasia which we shall consider below. Otherwise, we did not see such cells. In some cases, on the other hand, we observed glands or groups of them in which epithelial cells had large, eosinophilic cytoplasms and generally round and non-hyperchromatic nuclei revealing stratification. We have come to the conclusion that what these cells signify is not the same in every instance or area; they may represent what Anderson names "anaplasia,"[31] or degenerated cells, areas of adenomatous hyperplasia or transition to epidermoid metaplasia (Figure 2).

Cases of *adenomatous hyperplasia* were not rare (Figures 2 and 3). It was an independent lesion in four patients, with evidence of endometritis in two of them. Areas of adenomatous hyperplasia were present in five instances of "classical" hyperplasia. Moreover, a coincidence was observed with the changes due to *corpus luteum* hyperactivity in one and with the advanced secretory phase in another case. In still another, adenocarcinoma and this lesion were found together. (The youngest patient was a thirty and the oldest a fifty-year old (climacteric) woman). Adenomatous changes could also be seen in the surface epithelium. The cells of the lesion were eosinophilic, with rather lightly staining granular nuclei, and could reveal stratification.

In the lumens, darkly staining eosinophilic material, necrotic cells and debris were frequently observed (Figure 2). In general, these were more numerous in instances showing degenerative changes or bleeding. We regarded the amorphous eosinophilic material also as the outcome of desquamated cells and not as the indication of any functional activity, although they may remind us of the "dry" secretion of the late secretory phase.

As reported by others,[32,33] *clear cells* were more numerous than normally seen and their number increased in proportion to regressive changes. We were thus in a position to conclude that most if not all of them must indicate degeneration (Figure 4). Electron microscopic

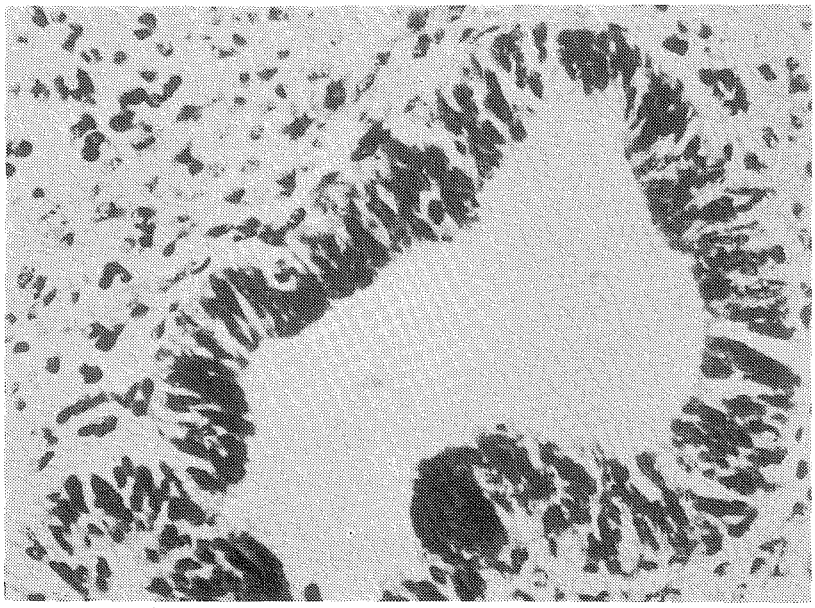

Figure 1
Mitoses in the glandular epithelium that shows true stratification. (x250)

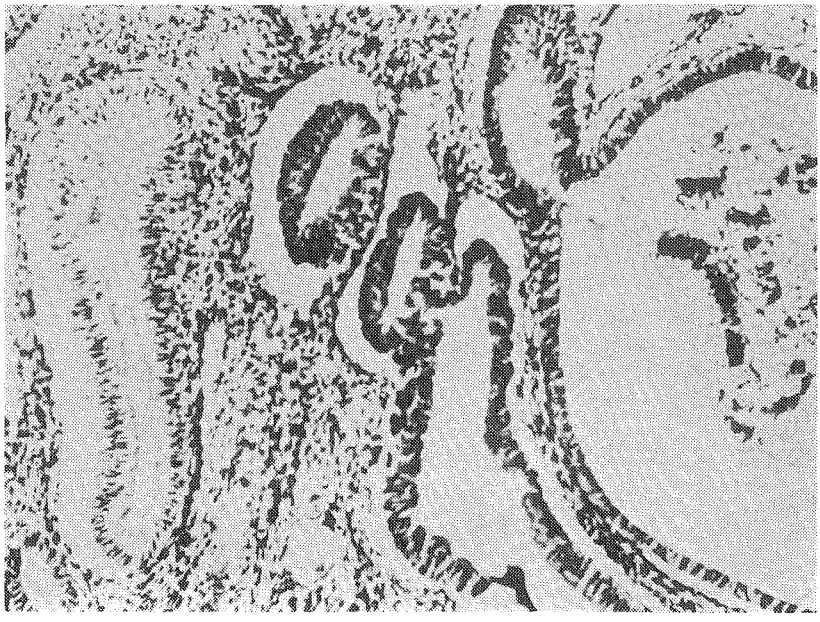

Figure 2
Cellular debris in the lumen on the right. The epithelium of the gland on the left shows endocervical metaplasia. In the middle are seen glands whose (eosinophilic) epithelium may be regarded as a transitional form to adenomatous hyperlasia. Pyknotic nuclei both in the epithelial and stromal cells. Postmenopausal case. (x100)

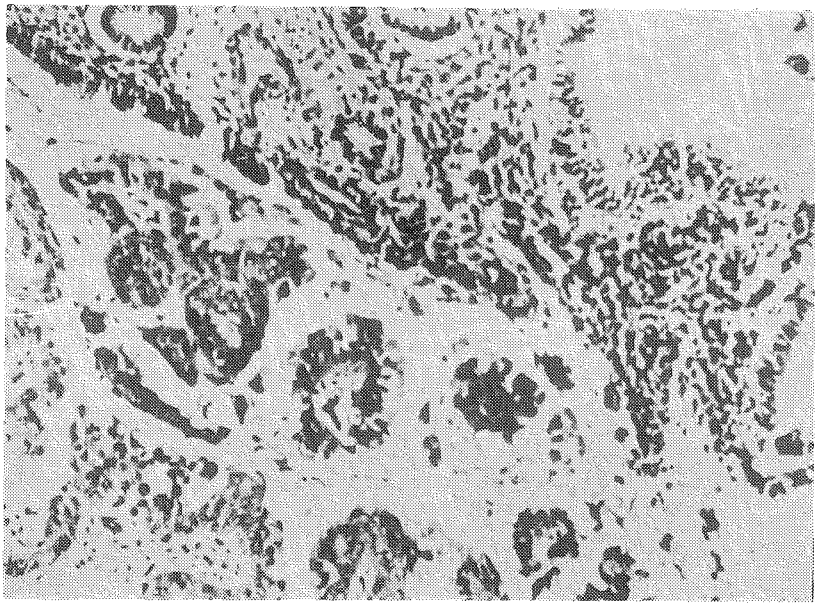

Figure 3
The lower-left half of the figure reveals adenomatous hyperplasia, and the upper-right one changes due to *corpus luteum* hyperactivity. (x100)

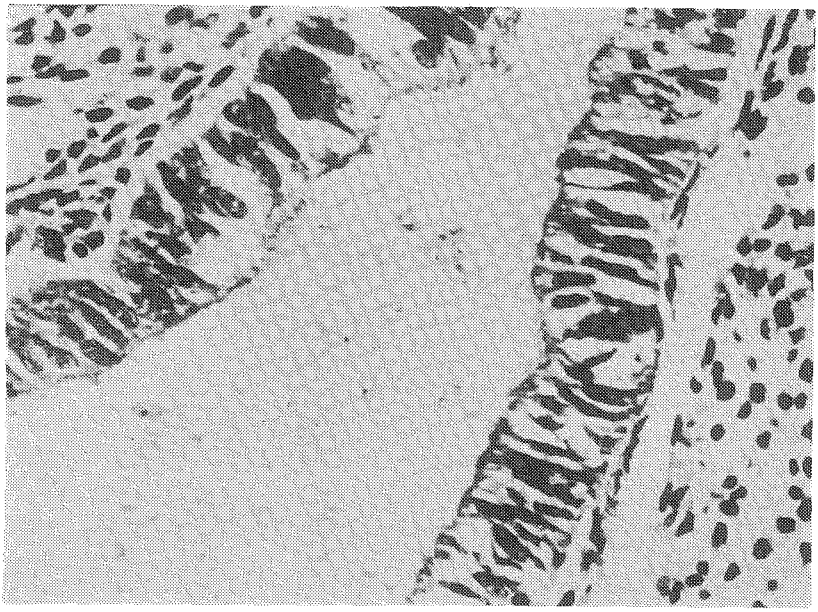

Figure 4
A gland with numerous clear cells; most of the nuclei are hyperchromatic and rather basally situated. Pyknotic nuclei of the stroma cells indicate regressive changes. (x250)

studies have revealed that some are in fact degenerated cells.[33] We do not believe that they may have any endocrine function which, according to Sarbach, some writers have attributed to them.[34] One or two polymorphs or lmyphocytes could be seen between epithelial cells and these, it must be noted, might be taken for mitotic figures.

Metaplasia of the tubal epithelium[7,18] was infrequent and observed also in the surface epithelium. All three types of cells could be seen in these cases, and this differs from the finding that the normally found ciliated cells increase in number in the lesion[33,35] (Figure 5).

We witnessed *epidermoid metaplasia* in the surface epithelium of two cases (Figure 6). We think that the eosinophilic glandular epithelial cells may represent a transition to the squamous type of epithelium.

In two cases we observed the *syncytium-like epithelial proliferation* described by Novak.[18] We came to the conclusion that it must merely signify some sort of degenerative change (Figure 7).

So far as we know there is no mention, in the literature, of the *metaplasia of endocervical epithelium* which is known to occur very rarely in other conditions. We observed the change to be present in five cases, occupying the whole or some foci of the glandular epithelium, and also in adenomatous hyperplasia (Figures 2 and 8). The basally situated nuclei were in some cases flattened, in others oval or elongated. This difference must suggest the different stages of response to endocrine stimuli that we find in the normal cervical epithelium.

Changes in the Stroma

Comparatively little has been said, generally, about the stromal changes in hyperplastic endometrium.[36,37] And our retrospective study has made us agree with those writers who are of the opinion that findings in the stroma are as constant and as important as those of the epithelium. Most of the writers, however, have not paid as much attention to them as they deserve. It requires a more careful and patient investigation to reveal the stromal changes which may otherwise be overlooked easily. The additional reason for this seems to be the fact that stromal tissue in general is given a secondary importance, and that the activity of secretion is more readily accepted within the concept of function. The specific reticular structure and the changes it undergoes in response to endocrine stimuli make things altogether different in the case of endometrial stroma, and hyperplastic changes are only to be expected in this tissue when exposed to excessive or prolonged estrogenic stimuli.

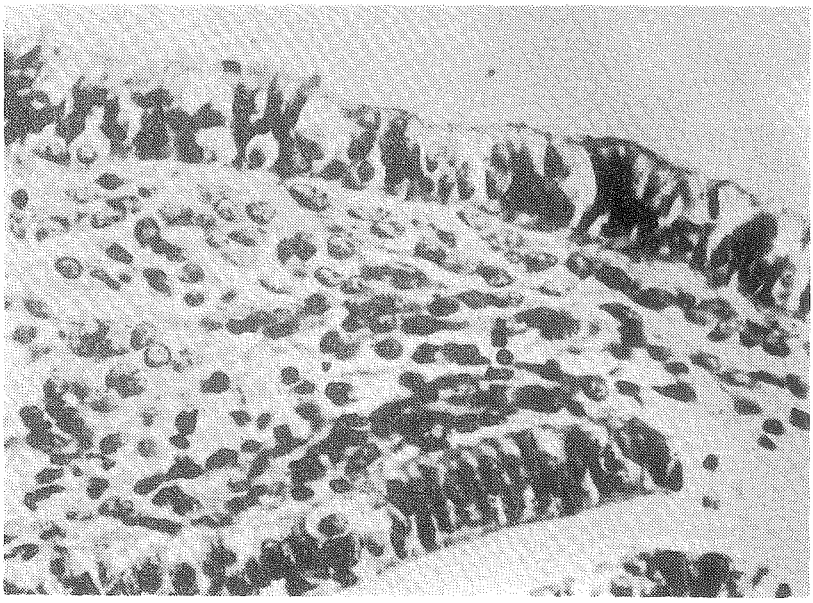

Figure 5

Metaplasia of the tubal epithelium. The "active" stromal cells are large. (x250)

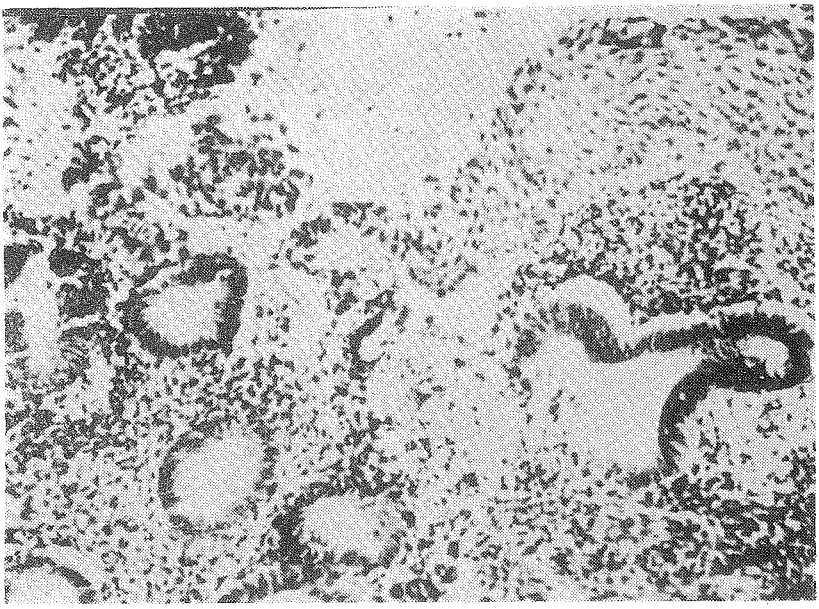

Figure 6

Epidermoid metaplasia of the surface epitelium. (x100)

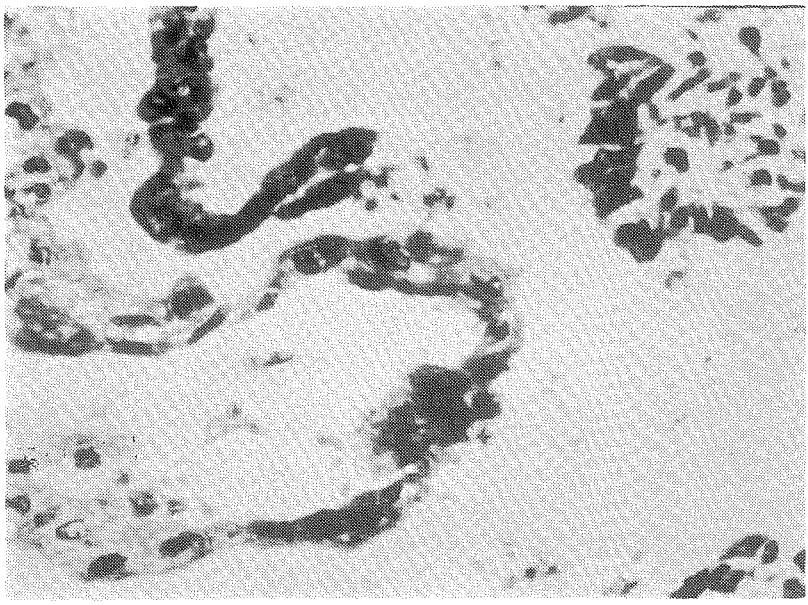

Figure 7
Syncytium-like epithelial proliferation. (x250)

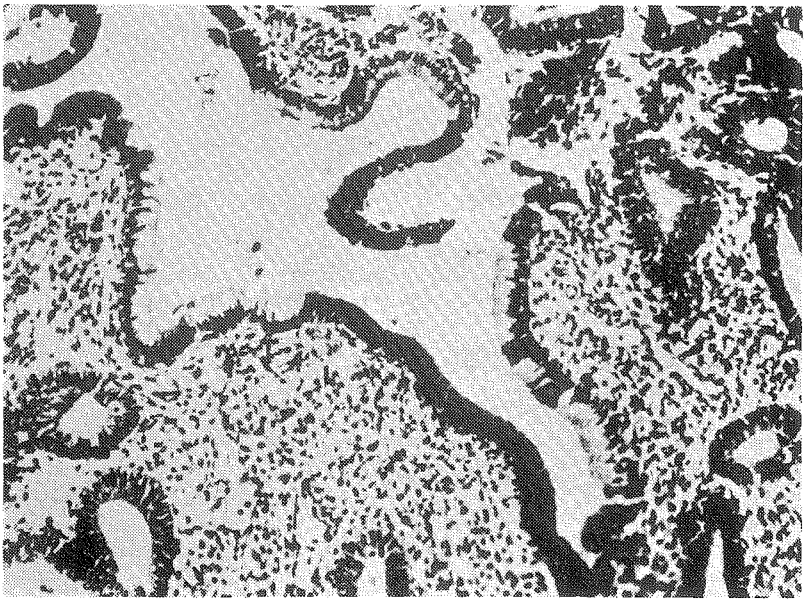

Figure 8
Foci of endocervical metaplasia in a dilated gland. (x100)

We found no instance of *stromal hyperplasia* which Schröder believes to occur in about five per cent of the cases.[38] We observed, however, that the stromal changes were more conspicuous here and there in some cases. An increased density of the stroma was present primarily in periglandular fields, as is also the case in the normal proliferative phase. These areas of stromal hyperplasia were surrounded by loose edematous fields which were poorly defined, of various size and shape, and mostly irregular. Some of these were at the periphery or in the vicinity of blood lagoons. In places where cellular density was not extreme, an eosinophilic intercellular substance could be discerned. This substance and edema fluid stained here and there more darkly and granularly, in other places more homogeneously, being associated with the elongation of stromal cells and thickening of the fibers.

As depicted by Hanson,[39] stromal cells are mostly oval, sometimes round, and under the basement membrane of the glands (as is the rule in other sites of the organism) elongated. We agree with this writer also in his observation that in active cases most of cells are larger than normally seen, that is to say, there occurs a hypertrophy of the stromal cells (Figure 5). Not less specifically, though also found in some cases of endometritis, we could observe pseudodecidual change (Figure 11). A constant finding was the increased variety in the shape and staining characteristics of stromal cells. We did not investigate the fine cytoplasmic changes which Hanson describes.[39]

In cases where there was no evidence of regression or hemorrhage, a fine network of reticulum fibers could be discerned in places. We did not search for the increase of these fibers, a finding reported by Centaro and Serra.[40]

We observed no evidence of the finding of Eckert that the stromal cells become smaller with age in the lesion.[41] As we shall discuss later, however, in instances which had undergone atrophic changes, and generally in the endometrium approaching or in the climacterium with or without hyperplastic changes, we witnessed *an atrophy in these cells*. They also showed elongation and an acquisition of fibroblastic change, a finding seemingly not less dependent on age. In four cases, the youngest being twenty-two and oldest fourty-five, stromal cells revealed almost diffusely a pattern between the normal reticular and simple fibroblastic cells. Whether in patients approaching the menopause or in a much earlier period, we believe that this finding indicates a slight or significant reduction of the blood estrogen level. Then a transition may occur into an atrophic pattern, probably into a non-functioning endometrium with

many cystic glands. In such cases the epithelium also showed regressive changes such as pyknotic nuclei and an increase of desquamated cells and clear cells (Figures 2, 4 and 9).

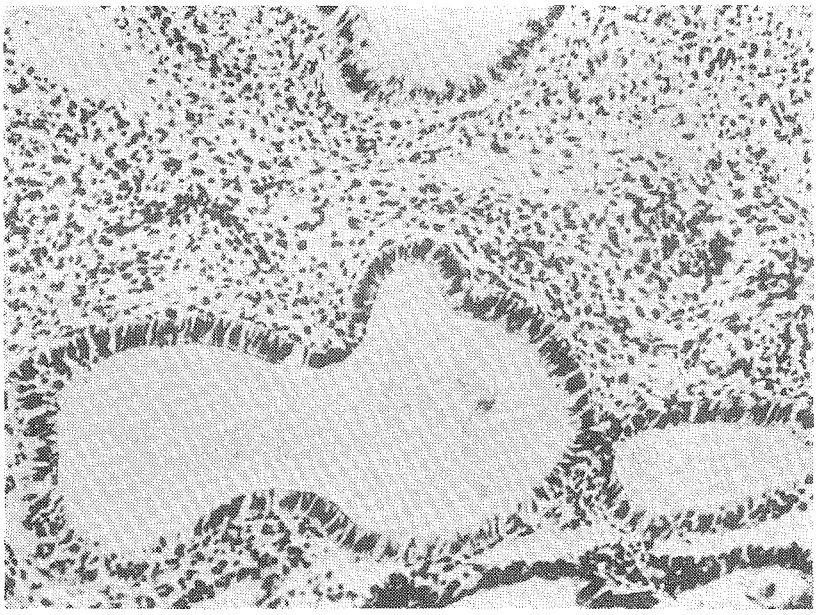

Figure 9

Hyperplasia in a thirty-six-year old patient. The epithelium is predominantly pseudostratified. Stroma cells are small, some of them being elongated (even in the area far from the glandular periphery): reticular-fibrous type of connective tissue. (x100)

Scattered among the stromal cells was an infrequent and different kind of cell with rather large, homogeneous and eosinophilic cytoplasm and pyknotic nuclei. They may be identical with those described by Numers and Nieminen, who believe that they are histiocytes.[42] At least some of them, however, may represent degenerated cells.

In contrast to the observations that the lesion characteristically lacks *inflammatory cells* unless bleeding is going on[5] or secondary infection has occurred,[18] we observed, as Hanson did also,[39] small and disseminated foci of lymphocytes and less frequently polymorphonuclears in our cases. The presence of the former in the lesion has been confirmed by others.[29] In the event of superadded infection, inflammatory cells certainly increase and other evidences of infalammation, such as fibrosis in chronic cases, are found.

One characteristic of the lesion was the increase of *blood lagoons* apparently similar to those normally seen in the secretory phase. The

walls could not be discerned in some of them, so that they could give the impression of edema fields or intercellular clumps of erythrocytes, depending on what was found in the lumens.

Capillaries and arterioles might show proliferation of the endothelium and in some cases hypertrophy and hyperplasia in their walls, as Schwarz and Sherman also observed.[26] *Congestion* was a frequent finding.

Apart from those observable during bleeding and desquamation, we witnessed *other degenerative events:* increase in the number of clear cells, more desquamated cells and eosinophilic material in the lumens, a higher number of cystic spaces and collapsed glands in some cases, and the absence of mitosis along with the presence of pyknosis in both the epithelial and stromal cells. These changes may be patchy, or so diffuse as to be seen all over the material, and closely resemble those described by Ratzenhofer and Schmid; they believed that they are due to the excessive or prolonged estorogenic effect.[28,43] Moreover, we found such changes also in cases of hyperplasia undergoing atrophy or in the climacteric endometrium. Fibrous changes in the stroma may help distinguish atrophy from the effects of excessive estrogen.

Other Significant Changes

Foci of Necrosis or Masses of Fibrin?

An important result of our study was on the nature of the so-called "localized areas of necrosis or necrobiosis" of the "classical" literature. Just as described by others, these are partly homogeneous and partly granular, sometimes lightly fibrillar, and sharply demarcated eosinophilic areas, some of which may reveal cellular debris. They may indeed be likened to infarcts.[18] We could find them also in the lumens of blood lagoons (Figures 10 and 11). On a more careful examination, some of the debris proved to be polymorphonuclears. The last two findings made us suspect as to what they really represented. A closer investigation revealed that some of them were passing through a split in the walls of the lagoons (Figures 10 and 11) and that clumps of erythrocytes could frequently be encountered in contact with or in the vicinity of those outside the latter. Moreover, the usually inconspicuous endothelial cells lining the blood lagoons could easily be discerned in places.

With the findings enumerated, we came to the conclusion that these structures *should be masses of fibrin rather than localized areas of necrosis or necrobiosis.* The positive finding in sections stained with Weigert's fibrin

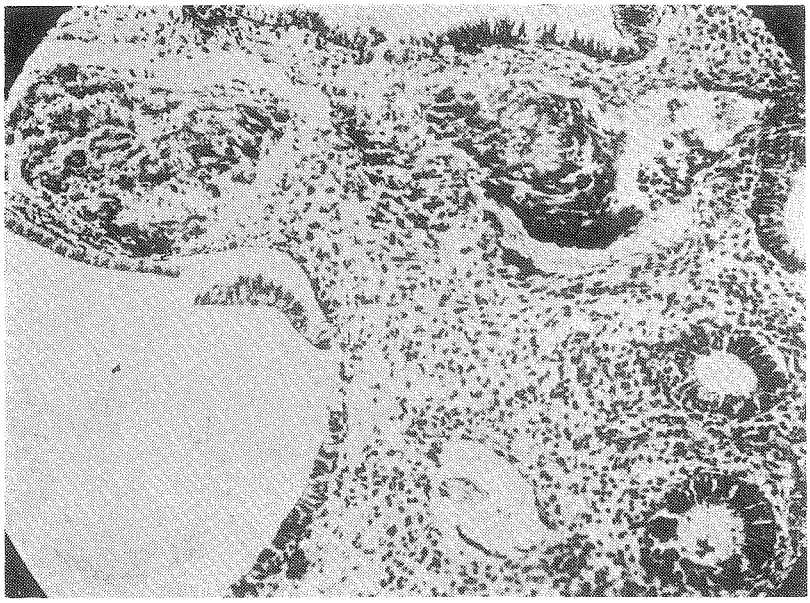

Figure 10

Two blood lagoons in whose lumens are seen infarct-like fibrin masses. Thrombotic material seems to be passing into the stroma through a rent in the wall. (x100)

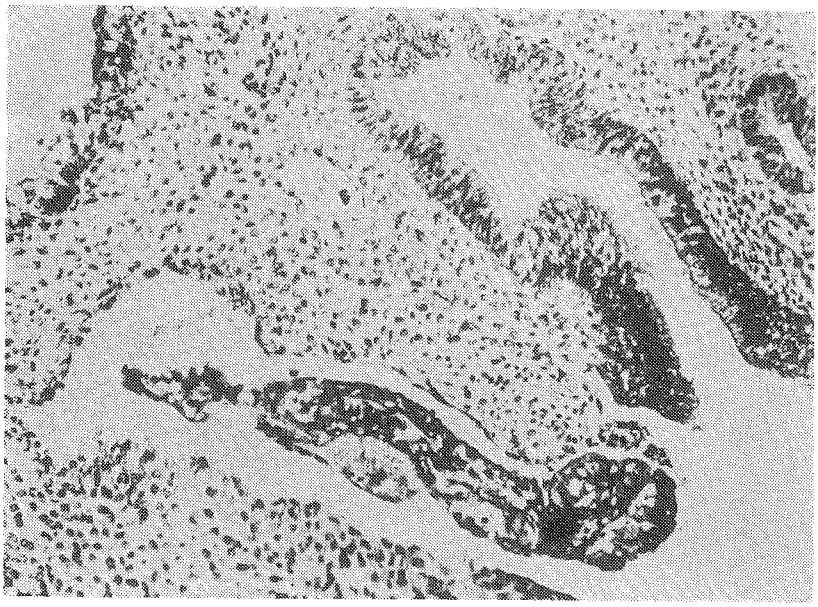

Figure 11

Thrombotic material passing through the rent in the wall of a lagoon. Pseudodecidual change in the stroma. (x100)

stain confirmed this conclusion. We also believe that the eosinophilic material seen where there was excessive edema fluid and showing fibrin-like staining properties might be diffusely extravasated and coagulated fibrinogen.

Boyd mentions the patchy necrosis of the surface, whose cause, he adds, is uncertain.[5] And Novak and Woodruff stress the uselessness of speculating about the details of the spiral arteries, role in the phenomena of "necrosis" until more is learned as to vascular events and the nature of their control by the endocrines. More worth mentioning in our context, however, are their morphological considerations. As supported by one of their figures, they define the necrosis in the lesion as "areas in which the endometrium shows marked degenerative change, with much round cell infiltration and with numerous thrombosis of the blood vessels. These are commonly rather sharply marked off from the surrounding endometrium."[18] Although we shall not dare say that all such areas must represent masses of thrombi of fibrinogen, it seems not impossible that they do. Nevertheless, we are not inclined to deny the necrosis, which Boyd restricts to the superficial layers and to the period of the lesion when bleeding goes on.[5] We are going to treat the latter in our next subchapter.

We observed the masses of fibrin also in cases of endometritis without the presence of hyperplasia and in a case of *corpus luteum* hyperactivity. As a matter of fact, these structures appear to be "nonspecific", although they may occur more frequently in hyperplastic endometrium.

Bleeding in the lesion: We have witness ed that hemorrhage in the lesion may be associated with the blood lagoons, and believe, as Robbins[22] and Anderson[31] do also, that they may at least partly be responsible for it as a final factor (Figure 12). According to Boyd, thrombosis of the small vessels is, together with the "superficial necrotic patches" another feature of the lesion during bleeding. Thrombosis may lead to local necrosis, the author remarks, and the latter is the chief factor in the hemorrhage.[5]

Thrombosis formed in the lagoons may cause ischemia. In fact, material obtained during bleeding in some cases revealed the presence of more or less diffuse disintegration and necrosis as seen in menstrual bleeding (Figure 13). The above mechanism may serve the same function as does the prolonged contraction of spiral arteries, in menstruation. Although the initiating factors may be different, there seem to be common features between the mentsrual bleeding and that of hyperp lastic endometrial tissue.

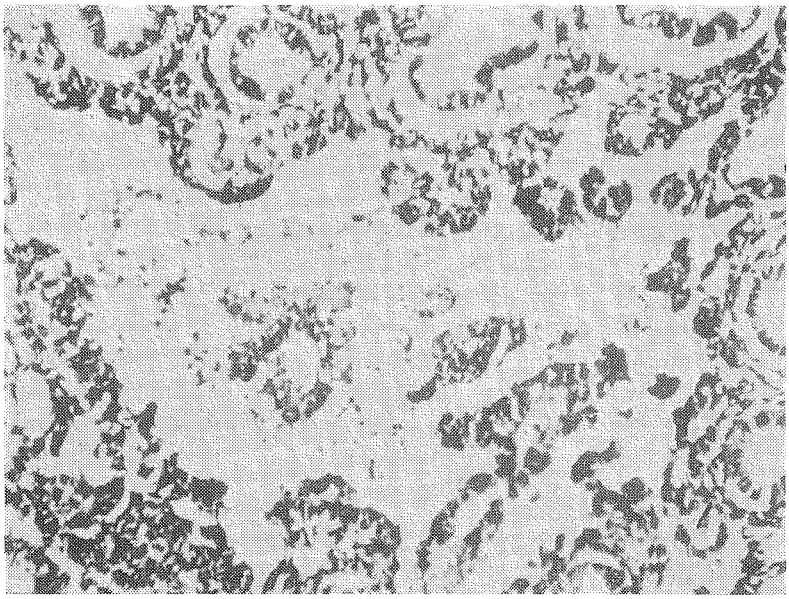

Figure 12

Section of a gland in the middle of a blood mass apparently brought about by hemorrhage from a lagoon. (x100)

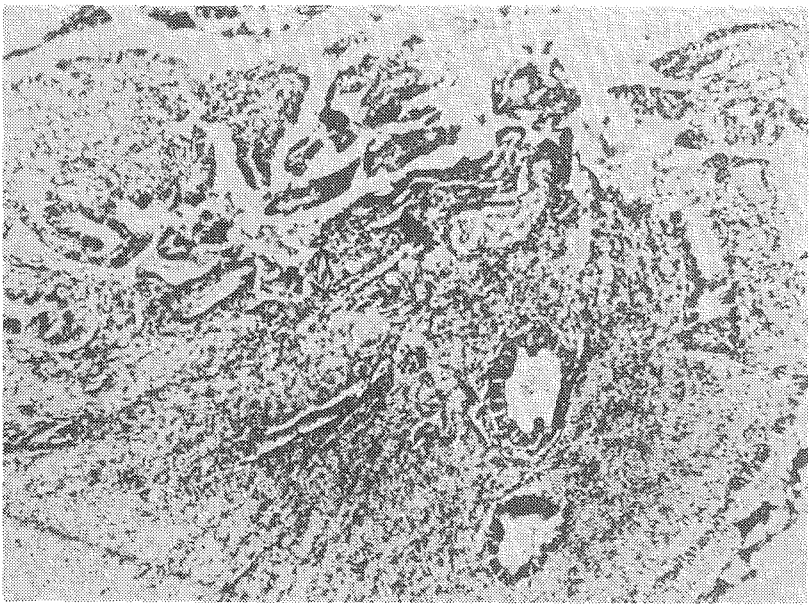

Figure 13

Bleeding like that seen in menstruation. Hyperplastic epithelial tissue is discerned. (x40)

In some cases that showed bleeding, a diagnosis of hyperplastic endometrium could be made by the presence of glands with hyperplastic features, the stroma having been almost completely destroyed by a possibile ischemia or by the invasion of blood. This finding has made us think that the endometrial stroma might be more sensitive to impaired blood supply than the epithelial tissue. The much closer relationship of the stroma with blood vessels and lagoons must not be excluded as a possible and at least partial factor here.

Another feature of the material obtained during or just before hemorrhage is, as Boyd also remarks,[5] the presence of foci of increased inflammatory infiltration rich in polymorphonuclears.

Less Frequent Events Associated with the Lesion

We found no evidence of the type of hyperplastic endometrium which Schröder describes and in which the surface epithelium is said to be replaced by fibrin, cellular debris and blood elements.[38]

An interesting and seemingly confusing condition is the so-called *mixed endometrium*. Witt considers it as contrary to the rule and not as pathological.[44] On the other hand, the presence of classically hyperplastic areas in an otherwise progesterone-phase endometrium has been reported,[45] and such cases and those we are just going to describe must be regarded as *the pathological forms of mixed endometrium*. Of three such cases, we observed in one the presence of adenomatous hyperplasia together with a functional polyp in an endometrium of late secretory phase, adenomatous hyperplasia and changes due to *corpus luteum* hyperactivity in another, and islands of "classical" hyperplasia in an endometrium otherwise undergoing atrophy in the third.

Whether in the normal or pathological endometrium, dissimilar local morphological features, representing, differing internal secretional effects in the same tissue at the same time, must indicate different responses to the same hormone on part of related sites.

Specific Types of Hyperplasia

Stromal hyperplasia: As we mentioned before, we found no instance that could be diagnosed as such.

Postmenopausal hyperplasia: The oldest of three instances was eighty years of age, and this confirms the observation of Novak that the lesion may occur at any age,[18] even in those far beyond the menopause.[17] All three cases showed the changes characteristic of hyperplastic endometrium. In one there were also areas of adenomatous hyperplasia.

Basal hyperplasia:[29] There was just one instance of hysterectomy among our material, and it revealed no evidence of this lesion.

Hyperplasia and Endometritis

Apart from the common finding of small foci of inflammatory cells, we observed true inflammatory changes in many cases, so *a diagnosis of chronic endometritis* should be added. Among 155 cases of hyperplastic endometrium 72 revealed such changes. On the other hand, 118 cases of the remaining slides were also diagnosed as chronic endometritis.

Cases with small amounts of leucocytes and lymphocytes, which may be seen in the normal endometrium[46] and in cases of hyperplasia, were excluded. We also excluded those slides that revceled almost solitary areas of fibrous tissue, because the latter could belong to the cervical stroma. Only when there were conspicuous inflammatory infiltration, disintegration and destruction of both stromal and epithelial elements by the process, and areas of fibrosis in the islands definitely of endometrial origin, did we arrive at such a conclusion. The majority of the inflammatory cells were polymorphonuclears.

35 out of 118 cases of chronic endometritis revealed changes which could be named *pseudohyperplastic*. A careful study of these cases showed the pseudostratification of the epithelium, frequent degenerative changes particularly in areas of dense inflammatory infiltration, and fibrosis. Such cases may be called *chronic endometritis with pseudohyperplastic changes*. Some instances of hyperplasia with chronic endometritis might be difficult to distinguish from these cases. As endometritis is essentially an interstitial inflammation, the superadded infection may shadow the specific changes in the stroma; it will then be the epithelial tissue which can help us make a differential diagnosis.

The claim that endometrium is generally free from inflammatory process and that endometritis is an infrequent lesion is certainly contradictory to our findings. We may explain this by pointing out that it is an unjustifiably generalized belief, because the general and venereal hygienic conditions are significantly worse in this country than in those where certain authors have come to this conclusion.

Hyperplasia and the Malignant Lesions of the Endometrium

In contrast to a possible common hormonal etiology[16] and enzymatic studies suggesting a correlation,[47] characteristics of the two lesions at the subcellular level have not appeared to justify a relationship.[48] In our series, malignant lesion was found in only one case. In

most of the areas foci of *adenocarcinoma* were side by side with those of the so-called adenomatous hyperplasia, and one could clearly consider the latter as the origin of the malignant change. In these areas the epithelial nuclei were hyperchromatic and atypical, and the cytoplasms basophilic. Other parts revealed clumps of more undifferentiated tumour cells with unsuccessful attempts at gland formation. The stroma was mainly composed of fibrous connective tissue in places, consisted otherwise chiefly of fibrin and polymorphonuclears.

No case or areas of the so-called *atypical hyperplasia* were present among our slides. In no case did we find any *sarcomatous change* in the stroma.

Endometrial Polyps

Five curettage materials showed the presence of polyps. In one of these the stroma was active, in another inactive and the third one revealed the presence of inflammation. The other two showed hyperplastic changes, with evidence of infection in one. None of the slides had any area suggesting malignancy.

Endometrial Changes due to Corpus Luteum Hyperactivity

As an interesting finding, one of the cases had also a focus of adenomatous hyperplasia, as we mentioned before (Figure 13). As Boyd describes them,[5] changes in the lesion are in general such that the whole secretory phase appears to be represented - evidence of secretion in both the apical and basal parts of the glandular epithelium, a tendency to stratification in the epithelium of some glands, small or large areas of pseudodecidual change and those of edema in the stroma which shows an abundance of vessels together with inflammatory cells (chiefly polymorphonuclears). Cystic glands could also be seen (Figure 14).

Nomenclature and Classification

So far we have abstained from using any qualifying word, except the non-committal adjective "classical", for "endometrial hyperplasia", which is in essence an exaggerated form of the proliferative phase. It would be more convenient to leave it to the subject of classification.

We do not agree with those writers who are, to use Boyd's expression, by nature "splitters" and who find it necessary to distinguish "glandular", "cystic glandular" or "stromal" types of hyperplastic enopmetrium. We are inclined to accept these as varieties of a species and not species of a genus, to apply what Willis not infrequently uses

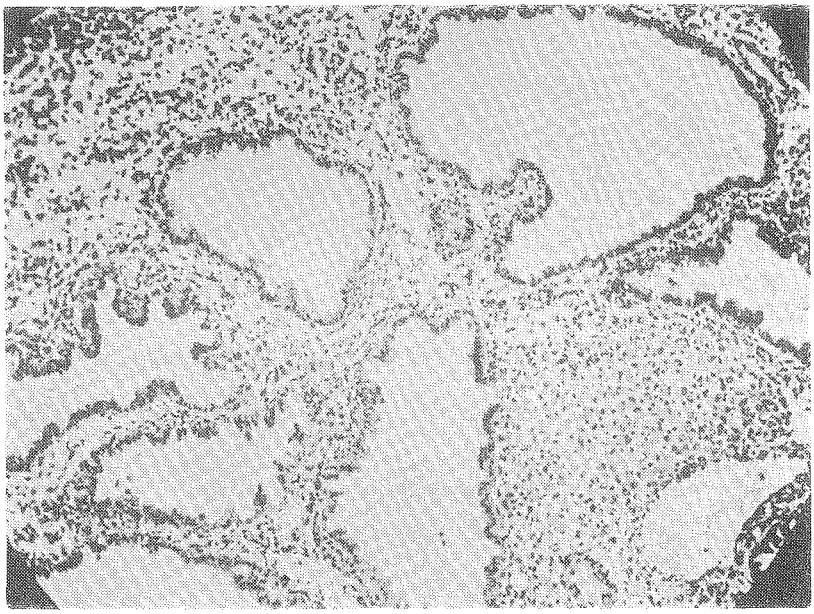

Figure 14
Endometrial changes due to *corpus luteum* hyperactivity. (x40)

in the classification of tumors. The fact that the epithelial changes become in the foreground in most cases and those in the stroma do so rather rarely, or that cystic glands may predominate the picture or may be quite few do not indicate that these represent different lesions. Different histopathological pictures in different instances or areas must be regarded, for the time being at least, as the result of different regional responses on the part of tissues, as observed in almost every pathological and, to a lesser extent perhaps, normal process. The relationship of differing parts of the target tissue with a certain internal secretion determine the local microscopic appearance, as we remarked above. We also mentioned before that cystic dilatation is brought about by the glands which cannot reach the surface.[28] Even normally the endometrium may reveal cystic glands,[44] but we do not call such an instance "cystic endometrium". In the light of our present knowledge and until future research shows a possible (?) causative relationship or correlation between the underlying physiopathological mechanisms and different histopathological pictures, we have to interpret what we have got at our disposal in a scientifically cautious way.

Kulyabko found, among 1500 cases of hyperplasia he investigated, four histopathological groups of the lesion apart from the so-called atypical one: glandular or cystic glandular hyperplasia in early or late

proliferative phase, mixed type and cystic hyperplasia.[49] We believe that this unnecessary classification was due to the author's partial consideration of the different stages and his almost complete disregard of the degree and or morphological characteristics which the same lesion can reveal. Such information may be given in histopathological reports, but do not constitute the really worth-mentioning characteristics of the lesion.

An important and seemingly not too infrequent type of the lesion is *adenomatous hyperplasia*. Some authors regard this as an advanced stage of "classical" hyperplasia,[31] some as identical with the so-called atypical hyperplasia and unjustifiably as Copenhaver has shown,[50] and others as "stage O" cancer of the endometrium.[51] According to others still, the intermediary step to adenocarcinoma is the atypical hyperplasia.[52] The adenomatous lesion reveals malignant change more frequently than the "classical" hyperplasia and normal endometrium, and adenomatous characteristics of the lesion must necessarily be reported.[9,51-54]

Localized hyperplasia: We must keep in mind that in all kinds of endometrial tissue, localized areas of truly hyperplastic process may be present. "Localized hyperplasia" is a more preferable term than "partial hyperplasia", because the latter may be taken as denoting a partially formed diffuse lesion while the former indicates what would actually exist.

Differential Diagnosis

Normal proliferative phase: Certain cases of the lesion may be difficult to distinguish from proliferative phase. A more advanced stratification together with a relative (perhaps even true) enlargement of the nuclei, hypertrophy of the stroma cells, irregular areas of cellular density and edema in the stroma must be looked for. In cases where hesitation still persists, it may be that an initial hyperplastic condition is present.

Endometritis: What is to be remembered here is that inflammation of the endometrium may likewise reveal fibrin thrombi inside and outside the blood lagoons, and areas of hemorrhage which are sometimes quite large. An evaluation of these findings, then, can only be made in the light of the primary ones. The presence of plasma cells must be regarded as a support for the diagnosis of endometritis, because this finding is generally believed to be an evidence of inflammatory process in the endometrium.

Senile and transitional endometria: Non-functioning senile endometrium is particularly apt to be mistaken for a true hyperplastic lesion chiefly because of microscopic anatomical characteristics of the glands. The inactivity in the gland and stroma cells, however, help make the diagnosis readily. It must be emphasized that foci of active hyperplasia may be found in both the senile and transitional endometria.

Polyps with active hyperplastic tissue: Such polyps are likely to be taken for a diffuse lesion, unless the long axis of the mass, the whole of the surrounding surface epithelium, or the attachment site can be seen. These too may be accepted, apparently, as instances of mixed endometrium. Parts of endometrial tissue wholly covered with the surface epithelium in hyperplastic endometrium are to be regarded rather as polypoid overgrowths, particularly when the lesion reveals such a structure macroscopically.

Malignant lesions: The term "atypical hyperplasia" is not a convenient one, although, it must be admitted, there exist cases where the decision of whether the lesion is benign or malignant is really difficult to make.[18, 20, 29, 55, 56] (Studies at the chromosome level[57, 58] as well as theoretical considerations[59] support the existence of this difficulty, in contrast to findings at the subcellular level[48] we mentioned above.) It may be interesting to note here that in some cases of a clinical study on hyperplastic endometrium in young women, development of adenocarcinoma occurred even as long as fourteen years after the initial diagnosis.[60] And we should expect this in cases of postmenopausal hyperplasia or of polyps in postmenopausal women with a hyperplastic focus.[17]

Endometrial changes due to corpus luteum hyperactivity: In the differential diagnosis of this lesion, the histology of pregnancy changes must be born in mind first. The latter may lack to reveal the invasion by chorionic elements. The early secretory change phases are not observed in pregnancy, pseudodecidual changes having been replaced by the true decidual reaction, although the difference is essentially one of degree. As the pregnancy advances, moreover, the glandular epithelium is so flattened that it may be taken for the endothelium of blood lagoons. The latter structures, as we observed in one case, have not been reported to have fibrin thrombi in pregnancy.

In endometrial changes seen in *dysmenorrhea membranacea* the picture is more simple, being essentially brought about by the areas of pseudodecidual change and a few glands.

The lesion is distinguished from the *normal secretory phase* by the presence of all the steps of secretory activity in the same endometrial material, and sometimes by the existence of cystic glands.

Summary

Among 347 cases diagnosed microscopically as endometrial hyperplasia in a ten-year period, 155 slides were re-diagnosed as such, and the results were analytically compared with the data given in the literature.

As a finding not reported in the literature, the epithelium revealed endocervical metaplasia in some cases.

In every case stromal changes must be taken into account when making a diagnosis or differential diagnosis of hyperplastic endometrium, because we found these as constant as those of the epithelial tissue.

We showed that (most if not all of) the structures, known as areas of necrosis or necrobiosis and accepted as specific to the lesion, are fibrin thrombi that have formed within lumens of blood lagoons. Some of them pass through the rents in the walls of the latter, and may thus be found outside the lumens. One may observe them, less frequently though, also in cases of endometritis and in endometrial changes due to *corpus luteum* hyperactivity.

Adenomatous hyperplasia was found either independently or together with other types of endometrial changes, chiefly in cases of "classical" hyperplasia.

72 cases were associated with chronic endometritis.

We are of the opinion that endometrial hyperplasia, better to be called hyperplastic endometrium, is a single histopathological lesion though not a clinical entity, so it does not seem justified to give different names to different instances just because cystic glands are few or many in number or stromal elements predominate the picture. The presence of adenomatous type of changes must be reported.

Five cases among our material revealed changes due to *corpus luteum* hyperactivity.

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Hacettepe Bulletin of Medicine / Surgery
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Kaposi's Sarcoma Involving the Ears

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Kaposi's Sarcoma, a condition thought to be a dermatological disease and most frequently reported in dermatology journals. Due to the infrequency with which it is seen in plastic surgery, a review of literature concerning the nature of the disease would be in order.

Kaposi first described this disease as *Idiopathic Multiple Pigment Sarcoma of the Skin* in 1872. Köebner suggested in 1891, that this condition be designated as *Kaposi's Sarcoma*, to which he agreed then, later changing it to "*Sarcoma Idiopathicum Multiplex Hemorrhagicum.*"[1,2,3] In his original description Kaposi believed the disease to be a special form of spindle cell which almost always begins bilaterally at the lower extremities.[1, 2] The belief that this was a dermatological disease, affecting certain races, mostly those located in symmetrical regions, and that it started on the lower extremities, lasted for many years. In recent years, however, several reports have shown involvement of upper extremities as well as inner organs of the body, Especially the head and neck lymph nodes and haematopoetic system involvement are not infrequently observed.[1, 2, 4-9] Until recently this disease was thought to occur primarily in the Jewish race and people of Eastern Europe, however, this idea is no longer considered valid[1, 2, 3, 7, 8] since cases have been found amongt the mixed populations with an especially high incidence amongst certain groups of African Negroes.[1, 2, 3, 7] It is also interesting to note that in post-war Germany these lesions are known to have been increasing, whereas in Israel, India and China it appears that they are very rare.[8] For this reason Kaposi's disease should not currently be considered as a specific racial disease.[8]

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At one time Kaposi's Sarcoma was considered to be an adult disease, usually occurring after the fourth decade. However, certain studies indicate that children under 11 could also be affected, with prognosis seeming to be most unfavorable.

The initial lesions in the majority of the patients is on skin of the extremities. However, lesions may appear on any skin surface, such as the tip of the nose, the pinna of the ear, the penis, the breast or in the oral cavity. Formerly all extracutaneous lesions were believed to be metastatic. Today it is known that the tumor can originate in any organ of the body and that the skin may never become involved. Primary Kaposi's Sarcoma has been reported in the nose, the eye, the ear, the nasopharynx and lymph nodes. Lothe and Muray showed that, with the exception of the eye and bone, every organ of the body could be involved; however, other autopsy reports revealed that these were not exceptions.[3] (Page 413) As much as the secondary involvement of the other organs, another most unusual feature of this diseases is, the exceptionally high frequency with which some type of second primary cancer is found. This may be a related origin such as malignant lymphoma or leukemia, or else some other type of carcinoma having an entirely separate histogenesis. There have been several reports of association with Hodgkin's disease.[5, 6, 7]

The etiology and the pathogenesis of the disease is not clear, but histologically there is a very characteristic pattern. According to Becker, the spindle cell is the characteristic feature. In the pathological tissue of this disease almost every type of cell has been considered as the possible origin of the spindle cell.

Most of those have been excluded with the exceptions of:

1. Schwann's cells of the adventitia of blood vessels
2. Perivascular primitive mesenchymal cells or
3. Cells of the reticuloendothelial system.[8]

Bluefarb includes the possibility of neoplasm and infectious granuloma with neoplastic potentialities as well.[1, 2] As we have mentioned before, the disease could attack almost any part of the body and amongst those parts, the ear seems to be one of the rarest sites. In our review of the literature we have found a total of 22 cases (19 of those have been reported and 3 are just mentioned in discussion of the papers.) See Table I. To those 22 cases we would like to add 3 more cases of Kaposi's Sarcoma involving primarily the ears.

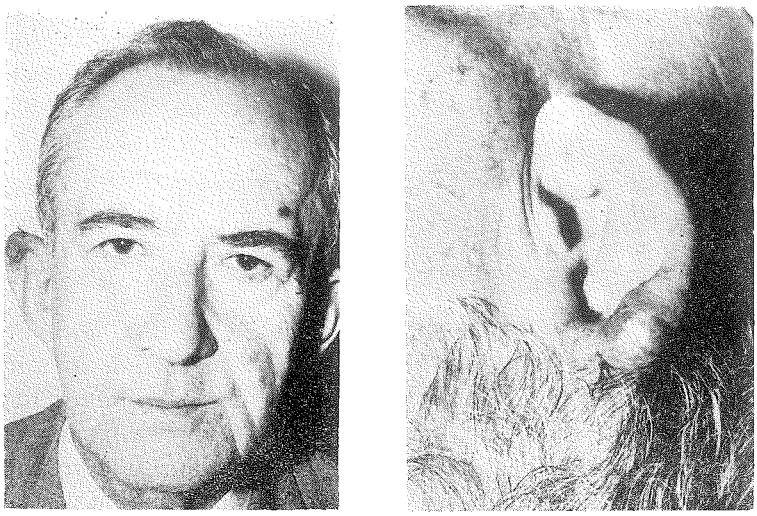
TABLE I

REVIEW OF REPORTED CASES OF KAPOSI'S SARCOMA

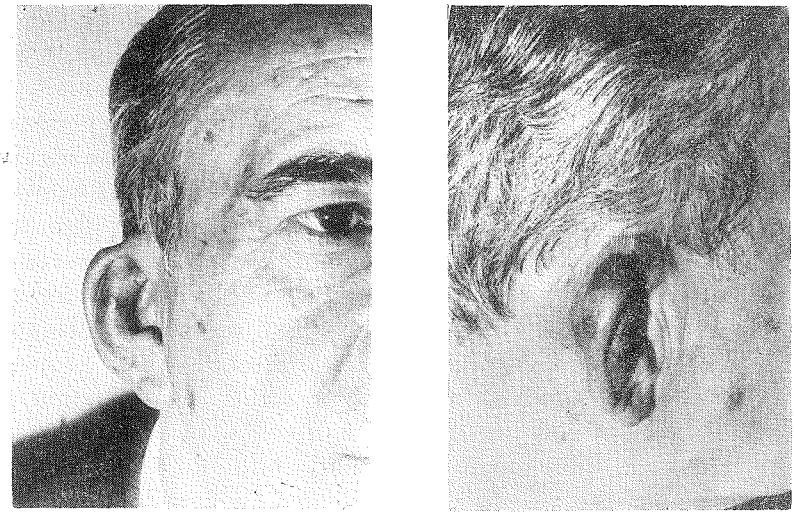
Author	No. of Cases	Year
Stratton[1,2]	1	1928
Traub[1,2]	1	1928
Spinner[10]	1	1934
MacKee and Cipollaro[9]	1	1936
Rulison[1,2]	1	1938
Becker and Thatcher[11,12]	2	1938
Mitchell[1,2]	1	1940
Symmers[13]	1	1941
Epstein[11,12]	1(2)	1941
Ronchese and Kern[1,2]	2	1953
Bluefarb[2]	1	1956
Rothman[3]	1	1962
Reynolds[6]	6	1965
Gibbs[14]	1	1968

Case 1: S. Ö., a 67 year-old male, first seen in the Plastic Surgery Clinic on September 16, 1968, had severe post-biopsy edema and pain of the right auricle. The patient gave the following history: He had observed a brownish nodule on his right ear about ten months prior and had noticed a spontaneous healing after peeling off the scar several times. Four to five months prior he had noticed another pigmented area about his left eyebrow. On September 5, 1968, he was first examined in the Dermatology Clinic and then referred to Otorhinolaryngology Department where an incisional biopsy of the right ear was performed on September 10. The pathology report was "Capillary Hemangioma", but the patient's auricle began to swell up and his pain was persistent. Due to these complaints he was referred to us, and at this time his right auricle was tender, swollen and there was a 3.6 x 2.7 mm dark brownish pigmented lesion at the superior pole. There was also another pigmented tumor above the left eyebrow which was not tender and measured 1.5 0.5 mm. The patient did not have any past medical history, except an eczema for 17 years on both hands and ears. Both lesions were diagnosed clinically as Kaposi's Sarcoma and surgical treatment was proposed, but due to existent chondritis of the right auricle the operation was delayed. The patient was treated with antibiotics, in spite of the conservative treatment, the chondiritis did not subside for 8 weeks. At the end of this period the patiens was considered fit for surgery and on November 21, 1968, both lesions were excised. The pathology report confirmed both specimens as Kaposi's Sarcoma. Post-operative period was uneventful and after a follow-up of 12 months, he did not return for

check-ups. In our recent survey we discovered that about a year after his surgery he had been admitted to another hospital and treated for Hodgkin's disease. Under this treatment in 1971 he had developed another pigmented tumor on the right anterior tibialis area. Since he was known to have Kaposi's Sarcoma, this lesion was not excised and thus we were unable to obtain pathological confirmation. The patient expired in August of 1972 due to generalized Hodgkin's disease.



Preoperative anterior and lateral view.



Postoperative 3 months After anterior and lateral view.

Figure 1
Kaposis Sarcoma of the Ears.

Cases 2 and 3: These both cases had isolated ear lesions. Following local excision there have been no recurrences nor has there been any other systemic involvement. Both patients are well and alive.

Summary

Three cases of Kaposi's Sarcoma involving the ears are presented and the literature is reviewed.

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Primary Carcinoma of the Appendix with Metastasis to Both Ovaries*

(A Case Report)

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Primary carcinoma of the appendix is rare with the recorded total number of cases being less than 200. Malignant tumors of the appendix are less common than benign tumors. Carcinoid tumors and mucoceles of the appendix comprise the largest number of appendical tumors.

This is a report of a case with primary carcinoma of the appendix with metastasis to both ovaries.

Case Report

This patient was a 42 year-old Gravida III., Para III who was admitted to the Ankara Maternity Center on August 10, 1975, with the chief complaint of metrorrhagia and the sensation of an abdominal mass of 3 months duration. The past and family histories were irrelevant.

The general physical examination was normal: Blood pressure, 125/70 mm Hg; pulse, 90 per minute. She was afebrile, the abdomen was enlarged, inguinal lymph nodes were not palpable. Pelvic examination revealed moderate cystourethrocele and rectocele. The cervix was normal. There was a firm, irregular, partially fixed, nodular cystic mass extending up to 2 fingerbreaths below the umbilicus and to the fornices.

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Laboratory studies were as follows: Hbg, 10 gm %.; Hct, 35; Urinanalysis, normal; Blood group, B Rh +; Sedimentation rate, 110 mm/hr.; BUN, 17 mg %; I.V.P., normal; ChestX-Ray, normal; and Blood sugar, 80 % mgr.

A diagnostic curettage was performed. The pathological examination showed endometrial stromal fibrosis and endocervicitis. Vaginal cytology showed no abnormal cells. Presumptive preoperative diagnosis was carcinoma of the ovary.

At laparotomy 100 ml of bloody serous fluid was found free in the peritoneal cavity. Uterus was approximately of 2 1/2 months pregnancy size. The right oviduct was 10 cm long and reached a diameter of 5 cm. The left oviduct was 7 cm. long and reached a diameter of 3 cm. Both ovaries had firm nodules on their surfaces and adhered to the uterus, bladder and the lower portion of the intestine. The neighbouring part of the greater omentum was thick, indurated and contained a mass of 5 cm. in diameter. The appendix was enlarged and solid, measured 7 cm in length and 2 cm at its widest point. The remaining parts of the gastro-intestinal tract and the liver were found to be free of tumors. A total abdominal hysterectomy, bilateral oophoro-salpingectomy, partial omentectomy and appendectomy were carried out.

Pathological examination of the specimen revealed primary mucinous adeno carcinoma of the appendix (Figure 1a and b), bilateral Krukenberg tumors of the ovary (Figure 2a and b) and tumoral infiltration in myometrium (Figure 3).

The patient tolerated surgery well. The postoperative course was uneventful with a full course of chemotherapy (5 F.U.) being started 2 weeks after surgery. After completion of the therapy she was discharged in good condition and followed up periodically as an out-patient basis. She is still alive without signs of a recurrence 11 months after the operation.

Comment

Primary carcinoma of the appendix is rare. In Stainberg and Cohn's studies,[1] adenocarcinoma of the appendix constituted 0.2 - 0.5 % of all tumors of the gastrointestinal tract. Collins[2] found adenocarcinoma in 41 of 50,000 appendices examined histopathologically. In 1970, 41 cases of malignant tumor of the appendix were reported to the Swedish Cancer Registry. Of these tumors, 31 were carcinoids, 9 were adenocarcinomas and 1 was a malignant mucocele.[3]

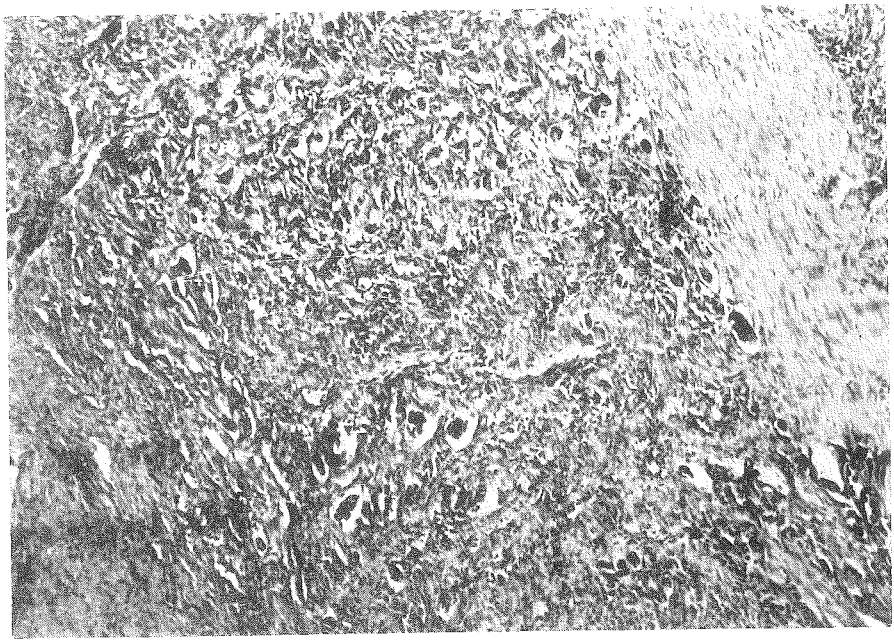

Figure 1 a

Section of primary mucinous adenocarcinoma of the appendix with muscular invasion.

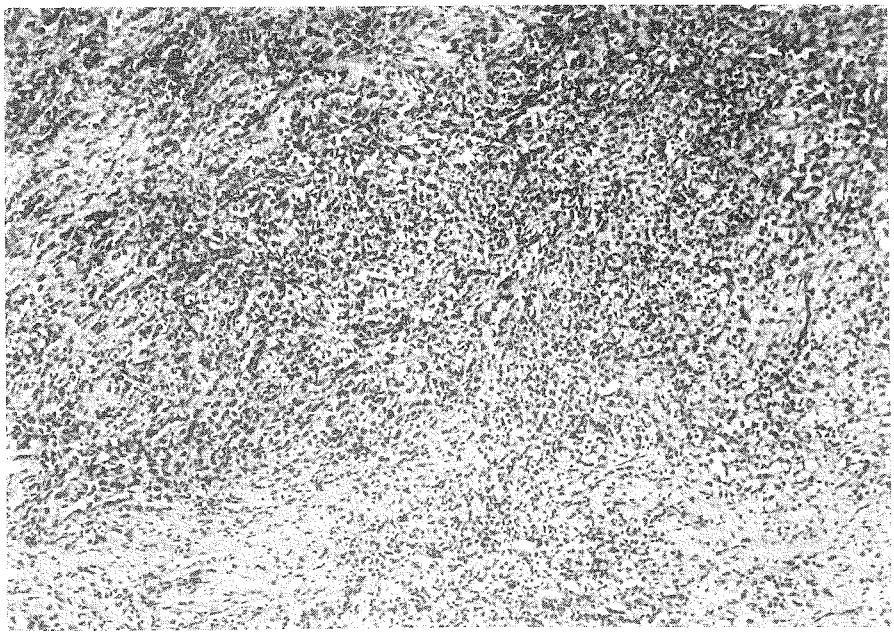

Figure 1 b

Peri-appendicular invasion of the tumor.

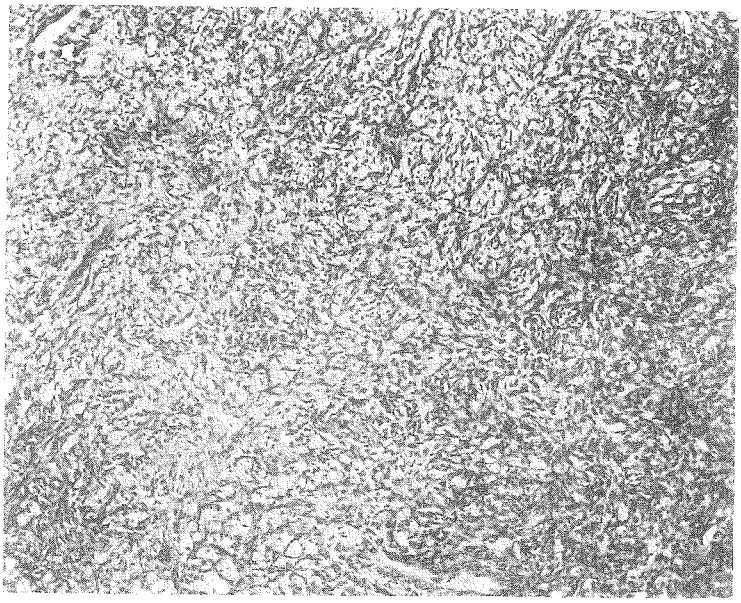

Figure 2 a

Characteristic signet cells in a Krukenberg tumor of the ovary. The nucleus is flattened and lies against the cell wall.

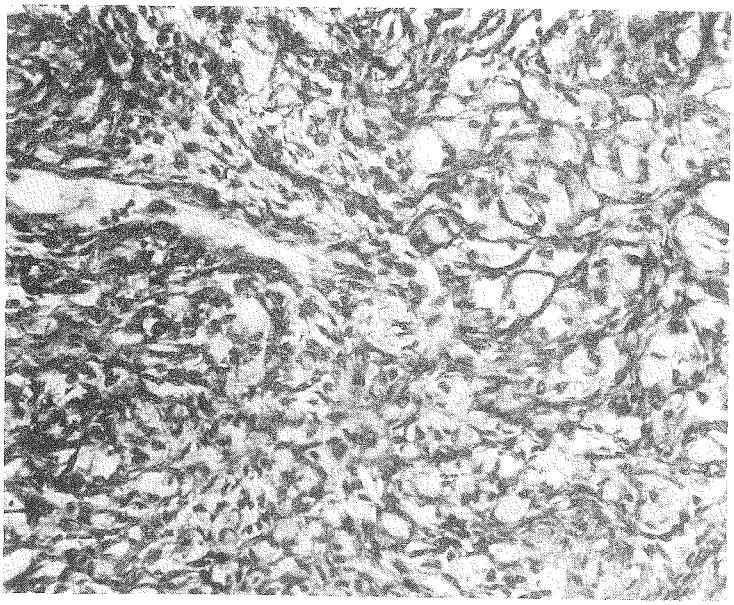

Figure 2 b

Same speciman with higher magnification.

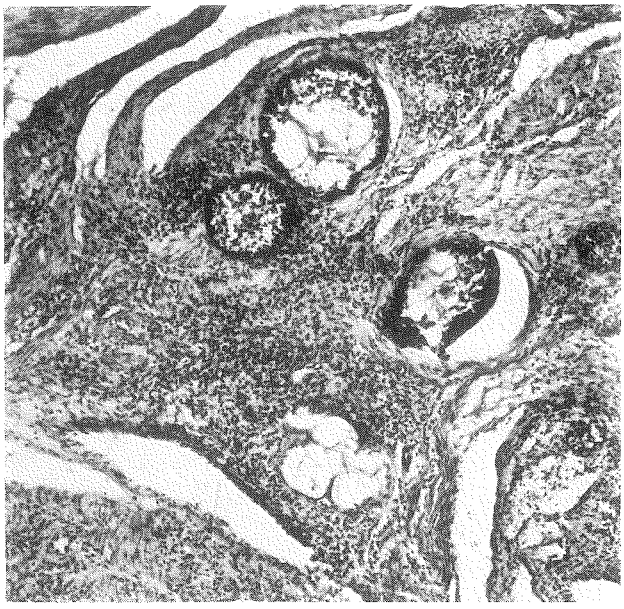

Figure 3
Multiple focal metastases in the myometrium.

Vihlein and Mc Donald[4] distinguished three types of primary tumors of the appendix:

1. Carcinoma of the carcinoid type,

2. Carcinoma of the cystic type, producing pseudomyxoma peritonei,

3. Adenocarcinoma of the colonic type.

The carcinoids were the most common and constituted up to 90 % of all primary tumors of the appendix.

The Krukenberg tumor is usually secondary to a gastro-intestinal tract or other mucinous gland lesion; but occasionally it is a true primary tumor of the ovary and diagnosis before surgical exploration is highly improbable. In our case presumptive preoperative diagnosis was carcinoma of the ovary. Histologic findings showed the origin to be within the appendix and no other lesion of the gastrointestinal tract was found during the laparotomy and in gastrointestinal x-ray studies.

Krukenberg tumors showing evidence of hormonal activity are rare. Turunen[5] was the first to suggest the possibility that metastatic ovarian tumors could elaborate estrogenic and androgenic hormones.

In support of this, he presented 2 women with postmenopausal uterine bleeding and cystic hyperplasia of the endometrium. Following removal of metastatic ovarian tumors in these patients, a return to normal levels of urinary estrogenes and 17 ketosteroids from elevated preoperative levels was observed. Scully and Richardson[6] reported an additional 3 cases of metastatic ovarian tumors in postmenopausal women associated with possible estrogenic activity. Nine cases were collected from the literature in which Krukenberg tumors were associated with virilization.[7] In our case there were no signs of virilization or other hormonal activity.

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Evaluation of ^{99m}Tc-Cyclophosphamide for the Detection of Nasopharynx Tumors

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Introduction

Diagnosis of the nasopharynx cancer is the most difficult among the cancerous growths effecting the head and the neck. The reason is the difficulty faced in physical examination of the nasopharynx, which may lead to a delay in treatment and to the progress of the disease. Sometimes the disease spreads to the neighboring organs such as the orbita and intracranial structure and this effects the prognosis of nasopharynx cancer. Since early diagnosis is very important for cancer therapy, new diagnostic methods giving somewhat definitive results have to be investigated.

Many radio pharmacevtical agents have been developed for tumor scanning in general; however, nasopharynx tumors have not been studied specifically.[1] Recently 99mTc- labeled cyclophosphamide has been shown to accumulate in cancerous tissue, in sarcoma and carcinoma both.[2] In this study 99mTc- Cyclophoshamide was used to scan patients suspected of nasopharynx pathology. Later biopsy was performed to correlate with the results of scintigraphy. The purpose of our study was to visualize nasopharynx tumors scintigraphically.

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Material and Methods

^{99m}Tc- Cyclophoshamide (^{99m}Tc-CPA) was used for nasopharynx scanning. This radio pharmacevtical agent was prepared and quality control performed as it had been described previously[2] to insure that no free Tc 0^{-}_{4} was present at the time of injection.

45 subjects were investigated, 12 of these were normal and the remainder had nasopharynx pathology. Before scintigraphy, each subject had a complete neurological and laryngological, and also radiological examination of the head (4 views) and lungs.

Each subject was i.v. administered 15 mCi of ^{99m}Tc-CPA. 400 mg. potassium perchloride (in water solution, 10 mg/ml) was given orally at about the same time. This was given to block the uptake of free TcO^{-}_{4} that might decompose from ^{99m}Tc-CPA after administration. 4 view gamma-camera pictures (Pho Gamma III, Nuclear Chicago) of the head were taken with low-energy parallel-hole collimator 6 hours after ^{99m}Tc-CPA administration. Some subjects were scanned after 2, 3, 4, 5 and 6 hours to find the optimum time of scanning.

After completion of scanning, biopsy was taken from nasopharynx in all the 33 patients who had nasopharynx pathology. If the scintigraphy indicated malignancy and the first biopsy result was negative, biopsy was repeated.

Results

The results are evaluated in four different groups:

1. Patients with malignant tumor in nasopharynx:

14 patients were scanned in this group. 12 were reported as pathological, 1 normal and 1 as doubtful. Malignant tissue concentrated the radioactivity more than the normal tissue. The 12 cases had hyperactivity in nasopharynx compared to neighboring tissues. According to the biopsy results 7 patients had indifferential epidermoid carcinoma, 3 had anaplastic carcinoma and one each had Hodgkin's disease, malignant lymphoma, transitional cell carcinoma and mucoepidermoid carcinoma. The histopathological report of the patient with normal scintigraphy indicated mucoepidermoid carcinoma and of the doubtful case showed anaplastic carcinoma.

In 9 patients malignancy was confirmed at first biopsy, in 3 patients at second and in 2 patienst at third biopsy. In this group, only one showed pathology radiologically.

2. Patients with benign tumor in nasopharynx:

Nine patients were studied in this group. Eight of them were reported as normal and 1 pathological. Histopathologically, 5 were reported to have chronic nasopharyngitis with lymphoid tissue hyperplasia and 1 each had inflammation polyp, chordoma, angiofibroma and juvenile angiofibroma. The juvenile angiofibroma case was reported to be pathological, scintigraphically.

3. Patients who had had radiotherapy for previous malignancies:

Ten patients were scanned in this group. Five patients had normal nasopharynx scans, 4 were pathological and 1 doubtful. Out of 5 patients reported normal, 2 had biopsies. According to the biopsy report they had chronic nasopharyngitis. Out of 4 patients reported to be pathological 2 had biopsies which indicated epidermoid carcinoma and anaplastic carcinoma. Biopsy of the only case with doubtful scintigraphy showed chronic nasopharyngitis.

4. Normals:

Twelve subjects with normal clinical, laboratory and radiological findings were chosen as the control group. Nasopharynx scintigraphies in all 12 subjects were normal, that is, no hyperactivity was observed in nasopharynx.

In Table I, scintigraphy and biopsy results of the groups of malignant tumor and benign tumor have been compared. Since biopsy could not be performed on all of the patients who had had radiotherapy, this group was not included in the table. In the group of malignant tumor scintigraphy results were 86 % correct and, if the doubtful case is also considered negative, 14 % false-negative. In the group of benign tumors we obtained 88 % correct and 11 % false-positive results. No false-positive results were obtained in the normal group.

TABLE I

SCINTIGRAPHY AND BIOPSY RESULTS OF PATIENTS WITH MALIGNANT AND BENIGN TUMORS, AND THE CLINICAL AND LABORATORY FINDINGS IN NORMAL SUBJECTS

	Biopsy		Clinical and Laboratory findings
Scintigraphy	Malignant tumor	Benign tumor	Normal subjects
Abnormal accumulation of radioactivity	12	1	—
Doubtful	1	—	—
Normal	1	8	12
Total	14	9	12

Normal distribution of ^{99m}Tc-CPA is indicated in Figures 1, 2 and 3 show scintigraphies of patients with malignant tumors and benign tumors, respectively.

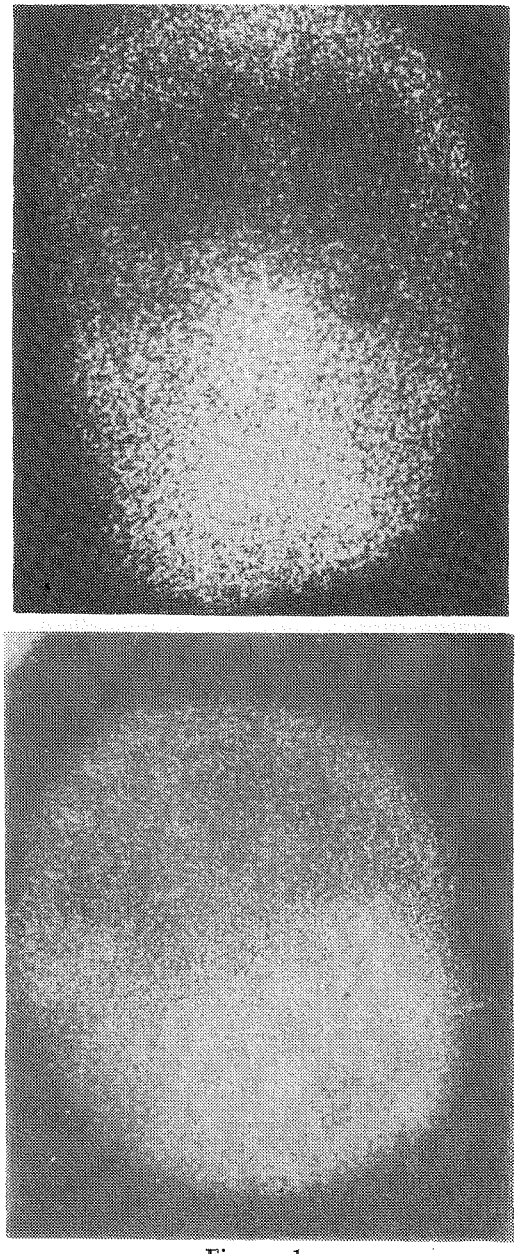

Figure 1
Photoscans taken by Gamma Camera show the distribution of ^{99m}Tc-CPA in a normal subject.

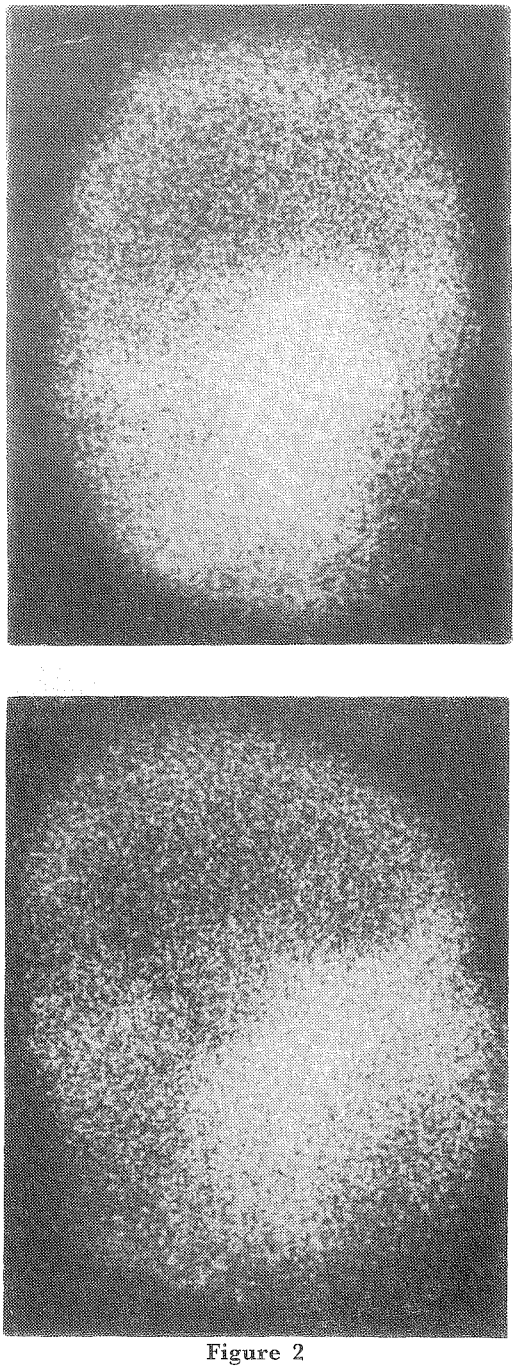

Figure 2

Photoscans of a patient with malignant tumor show increased accumulation of 99m-Tc CPA of by the nasopharynx.

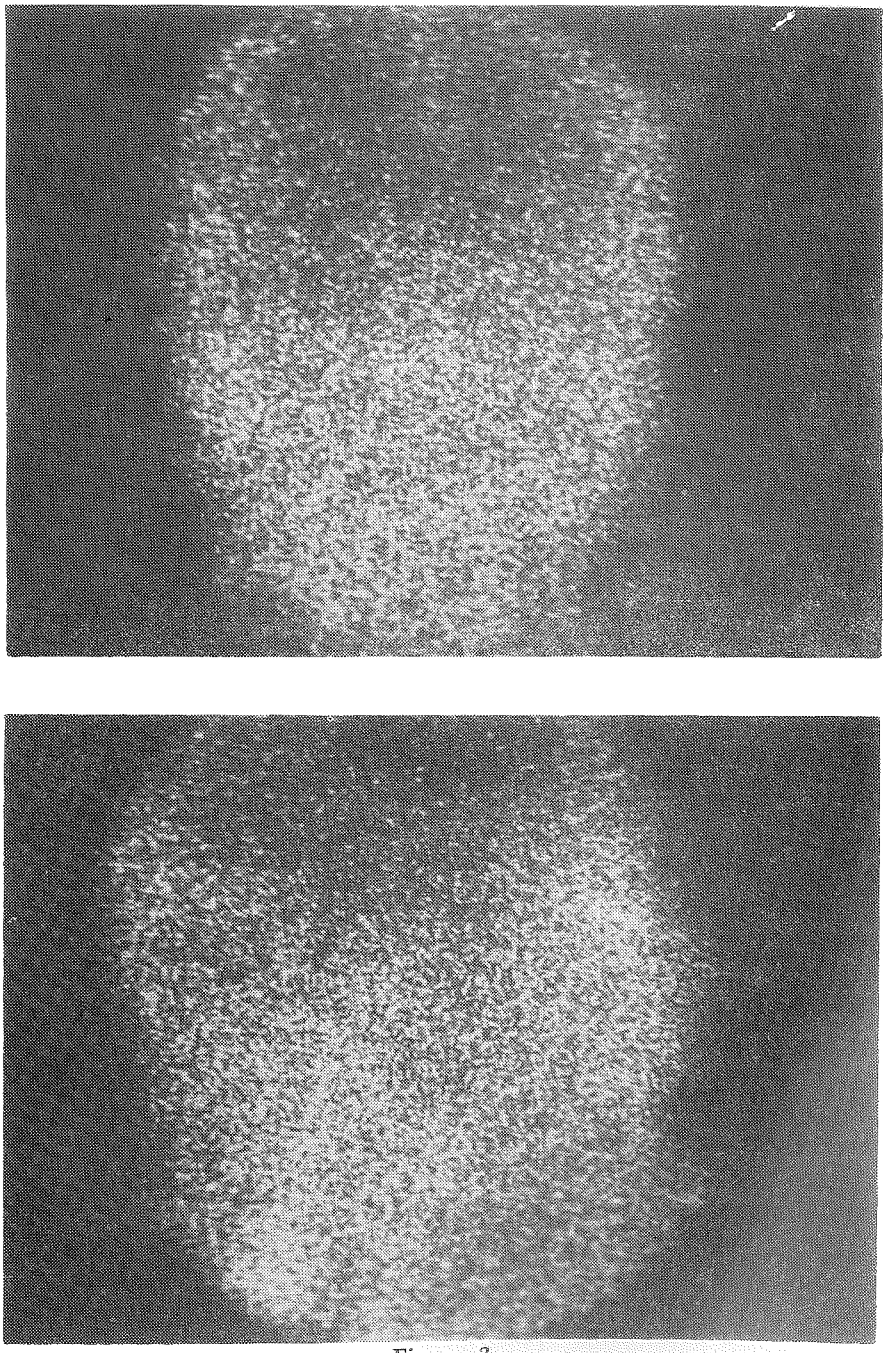

Figure 3

Photoscans of a patient with benign tumor. Note decreased accumulation of radioactivity by the nasopharynx.

Discussion

Nasopharynx cancers do not give any symptoms at early stages and develop very quietly. For this reason visits to the doctor are delayed. Besides, neighbouring organs such as the eye and the intracranial structure give symptoms earlier and patients go to the corresponding clinics at first. This again leads to time loss in prognosis.[3, 4, 5]

Patients who have one or more of the following: cervical adenopathy, ophtalmoneurologic, nasal or otologic symptoms have to be screened very carefully by the examining doctor as to nasopharynx malignancy. Negligence of nasopharynx examination may lead to late prognosis.[6] In one study ophtalmoneurological symptoms were the first symptoms in 16 % of the cases who had nasopharynx cancer; therofore the symptoms have to be evaluated well for early diagnosis.[7]

In our radiological investigations only one patient out of 14 malignant cases had positive findings. This patient had a large tumor in nasopharynx and bone decay. The remainder of the patients had negative findings. Thus radiological studies are of no value in early diagnosis of nasopharynx cancer.

At present the best method for the detection of nasopharynx cancer is biopsy. However, more than one biopsy is required usually for histological confirmation of malignancy, because the piece of tissue taken may be from normal or superficial tissue.[8] Another difficulty faced is that the patient himself might not accept more than one biopsy. In our study also 4 out of 10 patients who had had radiotherapy previously did not accept biopsy.

There is still a demand for easy, less objectionable and more effective diagnostic methods for the detection of nasopharynx tumor. It has been shown that cyclophosphamide labeled with a short-life isotope such as Technetium is concentrated by malignant tissue, both in carcinoma and sarcoma, more than normal tissue.[2] As a result, tumor could be shown scintigraphically. In this study we used this radio pharmacevtical agent to show nasopharynx tumor. In 12 of the patients (86 %) with nasopharynx tumor, the tumor could be clearly visualized. In 2 patients only (14 %) we had negative results. In 5 of the patients who had positive scintigraphic findings, malignancy was not prognosed by physical examination. The biopsy was repeated once in 3 patients and twice in 2 patients in order to get histological confirmation. In these patients tumor was thought to be the last in probable pathologies. After scintigraphy they became the first suspected pathologies. They were proved only after persistent biopsies. Therefore scintigraphy with ^{99m}Tc-CPA is indicated for patients who are suspected of nasopharynx pathology at physical examination.

In the group of benign tumors, in 8 out of 9 (88 %) patients nasopharynx did not show any abnormal concentration of radioactivity. Only in one patient (11 %) false-positive result was obtained. In benign tumors cell division is slow compared to that in malignant tumors. Besides, vascularization is less in benign tumors.[9] The only patient who gave false-positive result scintigraphically had juvenile angiofibroma. Histopathologically it was shown that it contained rich vascularization. This was confirmed by higher concentration of activity by the nasopharynx mass.

We have shown that tumor scanning with ^{99m}Tc-CPA is a valuable method in differentiation of benign and malignant tumors. Abnormal concentration of radioactivity in nasopharynx indicates malignancy with a high percentage (86 %), but it is necessary to get histological confirmation for final diagnosis.

No false-positive results were obtained in the control group, which is also a significant finding.

Summary

^{99m}Tc-Cyclophosphamide was administered i.v. to 45 subjects for nasopharynx scanning. The purpose was to evaluate this agent for the differential diagnosis of nasopharynx malignancies. The results of scintigraphy were compared with those of biopsy.

Malignant tissue accumulated this agent more than normal nasopharynx tissue. In 12 out of 14 patients with malignant tumor, increased radioactivity was observed in nasopharynx. 10 patients who had had radiotherapy, biopsy confirmed the results of scintigraphy.

In all 12 normal subjects and 8 of 9 patients with benign tumor, nasopharynx had normal distribution of radioactivity compared to that in neighboring organs.

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