

Intimal Vascular Lesions Associated With Female Reproductive Steroids

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Intimal proliferation, with and without associated thrombosis, has been found in women taking oral contraceptives, and in pregnant and postpartum women. Similar vascular changes have been demonstrated by others in pregnant and postpartum guinea pigs, and experimentally in animals receiving female reproductive steroids. This intimal lesion is not specific for or unique to steroid effect, since it is seen in many other conditions. However, the clinico-pathologic profile in this series of oral contraceptive, pregnancy, and postpartum cases suggests that exogenous and endogenous female reproductive steroids may be the common hormonal factor producing intrinsic vascular lesions with resultant circulatory compromise, and that these steroids should be included in the list of agents and conditions with which intimal proliferation may be associated.

Female reproductive steroids have been associated with hyperplasia in a variety of target organs in both human and animal subjects.¹⁻¹⁰ That the vascular system may also be

a target organ was suggested by the finding of intimal proliferation in four of 20 women taking oral contraceptives, as reported three years ago.³ In the intervening period, similar lesions have been found not only in seven additional cases associated with oral contraceptives but also have been observed in pregnant and postpartum women. The sites of intimal proliferation have included arteries and veins of the systemic and portal circulations, as well as pulmonary arteries. These findings raise the possibility that endogenous and exogenous female reproductive steroids are a common hormonal factor and may be the common denominator producing an intrinsic vascular lesion. The vascular compromise resulting from this lesion may be due to intimal proliferation alone or to intimal proliferation combined with overlying thrombus formation.

Methods

The 16 cases in this series were accessioned in the Institute during the period 1957 to 1971, 14 of them since 1966. The nine pregnant and postpartum women were selected from among 4,181 cases of pregnant or postpartum women ranging in age from 15 to 39. In this group, there were 70 instances in which cardiovascular abnormalities had been identified, and these were reviewed in detail. From the latter group, nine were found to have intimal proliferative lesions similar to those

found in the patients taking oral contraceptives reported earlier.

The clinical data were analyzed, and hematoxylin eosin-stained sections were supplemented in selected instances with the following special stains: Movat's pentachrome; Masson trichrome; the colloidal iron technique for acid mucopolysaccharides (AMP), with and without predigestion with hyaluronidase; and elastica van Gieson.

Results

Clinical Findings.—The 16 cases were divided into three groups: pregnant women (5); postpartum women (4); and women taking oral contraceptives (7).

Pregnant Women.—The five patients ranged in age from 21 to 31 years, averaging 27 years. Two were Oriental; one was Negro; one was white; and in one the race was not stated. In none of these women was there any evidence of disease that would predispose to thrombosis or thromboembolism. Four were in their second trimester; one was in the third trimester.

In two patients, the initial symptoms included chest pain with subsequent demonstration of vascular lesions in the pulmonary arteries. One patient had acute abdominal pain caused by a ruptured subserous leiomyoma of the uterus; one woman suffered an acute onset of convulsions and coma with subsequent demonstration of vascular lesions in the

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Table 1.—Oral Contraceptive (OC) Group

Age	Type of OC and Duration of Use	Indications for Use of OC	Site of Vascular Lesion	Comments
22	Norgestrel with ethinyl estradiol, 6 weeks	Contraception	Mesenteric vein	Resection of 74 cm of small bowel
34	Norethynodrel with mestranol, 5 years	Contraception	Mesenteric artery	Resection of segment of ileum
22	Ethinyl estradiol plus dimethisterone with ethinyl estradiol, 2 months	Irregular menses	Pulmonary artery	Found dead in bed
44	Norethindrone with mestranol, 4 years	Contraception	Pulmonary artery	...
27	Norethindrone with mestranol, 1 year	Unstated	Artery in cervix	Excision of cervical leiomyoma
29	Type and duration unstated	Contraception	Hepatic vein and pulmonary artery	Budd-Chiari syndrome
29	Type and duration unstated	Contraception	Subcutaneous vessels of inguinal region	...

heart, kidneys, liver, gastrointestinal tract, and adrenal glands. In another woman, the vascular lesions were found in a fibrovascular polyp of the vulva that had developed in early pregnancy and had grown rapidly over a period of seven months as pregnancy progressed.

Postpartum Women.—The four postpartum women ranged in age from 18 to 32 years, with an average of 25 years. All four were white. In none of these cases was there evidence of disease predisposing to thrombosis or thromboembolism. Two of these patients died of uremia with vascular lesions demonstrated in the kidneys. Both had initial complaints of facial edema. They died eight and 11 weeks, respectively, after delivery. In neither woman was there any record of hypertension during the third trimester, and both had normal urinalyses during their pregnancies. The other two postpartum patients had vascular lesions in the heart. Their initial complaints were chest pain and dyspnea. These women died five days and 11 weeks, respectively, after delivery. In addition to vascular lesions in the smaller coronary vessels, one showed recent and old foci of infarction, and in the other patient myocardial fibrosis was present.

Women Taking Oral Contraceptives.—The seven women taking oral contraceptives ranged from 22 to 44 years of age, with an average of 30 years. Six were white, and in one the race was not evident. In none of the seven was there any recognized concurrent disease predisposing to

thrombosis or thromboembolism. In five instances, the antiovulant hormones were used for contraception; in one, they were used for irregular menses; and in one, the indication was unclear. The duration of the use of these steroids varied from 6 weeks to 5 years, with an average of 24 months in the five cases on which information was available (Table 1).

In four patients, the initial symptoms were abdominal. The vascular lesions were found in the mesenteric vessels in two of these patients, in the hepatic vein in one, and in the inguinal vessels in one. Chest pain was the initial complaint of one woman in whom vascular lesions were later demonstrated in the pulmonary artery. One patient was found dead in bed, and there were no recorded prior symptoms. In the seventh woman, no initial symptoms were recorded.

Pathologic Findings.—The vessels involved in the 16 women includ-

ed branches of the pulmonary, coronary, renal, mesenteric, cervical, uterine, and adrenal arteries; mesenteric and hepatic veins; and subcutaneous vessels. Two patients had vascular lesions in multiple organs including arteries of the heart, mesentery, kidney, liver, and adrenals (case 1); and hepatic veins and pulmonary artery (case 6). A more detailed localization of these lesions in the pregnant women is contained in Table 2. The sites of the lesions in the postpartum group are listed in Table 3.

The vascular lesions were characterized by intimal proliferation, many of them being very cellular, with close-packed nuclei and very little intervening stroma. In some, however, the intercellular stroma was more prominent, varying from loose and myxomatous or mucinous, to dense and fibrous. The following cases were selected as illustrations of

Table 2.—Pregnancy Group

Age	Trimester	Sites of Vascular Lesions
30	2nd	Pulmonary artery
21	2nd	Arteries of kidneys, heart, liver, intestine, and adrenal
31	2nd	Uterine artery (in leiomyoma)
25	2nd	Pulmonary artery
26	3rd	Vessel in polyp of vulva

Table 3.—Postpartum Group

Age	Weeks Postpartum	Sites of Vascular Lesions
18	1½	Coronary vessels
27	1	Coronary vessels
24	4	Renal arteries
32	4	Renal arteries

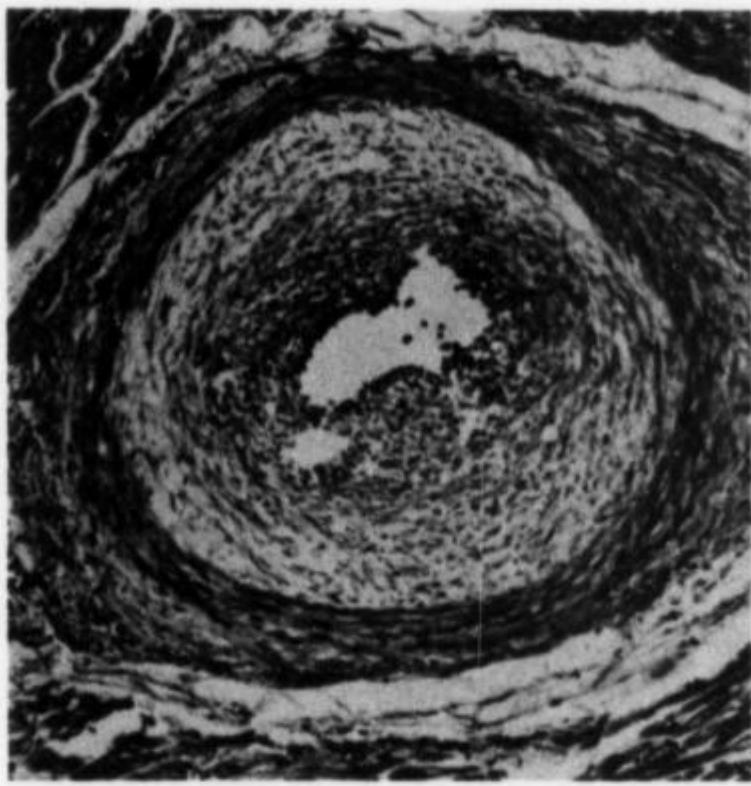


Fig 1.—Coronary artery branch (case 1, pregnancy). Lumen is markedly reduced by myxomatous intimal proliferation (AFIP Neg 70-5879; hematoxylin-eosin, original magnification $\times 110$).

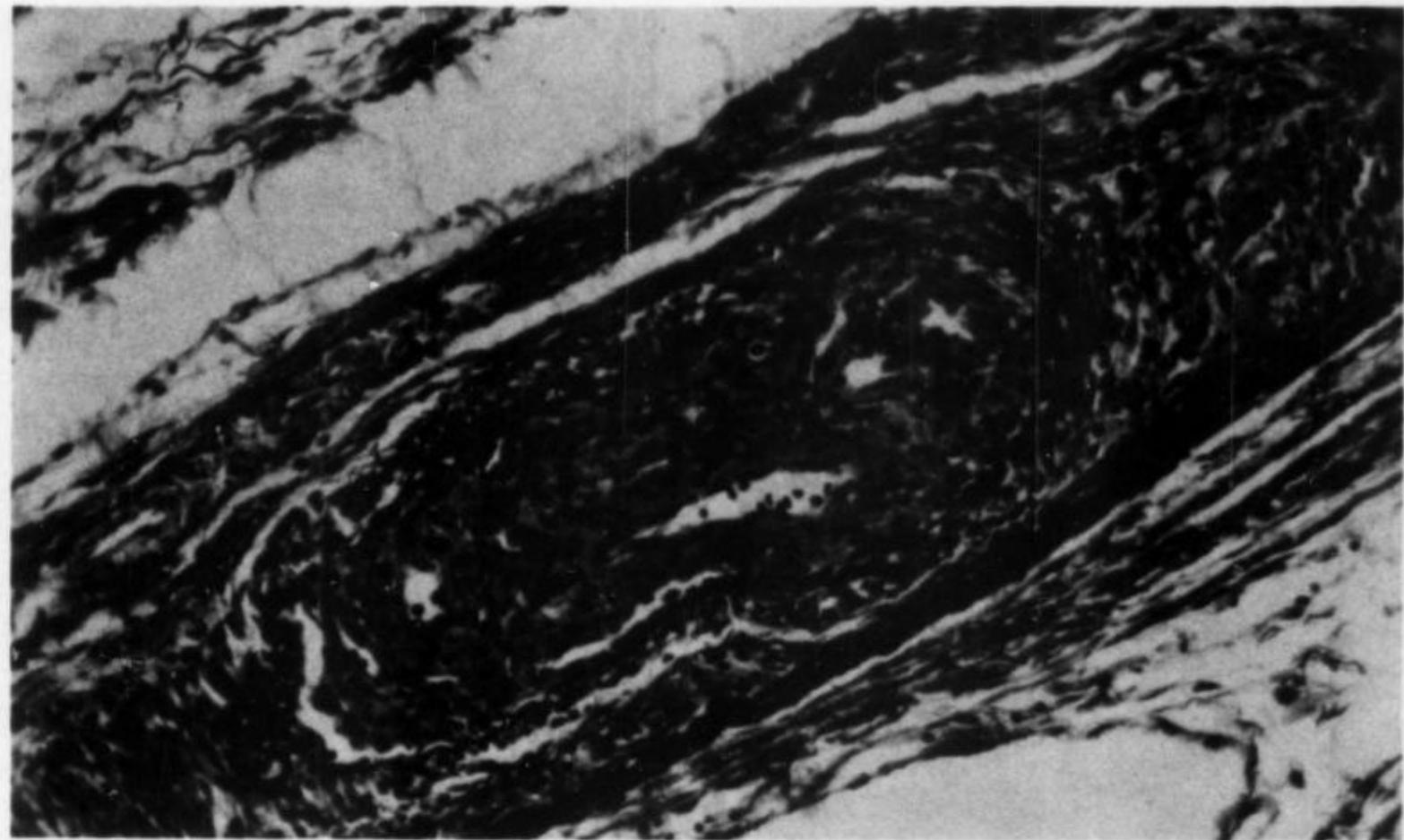


Fig 2.—Branch of mesenteric artery (case 1, pregnancy). Note cellular intimal proliferation within internal elastica (AFIP Neg 70-5878; Movat pentachrome, original magnification $\times 165$).

these vascular lesions.

Pregnant Women.—**CASE 1.**—A 21-year-old woman became pregnant while taking oral contraceptives. She received steroids until her fifth month, when she became hypertensive and suffered convulsions. Following evacuation of the uterus, she developed progressive congestive failure and uremia. In her third week of illness, an infarcted segment of small

bowel was removed. She died two weeks later in congestive failure and uremia. Autopsy revealed widespread vascular lesions characterized by intimal proliferation in arteries of the heart, mesentery, kidney, liver, and adrenals. A section of a branch of the coronary artery (Fig 1) showed marked reduction in the lumen by a loose, myxomatous intimal proliferation. Similarly, a branch of the mes-

enteric artery presented a cellular proliferation that had almost obliterated the lumen of the vessel (Fig 2).

CASE 2.—A 31-year-old pregnant woman suddenly developed abdominal pain in her fourth month. Laparotomy revealed a ruptured subserosal uterine leiomyoma. The resected tumor weighed 155 gm and contained an artery having marked cellular intimal proliferation with a prominent

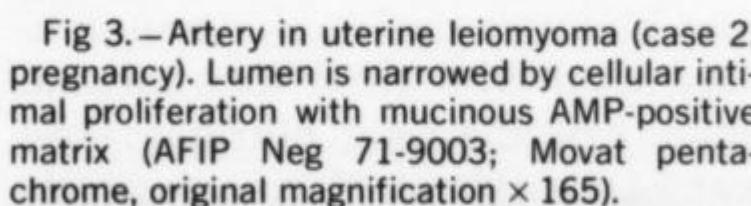
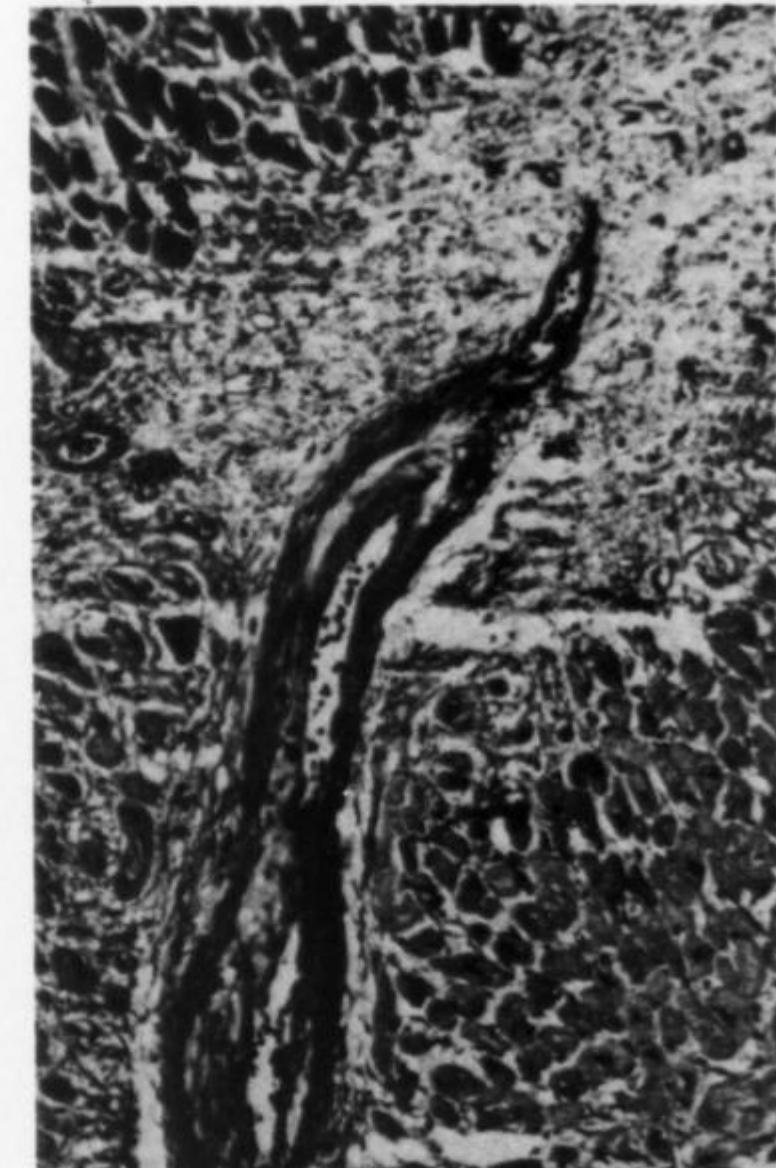
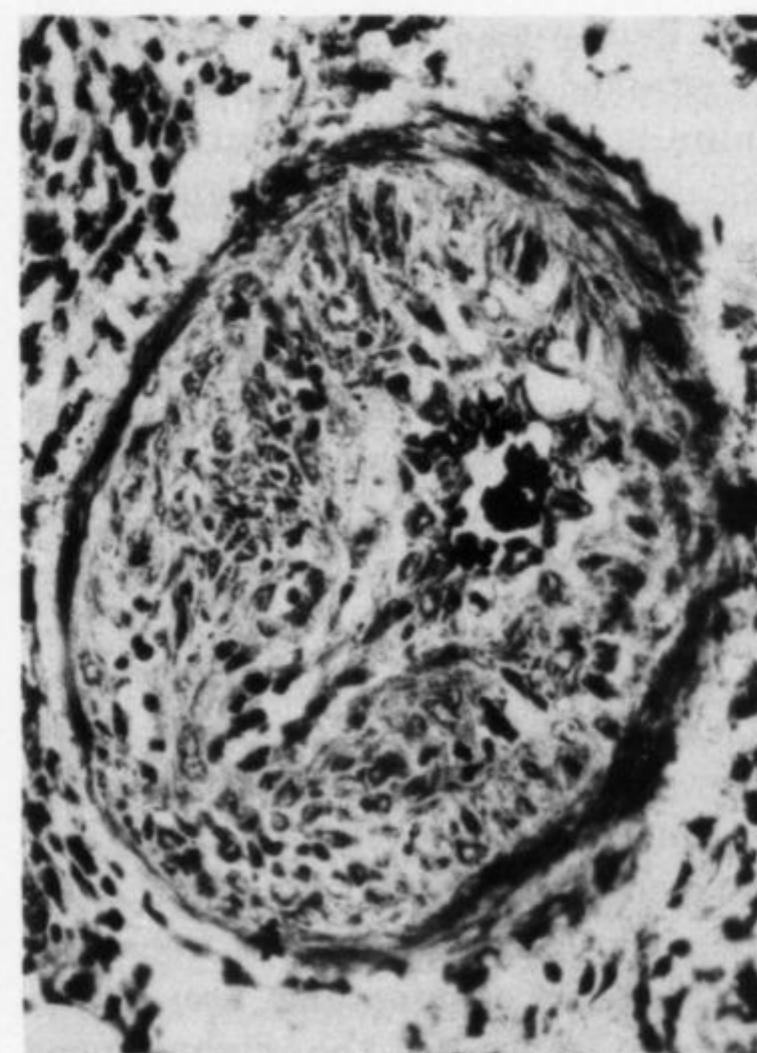


Fig 3.—Artery in uterine leiomyoma (case 2, pregnancy). Lumen is narrowed by cellular intimal proliferation with mucinous AMP-positive matrix (AFIP Neg 71-9003; Movat pentachrome, original magnification $\times 165$).

CASE 3.—A 21-year-old pregnant woman developed abdominal pain in her second month. Laparotomy revealed a ruptured subserosal uterine leiomyoma. The resected tumor weighed 155 gm and contained an artery having marked cellular intimal proliferation with a prominent

Fig 5.—Branch of coronary artery (case 4, postpartum). Note mucinous intimal thickening with distal focus of myocardial infarction (AFIP Neg 72-5025; Movat pentachrome, original magnification $\times 90$).



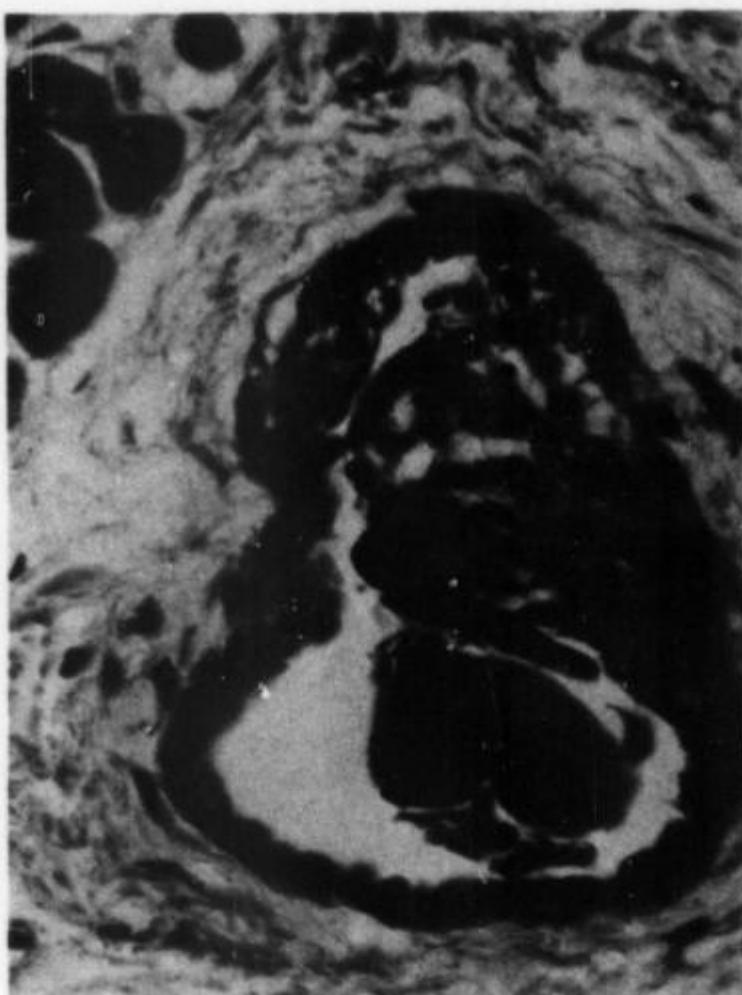


Fig 6.—Branch of coronary artery with nodular focus of intimal proliferation (case 4, postpartum). Note small thrombus in lumen (AFIP Neg 71-8164; hematoxylin-eosin, original magnification $\times 395$).

AMP-positive myxomatous matrix (Fig 3).

CASE 3.—A 30-year-old woman developed progressive dyspnea beginning in her second month of pregnancy. The pulmonic second sound was noted to be accentuated. She aborted in the fifth month, and 3 days later suffered severe chest pain, collapsed, and died suddenly.

Autopsy revealed cor pulmonale, and many of the smaller branches of the pulmonary artery in both lung fields showed marked reduction in their lumens by a very cellular intimal proliferation (Fig 4). Neither the clinical nor the autopsy records indicated any evidence of lesions in veins of the legs.

Postpartum Women.—CASE 4.—An 18-year-old woman developed anterior chest pain and numbness and tingling in her arms 11 days after delivery. Following bed rest she did well for five weeks, then she had a recurrence of the chest pain, which now radiated down the left arm. Two hours later she became dyspneic, cyanotic, and collapsed. Despite extracardiac massage and attempts at defibrillation, she was pronounced dead three hours later. At autopsy, the major branches of the coronary arteries were normal. The heart had scattered small areas of firm gray tis-

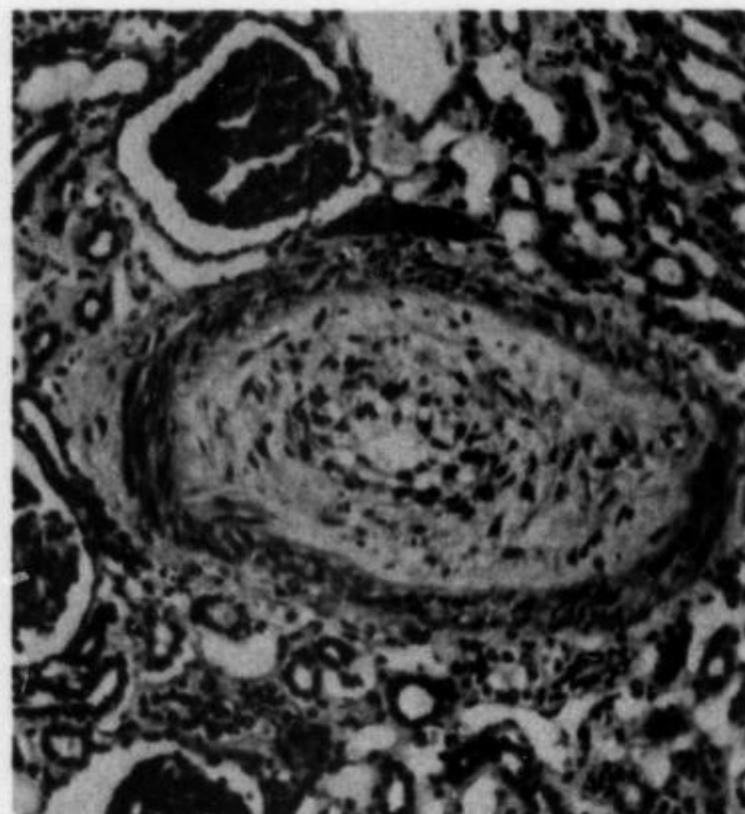


Fig 7.—Branch of renal artery (case 5, postpartum). Note marked reduction of lumen by myxomatous intimal proliferation (AFIP Neg 69-8116; hematoxylin-eosin, original magnification $\times 130$).

sue, as well as foci of relatively soft brownish discoloration characteristic of recent myocardial infarction. A small branch of the coronary artery (Fig 5) proximal to an area of myocardial infarction showed a mucinous intimal thickening. Other branches of the coronary artery showed more cellular and compact intimal proliferative lesions (Fig 6).

CASE 5.—A 24-year-old woman had been receiving for a long period of time steroids for suspected but unconfirmed lupus erythematosus. During her second and last pregnancy she was normotensive and had multiple negative urinalyses. On the 26th postpartum day she became anuric and remained so during her remaining four weeks of life. Her uremia progressed despite dialysis, and terminally she suffered recurrent episodes of pulmonary edema and congestive failure. At autopsy, many of the kidney arterioles were the site of concentric intimal proliferation with a loose myxomatous stroma. In most instances these intimal lesions severely narrowed the lumens of the vessels (Fig 7). Similar vascular lesions were not found in other viscera.

Women Taking Oral Contraceptives.—CASE 6.—A 29-year-old woman was taking oral contraceptives for an unstated time. She gradually developed abdominal pain and diarrhea. On examination two weeks after the onset of symptoms, ascites and a large mass in the right upper



Fig 8.—Branch of pulmonary artery (case 6, oral contraceptive). Note cellular intimal proliferation with severely narrowed lumen (AFIP Neg 70-8875; Movat pentachrome, original magnification $\times 195$).

quadrant of the abdomen were found. Laparotomy on the fifth hospital day showed a markedly congested and enlarged liver and ascites (approximately 10 liters). An inferior vena cavaogram was suggestive of thrombosis of the liver, and clinically, she had Budd-Chiari syndrome. On the fourth postoperative day the serum glutamic oxaloacetic transaminase level was 1,400 international units, and the total bilirubin level was 5.1 mg/100 ml. She progressively deteriorated, developing oliguria, dyspnea, confusion, and coma, and died on the 13th postoperative day.

At autopsy, multiple thromboses of the hepatic veins and the inferior vena cava were found. The hepatic veins presented fibrotic intimal changes overlaid by fresh thrombotic material. In addition, intimal proliferation was found in a number of the smaller pulmonary vessels severely narrowing their lumens (Fig 8).

CASE 7.—A 22-year-old woman had been taking oral contraceptives for six weeks when she developed thrombophlebitis of the leg with subsequent pulmonary embolism, from which she recovered. Six weeks later she developed nausea, vomiting, and melena, considered preoperatively as indicative of upper gastrointestinal obstruction. Laparotomy revealed multiple fibrinous adhesions of the small bow-

el and an area of stenosis in the jejunum. The serosa was lustreless and edematous, and the bowel wall was firm and leathery. The surgical specimen consisted of a 74-cm segment of infarcted bowel (first entry, Table 1) in which the venous channels of the bowel and the mesentery contained multiple proliferative intimal lesions. A section of the mesenteric vein (Fig 9) demonstrated intimal thickening of a moderately acellular composition with a collagenous matrix. Several venous channels of smaller calibre in the mesentery showed similar intimal changes.

CASE 8.—A 34-year-old woman had been taking oral contraceptives for five years. She developed lower abdominal cramps, diarrhea, and fever. Laparotomy revealed an ischemic segment of distal ileum. In the resected specimen of ileum, branches of the mesenteric artery showed moderate reduction in their lumens by intimal proliferative lesions with a loose intercellular stroma (Fig 10). In addition, some sections revealed a more compact cellular intimal proliferation overlaid by a thrombus that contained numerous pigmented macrophages.

Control Group

The controls were divided into two groups. The first group consisted of women dying suddenly (automobile accidents, suicide, and other forms of sudden death). This group was studied to determine whether or not the vascular lesions described in this paper occurred spontaneously in asymptomatic women of reproductive age who were not receiving steroids. The second group consisted of women dying with a variety of cardiovascular diseases, and was surveyed for the same reason.

In the first group, the ages of the women ranged from 20 to 40 years, with a median of 25 years. Thirty-five were white, 3 were Negro, and 2 were Japanese. A total of 802 autopsy slides from these 40 control women were reviewed, an average of 20 slides per case. There were no vascular abnormalities in 19 women. In 21 patients a variety of alterations were present, all in the arterial system.

Arteriosclerotic changes were common, occurring in 17 women of the control group. Arteriosclerotic changes of varying severity were present in the coronary arteries (three patients), aorta (three patients), pulmonary arteries (three patients), central nervous system (three patients), and renal arteries (two patients). Arteriosclerotic changes were also present in some tracheal and thyroid vessels. Other vascular abnormalities were also noted. The aorta of one patient showed early cystic medial necrosis, another patient had a mural fibrous defect in proximity to a ruptured aneurysm of the anterior cerebral artery, and two patients had thrombi in pulmonary arteries.

Changes resembling the vascular abnormalities found in patients in this study were present in only three microscopic sections of two patients. In one, there was a single small pulmonary artery with a concentric, moderately cellular intimal thickening. In another patient, there were two medium-sized uterine arteries and one small ovarian artery with loose fibrous proliferation of the intima with narrowing of the lumen. This patient had been taking an oral contraceptive combination of mestranol and norethynodrel.

In the second control group, women dying with cardiovascular disease, autopsy material from 67 patients was examined. Their ages ranged from 19 to 39 years, with a median of 33 years. Fifty-eight were white, seven were Negro and two were Oriental. A total of 1,860 autopsy slides from these 67 women were reviewed, an average of 28 slides per case.

A variety of intimal lesions were found in this second control group, the most frequent sites being the kidney, uterus, lung, ovary, and heart, in that order, and were noted on the arterial side of the circulation. In the five of the 67 cases, intimal lesions resembling the cellular type (with minimal intercellular matrix) were found in the following instances: (1) in the pulmonary vessels in a patient with rheumatic heart disease and mitral stenosis; (2) in myocardial vessels in a woman with malignant hypertension; (3) in the renal vessels in

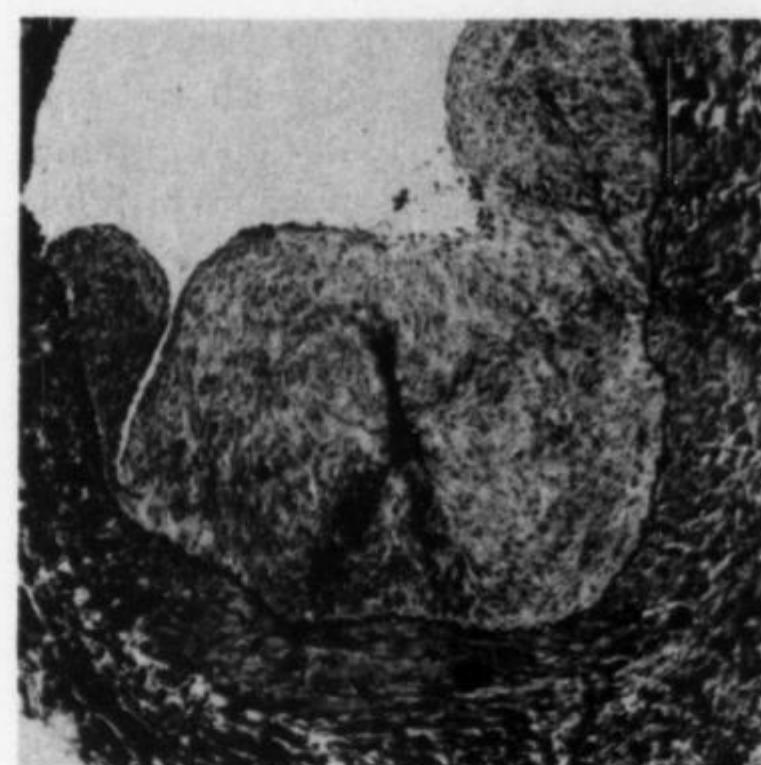


Fig 9.—Branch of mesenteric vein with fibrous intimal proliferation (case 7, oral contraceptive) (AFIP Neg 70-9834; elastica van Gieson, original magnification $\times 80$).

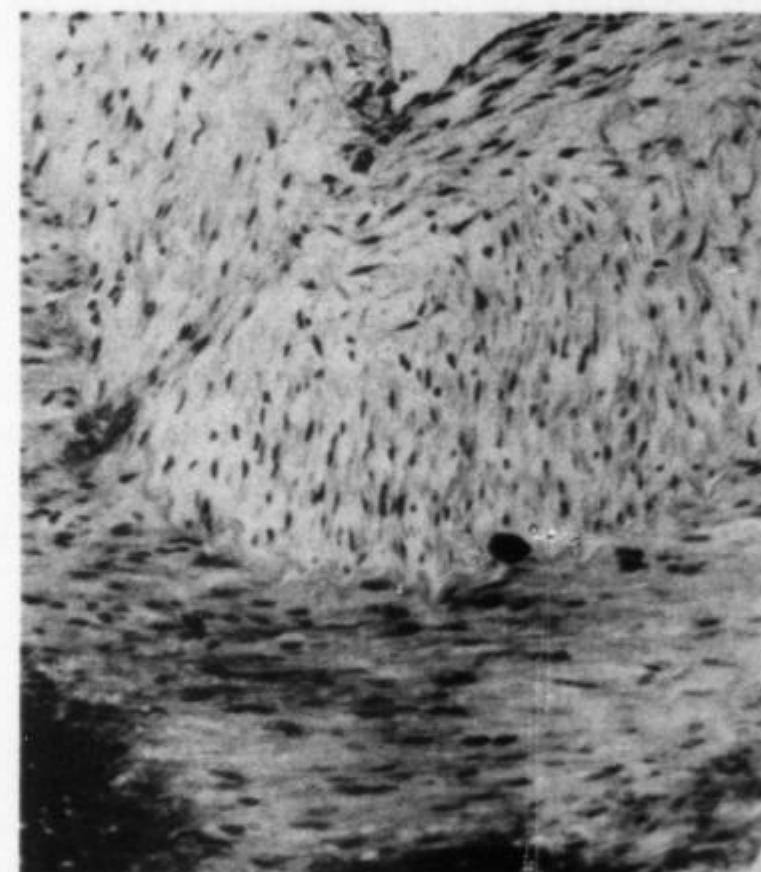


Fig 10.—Branch of mesenteric artery (case 8, oral contraceptive). Myxomatous intimal proliferation is present (AFIP Neg 70-4552; original magnification $\times 115$).

a patient with scleroderma; (4) in the pulmonary vessels in a woman with monilial septicemia; (5) in a duodenal artery branch in a woman with arteriosclerotic heart disease and myocardial infarction.

Intimal lesions with relatively more intercellular stroma (with a myxomatous or mucinous appearance) were found in four cases:

- (1) In renal vessels in a patient with scleroderma;
- (2) In a periadrenal artery in a woman with diabetes and the Kimmelstiel-Wilson syndrome;
- (3) In a pancreatic vessel in a patient with chronic glomerulonephritis;
- (4) In the pulmonary vessels in a woman with an acute myocardial infarction.

Lesions morphologically similar to early stages of atherosclerosis and to

aging were found in 30 cases in this second control group. These were characterized by relative prominence of the intercellular stroma which had a fibrous and collagenous appearance. This type lesion, in contrast, was seen in only two of the steroid group presented in this paper. A further difference in this control and the steroid group was the relatively low incidence of the more cellular intimal lesions in the control group, and their dominance in the steroid cases.

These areas of overlap in the findings in women who had died of a variety of cardiovascular diseases and those associated with steroids is not unexpected, as they reflect the limited capacity of the vascular system to react to a variety of injurious processes.

Comment

The vascular lesions found in this series of patients consisted of intimal thickening that produced varying degrees of narrowing of the lumen and only occasionally was associated with overlying thrombus formation. These lesions had serious consequences: myocardial infarction, myocardial fibrosis, renal failure, bowel infarction, and pulmonary hypertension and cor pulmonale.

A number of possibilities arise as to the nature and origin of these vascular lesions, many of which are unlikely. They might be organizing or or-

ganized thrombi of local origin based on focal disease of the vessel, or they might be embolic from some distant site. They also could be a result of vascular injury or changes associated with a number of entities such as scleroderma, periarteritis nodosa, hypertensive cardiovascular disease, giant cell arteritis, Takayasu disease, syphilis, or Buerger disease, all of which may be associated with intimal proliferation.

The likelihood that these changes in the vessels were either organized or organizing emboli appears remote, particularly in those cases in which the lesions were found on the arterial side of the systemic circulation. Ten of the patients (62%) had arterial lesions, and in none were there any demonstrable sources of emboli such as endocarditis or mural thrombi of the heart or aorta. In the five women with pulmonary artery lesions, sources of emboli were not evident in the venous circulation of the legs or pelvis on either clinical or autopsy examination, despite a high index of suspicion and investigation. Similarly, in the woman with obstruction of the mesenteric vein there was no evident source of embolization. Only the patient with the Budd-Chiari syndrome had fibrin thrombi in some of the pulmonary vessels, their source most likely being the thromboses in either the hepatic vein or the vena cava. This woman, however, had sev-

eral lesions in pulmonary vessels, characterized by closely packed intimal cells with conspicuous absence of associated fibrin (Fig 8).

Could the vascular lesions be of local origin, based on preexisting disease such as atherosclerosis or vasculitis? Microscopic examination appears to have eliminated these possibilities. In no instance was there an atherosclerotic base, nor was there significant atherosclerosis elsewhere in these young patients. Furthermore, there was a conspicuous absence of associated inflammatory infiltrate and fibrinoid necrosis of the vessel walls in all examples, appearing to eliminate vasculitis.

Intimal thickening, such as that which was found in the women in this study, is seen in a number of clinicopathologic syndromes, as previously mentioned, including scleroderma, periarteritis nodosa, hypertensive cardiovascular disease, giant cell arteritis, Takayasu disease, syphilis, and Buerger disease. While the renal vessels in the two cases of postpartum renal failure were very similar to those seen in scleroderma, neither patient showed stigmata of that entity in the skin, the gastrointestinal tract, or elsewhere. The absence of an inflammatory infiltrate would appear to rule out the diagnosis of periarteritis nodosa, giant cell arteritis, and Takayasu disease. Certainly, a clinical basis for those entities was ab-

Fig 11.—Branch of pulmonary artery. Cellular intimal proliferation is above internal elastica with fibrin deposits on surface (from 22-year-old woman on oral contraceptives) (AFIP Neg 70-1687; Movat pentachrome, original magnification $\times 190$).

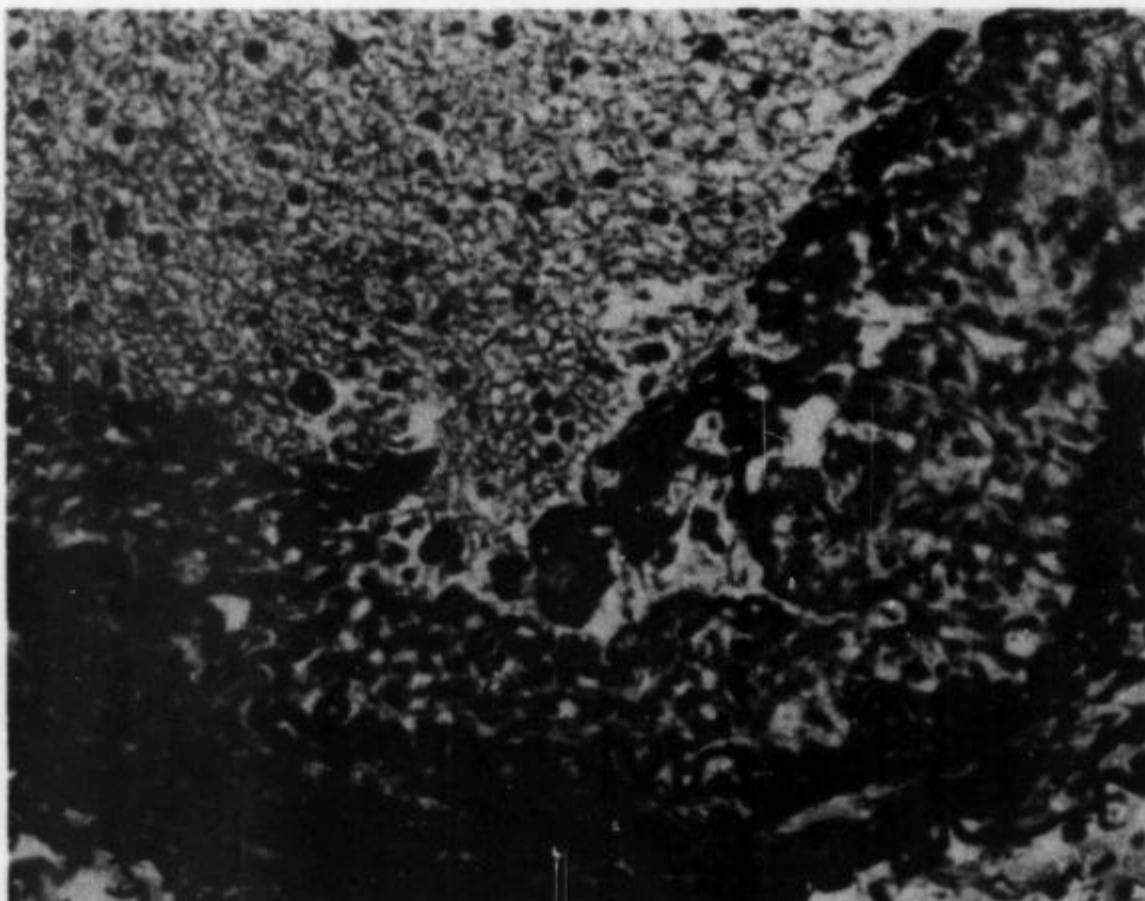
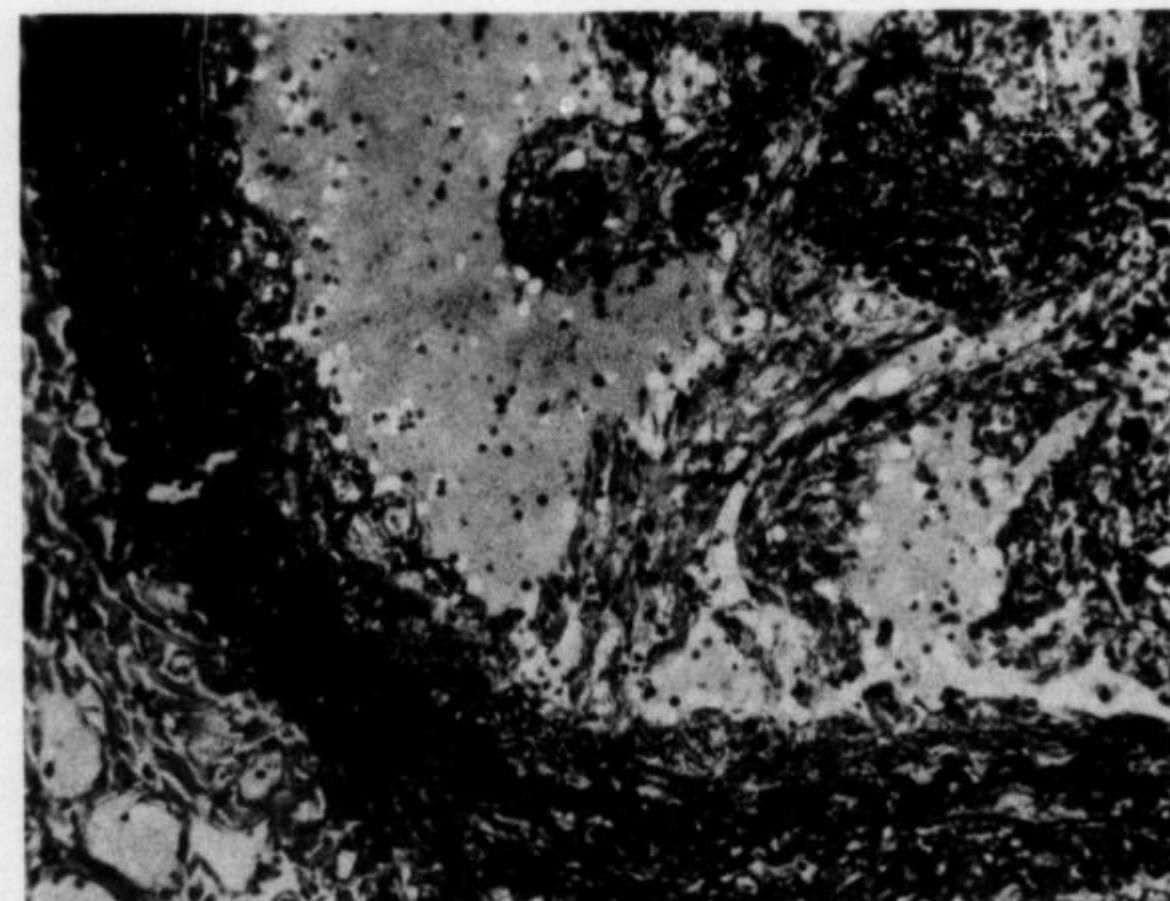


Fig 12.—Branch of pulmonary artery. Note intimal proliferation with projections into lumen and fibrin deposits on tips (from 41-year-old woman on oral contraceptives) (AFIP Neg 71-11193; Movat pentachrome, original magnification $\times 110$).



sent. Also, none of these patients had a hypertensive background preceding their illness. In no instance could syphilis be seriously considered either on clinical or serologic grounds.

The appearance of these vascular lesions suggests that they were not organizing or organized thrombi, but a proliferation of intimal cells. The identity of these proliferating cells could not be established by light microscopy. They might be endothelial cells, fibroblasts, or smooth muscle cells or any one of the three, in any combination. Although smooth muscle cells are not normally found in the intima, the possibility that the intimal proliferation might consist of or include them is prompted by the finding of accumulations of spindle cells in the region of the intima in the experimental production of early atherosclerosis.¹¹ These spindle cells are believed to be smooth muscle on the basis of ultrastructural and tritiated thymidine studies, and are thought to be derived from totipotent mesenchymal cells in the intima.¹²

While the vascular alterations consisted of an intimal proliferation not associated with thrombosis in most instances, the combination of an intimal lesion with overlying thrombosis was observed in three patients. The three combined lesions were found in coronary, renal, and mesenteric arteries. In each of these three instances, intraluminal thrombi were recent, superficial, and were interpreted as opportunistic thrombosis on an altered or damaged vessel. We speculate that the formation of thrombi under these circumstances could have been related to a combination of several or all three of the fundamental factors that predispose to thrombus formation, intrinsic vascular damage, slowing of blood flow, and alterations in coagulation. Morphologically, there were changes in the intima in the form of proliferation and thickening and moderate to severe reduction in the diameter of the lumen. These two changes could have introduced the element of sludging of blood related to eddy currents and stasis. Third, coagulopathy may have also played a role in the formation of thrombi. The literature contains

many reports of variations from the normal in platelet counts, platelet adhesiveness, platelet agglutinability, lability of clotting, elevation or decrease of fibrinogen levels, and variations in coagulation factors in association with oral contraceptives, pregnancy, and estrogen therapy, and these have been summarized elsewhere.¹³ In view of the lability of the clotting system reported by many observers in some women on oral contraceptives and in some pregnant and postpartum women, formation of thrombi may result from a combination of an intrinsic vascular lesion (intimal hyperplasia) and a hypercoagulable state. Two examples of this combination are shown in Fig 11 and 12, which demonstrate the deposition of fibrin on the surface of foci of intimal proliferation. (These examples were taken from the oral contraceptive series reported earlier.³)

Supporting the observation of intimal proliferation in women who are pregnant or recently postpartum, proliferative intimal lesions have been described by others in pregnant or postpartum women and in animals administered steroids under a variety of experimental conditions. Wagoner et al¹⁴ and Robson et al¹⁵ in separate reports, described seven postpartum women with renal lesions similar, if not identical, to the two postpartum women with these lesions in this study. In their reports, intimal thickening and proliferation were found in women with postpartum renal failure. Not only was there close morphologic similarity between the changes in renal vessels in these reports and in the postpartum women in this study, but the women also had a similar clinical background of normotensive pregnancy and limitation of the vascular lesions to renal arteries and arterioles.

Pulmonary vascular obstruction by "intimal fibroelastosis" and "intimal fibrosis" was reported by Oakley and Somerville⁴ in one of three women with congenital septal defects who "deteriorated while taking contraceptive pills." There is a similarity in the syndrome of that woman and patient 3 of this series.

Arias-Stella,¹⁶ in studying gesta-

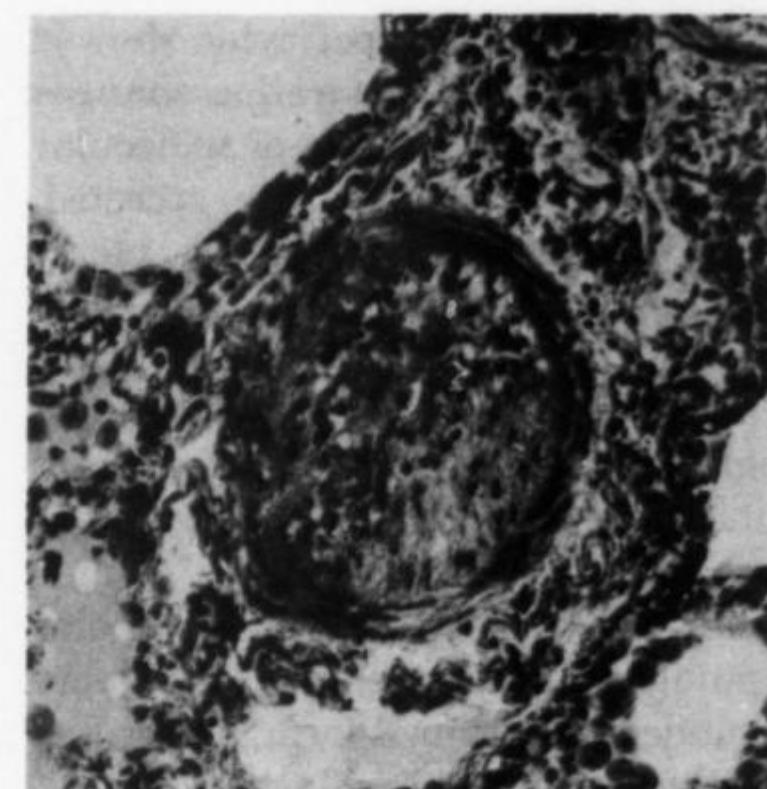


Fig 13.—Branch of pulmonary artery with lumen markedly reduced by cellular intimal proliferation (from 19-year-old male patient with juvenile cirrhosis) (AFIP Neg 71-9442; Movat pentachrome, original magnification $\times 165$).

tional endometrium, found an increase in the thickness of the wall and the diameter of spiral arterioles in both intrauterine and ectopic pregnancy. The number of cases with this finding was statistically significant. This increase resulted from endothelial hyperplasia and medial hypertrophy.

There is a morphologic similarity between these vascular lesions in women and those in pregnant and postpartum guinea pigs.^{5,6} Albert found that the subendothelial cells in myometrial arteries began to proliferate in early pregnancy and that by term the subendothelial cells had formed a cushion several layers thick. Comparison of several of his photomicrographs with the lesions in this series of human cases shows similarity of the intimal lesions. A similar change was illustrated by Schwarz and Hawker¹⁷ in their presentation and discussion of hyperplasia and hypertrophy of uterine arteries and veins in human pregnancies.

Intimal proliferation has also been described by Bruzzone et al⁷ in the guinea pig in association with estrogen-induced fibroid tumors of the thoracic serosa, and similar lesions have also been noted by Lipschutz⁸ in experimental work with steroids.

Friederici,⁹ in an electron microscopic study of the response of uterine capillaries to estrogen stimulation, showed that "the cytoplasm of en-

dothelial cells and pericytes showed evidence of growth as well as changes suggestive of synthesis of molecular complexes destined to be secreted, such as mucopolysaccharides, mucoproteins, or collagen." In a review of tissue culture work, Dawson¹⁸ noted "a positive stimulation of fibroblast cultures" by steroids. The fibroblasts under the influence of steroids in tissue culture were found to "change from the typical elongated, bipolar spindle or stellar shape to a more rounded or flattened form, a so-called epithelialization of fibroblasts."

From the preceding considerations there is evidence, as demonstrated in this group of 16 women, and as reported in the literature in both human and animal cases, to suggest that the intimal lesions may be primary intrinsic vascular alterations and that they do not appear to be secondary to systemic disease or to embolization.

The 16 patients in this study had three common denominators: the vascular system was the site of the lesion; intimal proliferation was common to all; and they all had the common female reproductive steroid factor related to pregnancy, the postpartum state, or to the administration of oral contraceptives.

There are several reasons why these lesions have not been more commonly reported. They are relatively rare, they may have been overlooked, or they may have been interpreted as atherosclerotic or as a residual of an old inflammatory process.

As previously stated, intimal proliferation is found in many other conditions, and the vascular lesions in these 16 cases are interpreted as neither specific for, or unique to, a female reproductive steroid effect.

Consideration of the total clinicopathologic profile of these 16 cases, however, suggests that these steroids should be placed in the list of agents and conditions with which intimal proliferation is associated.

For the future, search should be made for similar vascular lesions in animals receiving oral contraceptives. Other areas for further investigation include patients with hormonally active gonadal tumors; those receiving steroid therapy (particularly the phenanthrene derivatives) for malignancies, for replacement therapy, for immunosuppression; and those with hepatic disease. The latter group is mentioned because we have seen two instances of similar lesions in pulmonary vessels in males with severe liver disease (Fig 13).

In summary, the morphologic findings in the 16 women in this series suggest that female reproductive steroids (exogenous or endogenous) may act directly on the vascular system as a target organ in predisposed individuals and induce intimal proliferation. The resultant reduction in the lumen of the vessel and the alteration of hemodynamics may or may not be associated with a thrombotic overlay. Thus, the final vascular compromise may be due either to the severe intimal proliferation or to a combination of an intrinsic vascular lesion and a labile clotting system.

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