

Original Articles

Vascular Lesions in Women Taking Oral Contraceptives

Nelson S. Irey, MD; William C. Manion, MD; and Herbert B. Taylor, MD, Washington, DC

Distinctive vascular lesions in association with thrombosis were found in arteries and veins in 20 relatively young women receiving oral contraceptives. These lesions were characterized by structural and histochemical changes in the intima and media. Occlusive thrombi were associated with relatively small, organized bases, the age of the latter measured in days to weeks. Nonocclusive and possibly earlier lesions were dominated by endothelial proliferation with minimal thrombus formation. It is postulated that this endothelial and intimal hyperplasia may be related to the steroids received and that it parallels similarly induced hyperplasias that have been found in cervical gland epithelium, in leiomyomas, and in a variety of mesenchymal derivatives under experimental conditions. Further control and experimental studies are required to clarify the possible relationship between these vascular lesions and oral contraceptives.

ALTHOUGH the clinical aspects of thromboembolism in women taking oral contraceptives have been reported in detail,^{1,2} remarkably little attention has been paid to the pathologic findings in these patients. In the course of reviewing 20 examples of thromboembolism associated with the use of oral antiovulants, definite histologic changes in both arteries and

veins were identified. These alterations are quite distinctive and have not been found in patients with thromboembolism who were not taking oral contraceptives. This paper describes the clinical and pathologic findings in a study of these 20 patients, with particular emphasis on the vascular lesions and their possible histogenesis and significance.

Material and Methods

The 20 examples forming the basis for this study were contributed to the Registry of Tissue Reactions to Drugs during the years 1966 to 1968. The available clinical data were tabulated, and routinely stained sections were reviewed. Histologic study was supplemented by preparation of additional slides from available formalin-fixed tissue. The blood vessels were also studied with the following special stains: Masson's trichrome stain; Wilder's reticulum stain; Movat's pentachrome stain; PAS reagent, with and without predigestion with diastase; and the colloidal iron technique for acid mucopolysaccharides (AMP), with and without predigestion with hyaluronidase. Twenty-two examples of thrombosis or thromboembolism in women in the same age range were utilized as controls.

Clinical Findings

The 20 patients ranged in age from 18 to 41 years, with a median age of 29 years (Table). Fifteen were white and five were Negro. None had clinical or pathologic evidence of any concurrent disease that would predispose to thrombosis or thromboembolism.

The indications for the use of oral contraceptives were known in 14 patients: Contraception in nine; dysmenorrhea in

Accepted for publication Sept 3, 1969.

From the Armed Forces Institute of Pathology, Washington, DC.

Read in part at the Ninth Annual Lectures, Armed Forces Institute of Pathology, Washington, DC, March 27, 1969.

Reprint requests to Armed Forces Institute of Pathology, Washington, DC 20305 (Dr. Irey).

Clinical Data on 20 Cases of Vascular Lesions Associated With Oral Contraceptives

Case No.	Age	Type of Antiovulant	Indications for Antiovulant	Time on Antiovulant	Other Medications	Initial Symptoms	Interval From Symptoms to Death
1	26	Norethynodrel and mestranol	Dysmenorrhea	3½ mo	...	Pain in shoulder	5 days
2	27		Dysmenorrhea	13 mo	Cortisone	Dyspnea	10 days
3	23		Contraception	37 days	...	Apprehension, syncope, tachycardia	3 days
4	41		Contraception	5½ mo	Thyroid extract, tranquilizer	Pain in leg	3 wk
5	40		Menorrhagia	2 mo	...	Dyspnea, syncope, cold sweats	7 days
6	36		...	12 mo	...	Blindness, right eye	...
7	34		...	2 mo	...	Pain in leg	5 days
8	18	Mestranol and norethindrone	Anorexiant, tranquilizer	Died unexpectedly at home	...
9	25		Chest pain	5 days
10	33		Contraception	6 mo	...	Died unexpectedly at home	...
11	24		Contraception	6 wk	...	Dyspnea, syncope, palpitation	3 days
12	24		...	4½ mo	...	Chest pain	9 days
13	22		Contraception	3 mo	Tranquillizer	Chest pain, leg pain, dyspnea	5 hr
14	27	Mestranol and norethindrone	Contraception	6 wk	Anorexiant	Syncope, abdominal pain	7 days
15	20	Mestranol and chlormadinone	Irregular menses	3 mo	...	Rectal pain	12 days
16	41	Mestranol and ethynodiol	Contraception	71 days	Thyroid extract	Abdominal pain	11 days
17	26	Norethindrone and ethinyl estradiol	Contraception	9 mo	Anorexiant	Chest pains, dyspnea	1 day
18	29	Type unstated	Dysmenorrhea	12 mo	Tranquillizer	Swelling abdomen (ascites)	2 mo
19	30		Contraception	...	Tranquillizer	Chest pains	3 wk
20	34		Chest pains, dyspnea	7 days

three; irregular periods in one; and menorrhagia in one. The duration of oral contraceptive medication ranged from five weeks to 13 months, and averaged five months. Other drugs were being taken by nine of these patients; including tranquilizers, anorexiants, and thyroid extract. One patient was receiving cortisone acetate for ulcerative colitis.

Symptoms associated with the terminal episode varied. Pain was the most frequent, occurring in the chest in six, in the leg in three, in the abdomen in two, and in the rectum and shoulder in one patient each. Dyspnea was noted in six patients, syncope in four. Tachycardia, apprehension, palpitation, sudden blindness, and cold sweats were each described in a single instance. Ascites was the initial finding

in one patient with hepatic vein thrombosis (Budd-Chiari syndrome).

Most patients were taking a combination type preparation, but a sequential product was used by two. The estrogenic component in 16 cases was mestranol and in one case was ethinyl estradiol. The progestins included norethynodrel, norethindrone, chlormadinone acetate, and ethynodiol diacetate. All of these are 19-nortestosterone compounds except chlormadinone (6-chloro-progesterone [17 α] acetate). In terms of the relative effect of the constituents as evaluated by Dickey and Dorr,³ most agents used were of intermediate estrogenic and progestational effect, but five patients received products with strong progestational effect and weak estrogenic effect, and the sequential agents

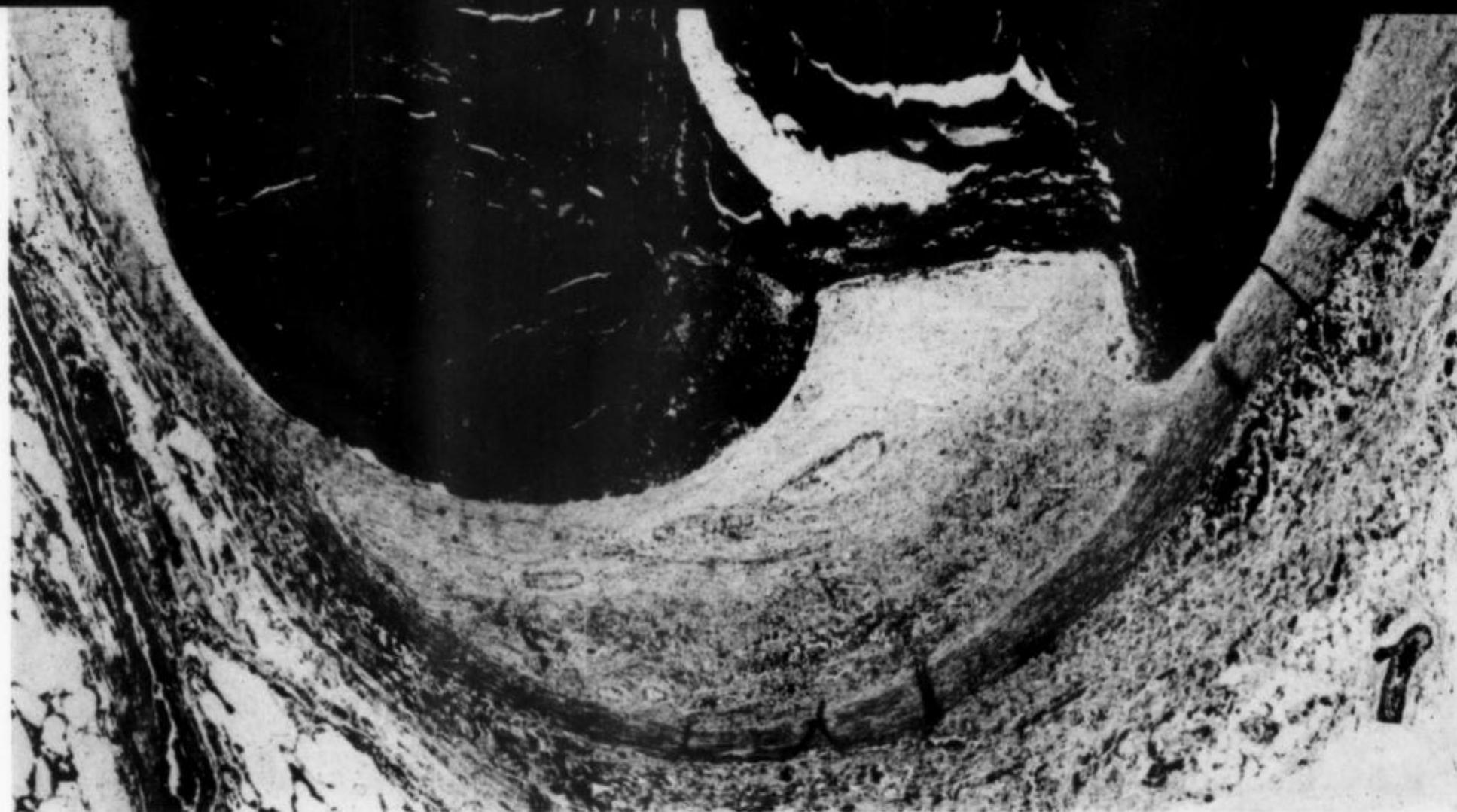


Fig 1.—Pulmonary artery. Organized and vascularized base of thrombus in lower field. Organizing component above center of this base. Remainder of thrombus is laminated, recent (AFIP Neg 69-1713; Movat, reduced from $\times 13$).

taken by two women had strong estrogenic and weak progestational effect.

There was no apparent relationship between the type of oral contraceptive taken and the development of thromboembolism.

Pathologic Findings

Gross.—Thrombi and associated lesions of the vascular wall were widely distributed in these patients. They were found in the pulmonary, systemic, and portal circulations, in arteries and veins, and in vessels of large, medium, and small caliber. Thrombi were limited to the pulmonary artery in nine patients; in eight, they were found in the pulmonary artery and in the pelvic, iliac, hypogastric, or leg veins. They were limited to the mesenteric vein, temporal artery, and hepatic vein in one patient each.

Microscopic. — Vascular Changes. — Three types of intrinsic vascular lesions were identified in these patients:

1. Three-layered thrombi with underlying structural and histochemical changes in the vessel wall, found in 19 instances.
2. Endothelial proliferation and intimal thickening, with no changes in the media or adventitia, found in four patients.
3. Focal nodular thickening of the intima, media, and adventia, found in only one instance.



Fig 2.—Higher magnification of portion of Fig 1. Organized, collagenized, and vascularized base of thrombus above arterial wall. At top center, darker area of organizing layer. Top left, fresh and unorganized portion of thrombus (AFIP Neg 69-1725; Movat, reduced from $\times 42$).

In the first type (Fig 1 to 4), the thrombi usually included three layers: an adherent and organized base with revascularization, collagenization, and in some instances hemosiderin-laden macrophages; over this a zone of fibrin with ingrowth of fibroblasts; and a superficial layer of recent laminated thrombus without evidence of organization. The latter usually formed the bulk of the intraluminal mass and was

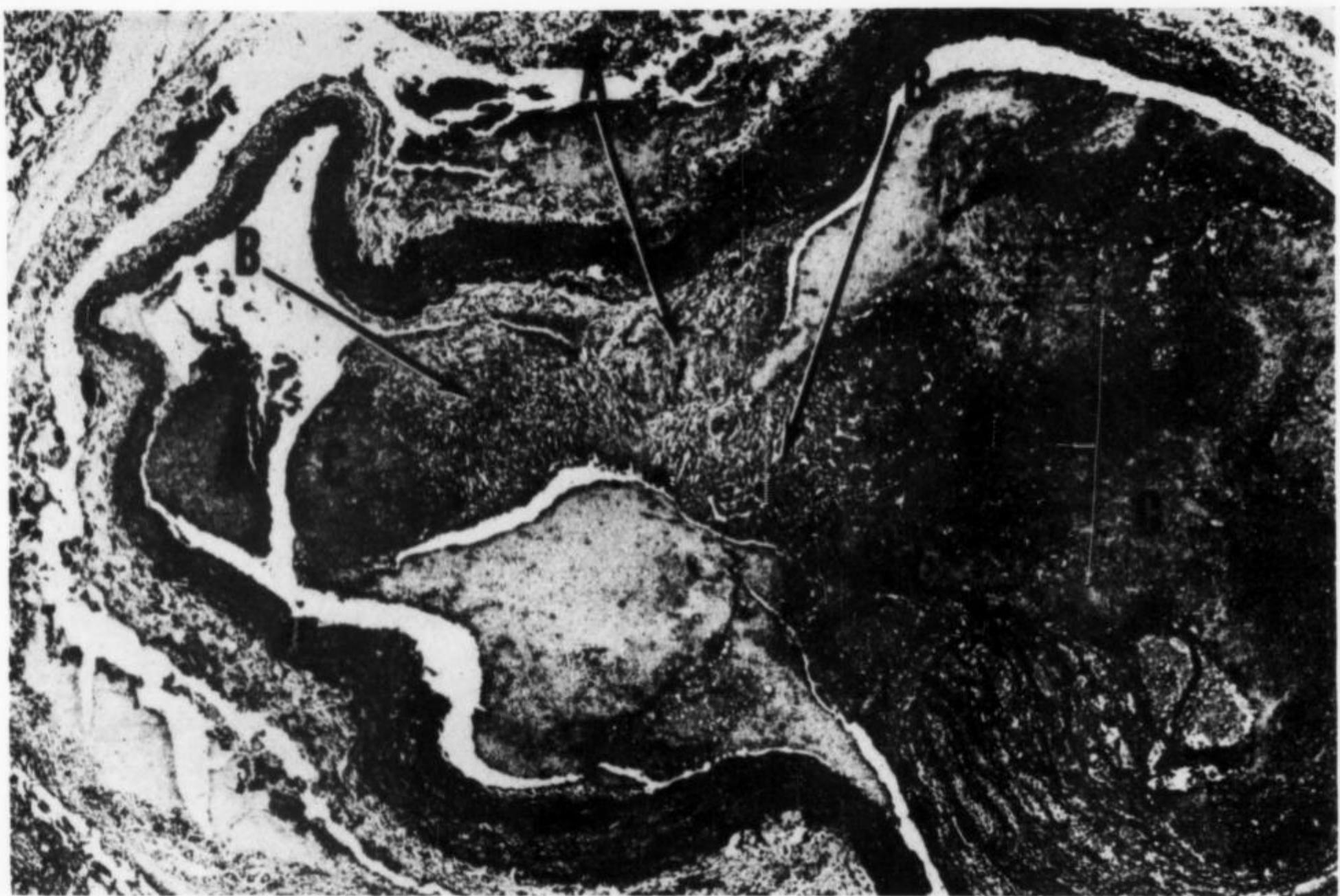


Fig 3.—Pulmonary artery. Base of thrombus (A), small and nodular, with organization and vascularization. Cellular extension (B) from base. Occlusive masses of fresh, laminated thrombus (C) (AFIP Neg 3708-1; Movat, reduced from $\times 17$).

Fig 4.—Higher magnification of portion of Fig 3. Note intimal thickening flanking fibrous base (A). Hemosiderin deposits in base. Cellular masses (B) extending from base to right and left. Fresh and unorganized laminated thrombus (C) (AFIP Neg 3714-1; Movat, reduced from $\times 56$).

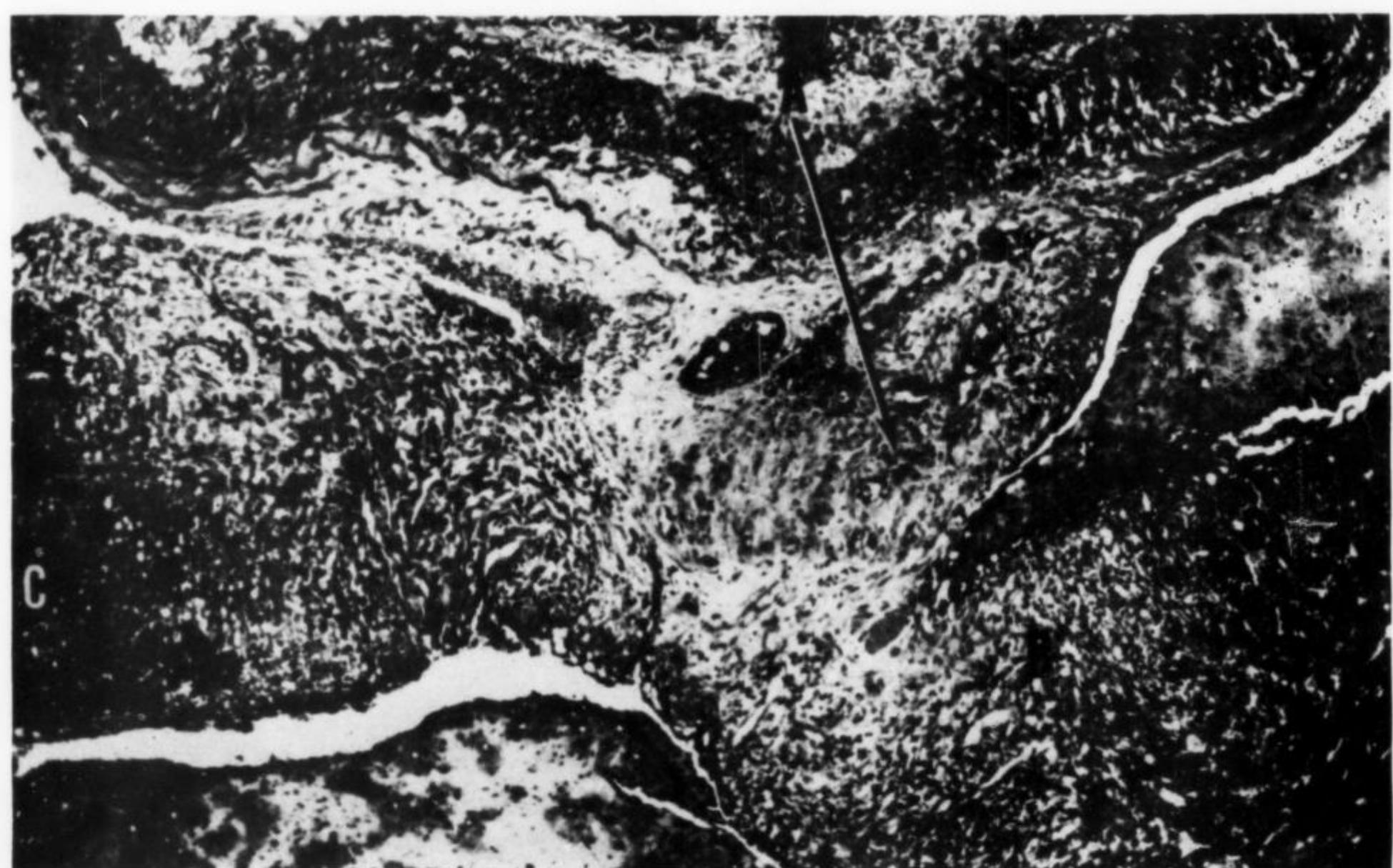
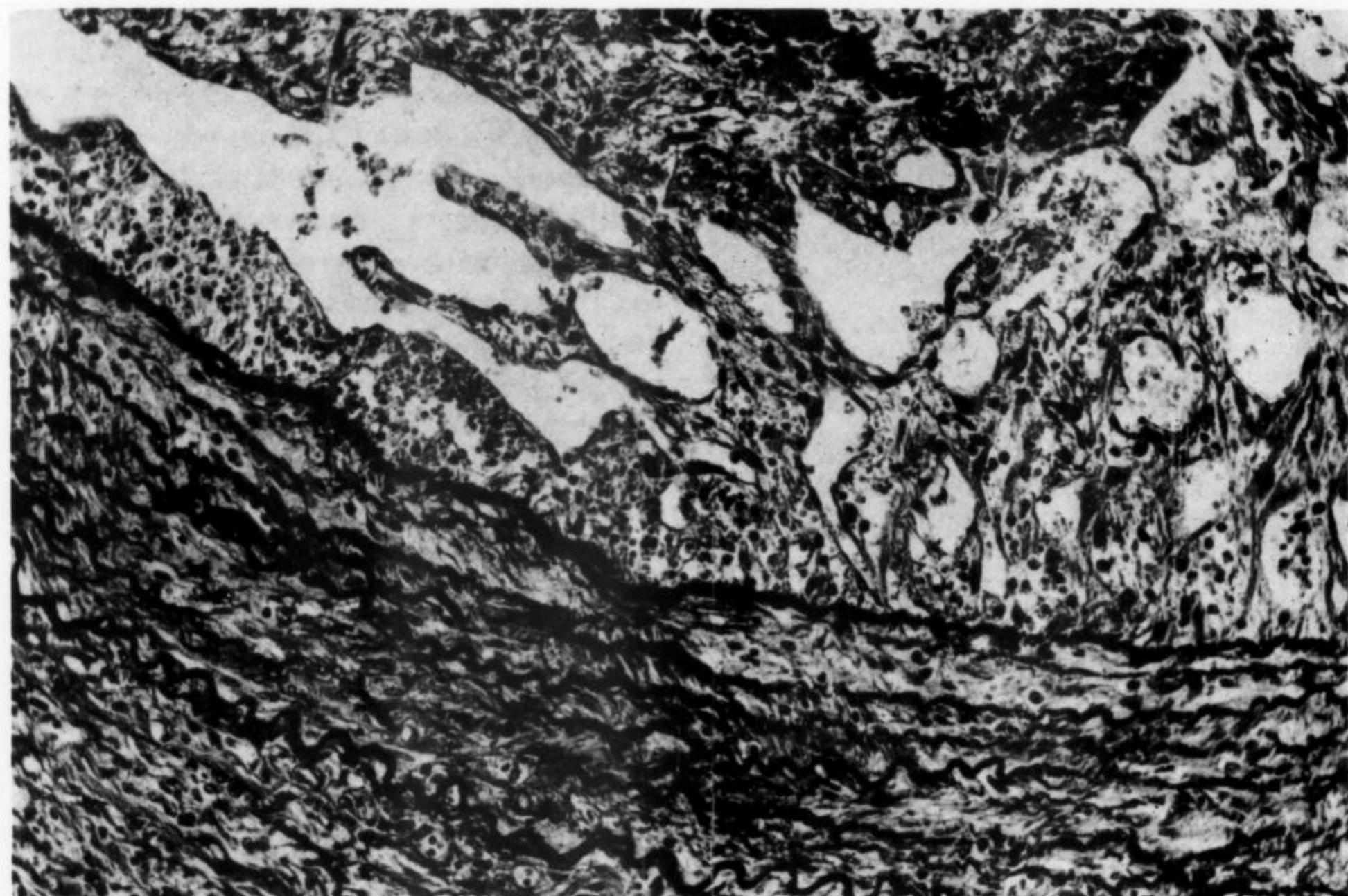




Fig 5.—Pulmonary artery branch. Intimal thickening above. Left center, papillary proliferation of endothelial cells. Dark streaks and masses in center and to right, fresh thrombus formation (AFIP Neg 69-4034; Movat, reduced from $\times 45$).

Fig 6.—Higher magnification of portion of Fig 5. Intimal thickening on left above internal elastica. Endothelial papillations center and right. Darker material in upper field represents recent thrombus formation (AFIP Neg 69-4035; Movat, reduced from $\times 135$).



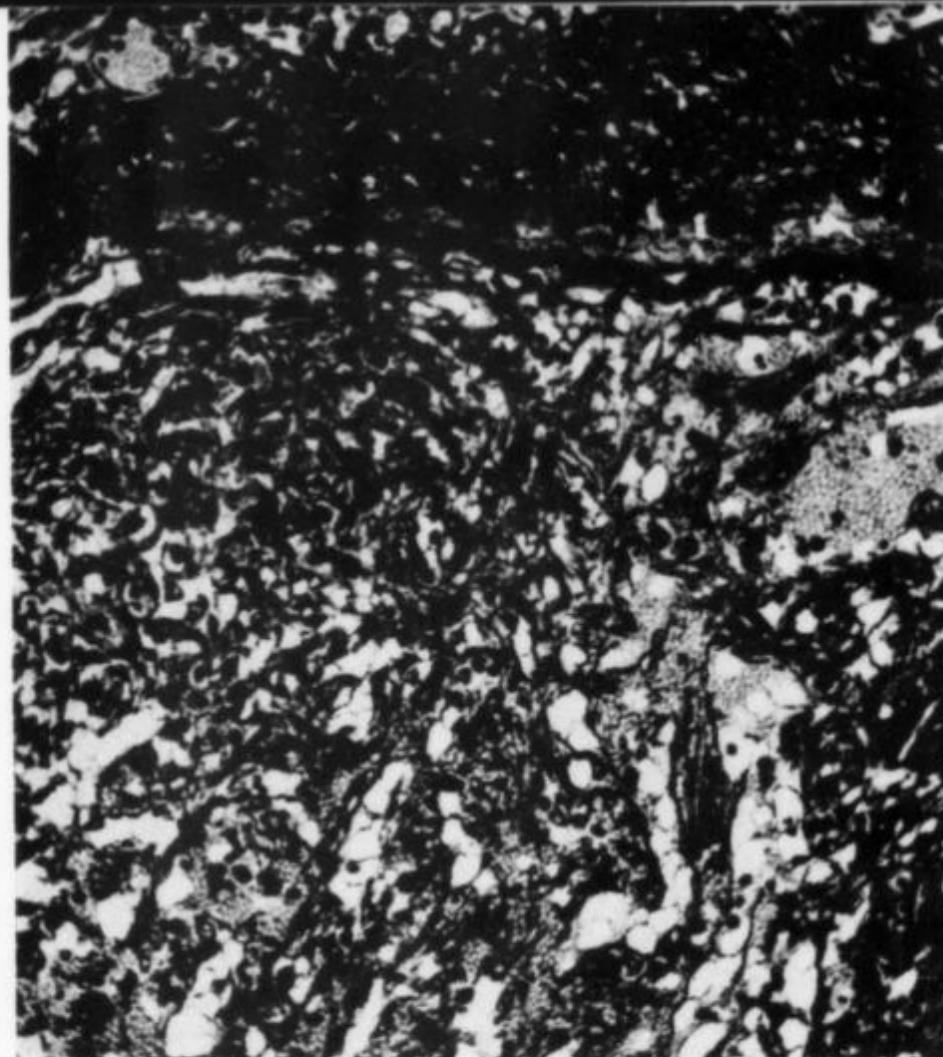


Fig 7.—Pulmonary artery branch. Endothelial proliferation, lower two thirds. Thrombus formation, lower right (AFIP Neg 69-3717; Movat, reduced from $\times 115$).



Fig 8.—Small pulmonary artery branch. Intimal thickening, upper and lower portions of vessel. Endothelial proliferation in upper portion (AFIP Neg 69-3438; hematoxylin and eosin, reduced from $\times 180$).

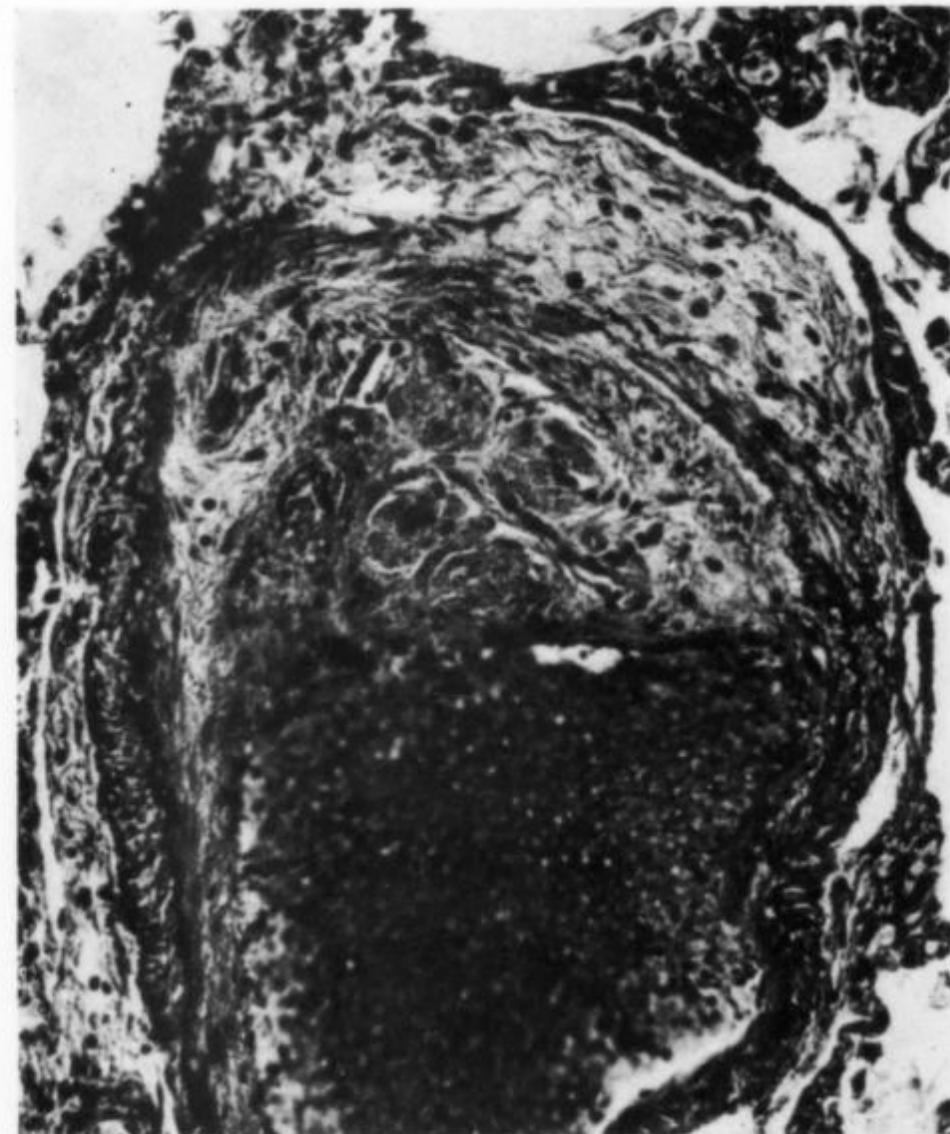


Fig 9.—Small pulmonary artery branch. Above, focal fibrous thickening of intima, media, and adventitia. Internal elastica not demonstrable in this fibrous area (AFIP Neg 69-1630; Movat, reduced from $\times 145$).

The second type of vascular lesion was found in smaller pulmonary vessels and consisted of endothelial and intimal proliferation characterized by formation of slender to broad papillary projections (Fig 5 to 8). These projections often formed anastomosing plexiform networks that in some instances almost filled the lumen of the vessel. Recent thrombi were sometimes found in association with this type

of change. The intima beneath the endothelial proliferation was often thickened, and hyaluronidase-sensitive, AMP-positive material was present in the interstices. The underlying media and adventitia were unaltered.

The third type of lesion was found in only one patient, in a small branch of the pulmonary artery. It consisted of a focal nodular, fibrous thickening of the intima, media, and adventitia, with no associated endothelial proliferation or thrombosis (Fig 9).

Other Tissues.—Sections of one or both ovaries were available from nine patients. Corpora lutea were absent in all instances. Multiple cystic graafian follicles were noted in the ovaries of one patient, but the theca interna was not well developed, and there was no luteinization. The paucity of developing graafian follicles and absence of corpora lutea made the cortical and medullary stroma appear relatively more prominent than usual for women in this age group, but there was no evidence of actual stromal hyperplasia.

Clear-cut decidual transformation of the endometrial stroma, together with inactive-appearing endometrial glands, was found in two patients. Similar changes were probably present in four others but were obscured by the degree of postmortem autolysis. The endometrium was in

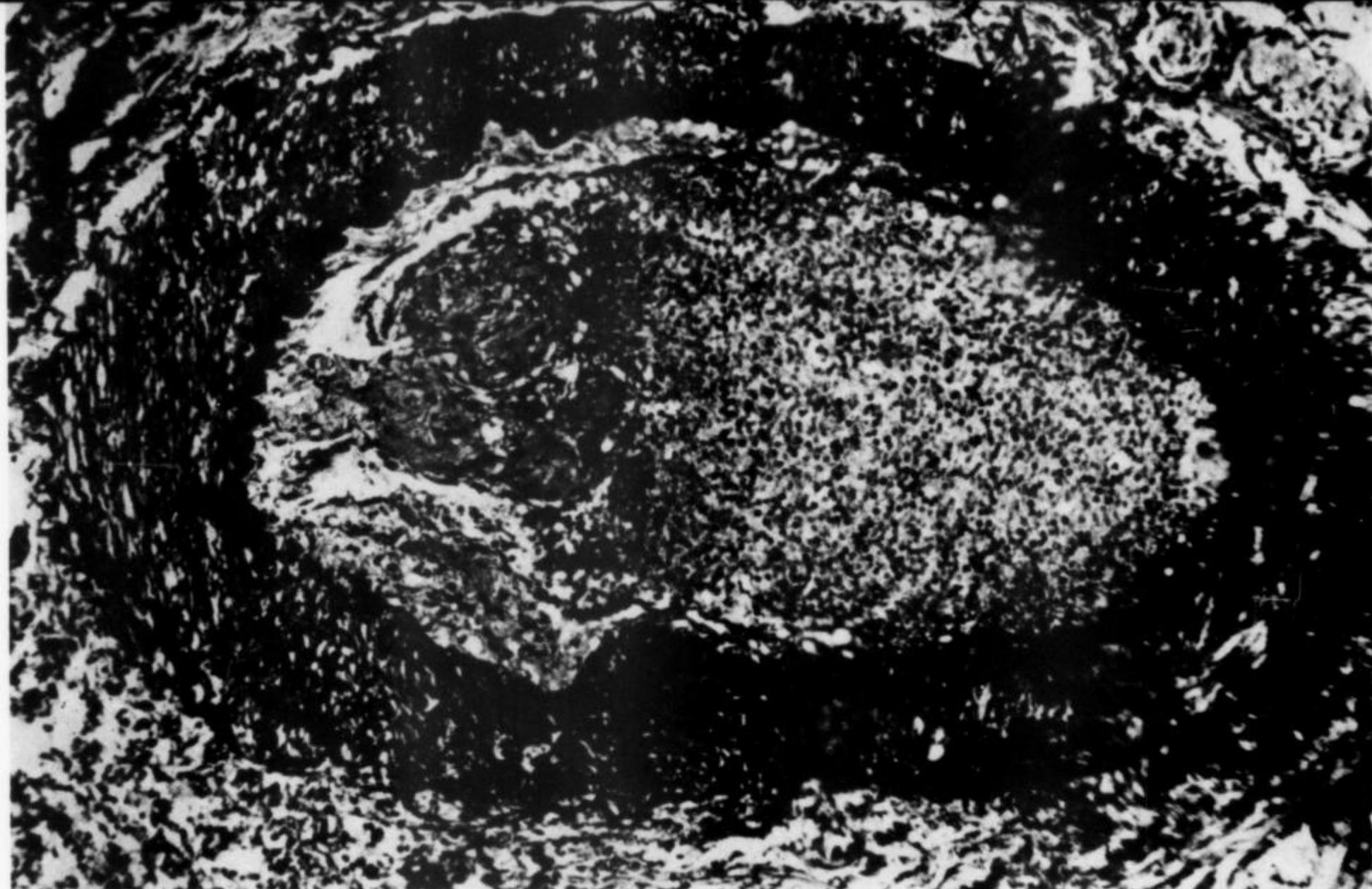


Fig 10.—Small pulmonary artery branch. Focal fibrous intimal thickening on left. Elastica interna intact. No evident medial or adventitial changes (AFIP Neg 69-3120; Movat, reduced from $\times 100$).

the menstrual phase in one patient and in the early proliferative phase in three others. Two women had uterine leiomyomas. One of the myomas was quite cellular, with marked nuclear hyperchromasia but negligible mitotic activity. This picture has been associated with the use of oral contraceptives.⁴ In the myometrium of one patient, there was a rather pronounced thickening of blood vessel walls. Marked chronic inflammation was present in the cervix of three patients, but no epithelial change or glandular hyperplasia was evident in the available sections.

Sections of breast were available from five patients. In three, no particular lobular development or other changes were noted. Lobular development was evident in the other two. It was relatively slight in one, but quite marked and associated with secretory activity in the other. The degree of lobular hyperplasia and lactational change in this patient appeared greater than usually seen in women taking oral antiovulants, although there is considerable variability.

Controls

The diseases associated with thrombosis and thromboembolism used as the control

group are listed in the following tabulation:

Disease or Condition	No. of Cases
Rheumatic heart disease	5
Postoperative status	4
Postpartum	2
Pulmonary hypertension	2
Bacterial endocarditis	2
Aortitis with congestive failure	1
Congenital heart disease	1
Lupus erythematosus	1
Myocarditis with mural thrombosis	1
Pregnancy	1
Pulmonary arteritis and pneumonitis	1
Renal disease with anasarca	1
Total	22

In only one patient, intrinsic vascular lesions were observed resembling those in patients taking oral antiovulants. This one exception was a woman with pulmonary hypertension associated with congenital heart disease in whom pulmonary arterial branches showed circumferential intimal thickening associated with foci of foam cells. In addition, one artery presented a focal nodular thickening of the intima resembling the focal lesion found in one patient in the oral contraceptive group having a lesion of the third type (Fig 10). Further inquiry disclosed that she had taken an antiovulant for six weeks prior to death.

Comment

The present study has shown (1) that in many instances vascular occlusion resulted from locally formed thrombi rather than from embolization, and (2) that the lesions developed over a period of several days or weeks, with only the final occlusive event representing an acute phenomenon. Changes in walls of blood vessels were invariably found at the site of attachment of the thrombi, and vascular lesions without occlusive thrombi were present in four patients, strongly suggesting that the changes in blood vessels were primary. These changes—endothelial proliferation and subendothelial fibrosis—were not found in the control patients. Hyperplasia of various tissues, including endothelium, has been produced experimentally by administration of steroids.⁵ Endothelial hyperplasia in blood vessels has been described in the endometrium and other sites in women receiving oral contraceptives.⁶ Hyperplasia of endocervical glandular epithelium has been associated with the use of oral contraceptives by several investigators,⁷⁻¹⁰ as has increased cellularity in uterine leiomyomas.⁴ These observations provide support for postulating a causal relationship between the intimal hyperplasia and ingestion of the steroid hormones.

It is obvious, however, that not only are detailed studies of additional examples necessary to clarify the possible relationship between the vascular lesions and the use of oral antiovulants, but that parallel studies on control groups of women with thromboembolism who were not taking exogenous hormones, and on women taking these agents who died of unrelated causes, are equally essential, as are additional experimental studies. Nonetheless, the consistent findings of these characteristic vascular changes in women taking oral contraceptives who developed thromboembolism, the absence of comparable changes in women with thromboembolism who were not taking these agents, and the apparent specificity of the histologic alterations all suggest that a relationship exists, and that further studies are, therefore, eminently justified.

Dr. Irey is Registrar of the Registry of Tissue Reactions to Drugs, which is jointly sponsored by the American Medical Association, the Food and Drug Administration (under contract FDA 67-53), the Pharmaceutical Manufacturers' Association Foundation, and the National Institute of General Medical Sciences, National Institutes of Health (under contract PH-43-66-966), under the auspices of Universities Associated for Research and Education in Pathology, Inc., Bethesda, Md.

Nonproprietary and Trade Names of Drugs

Norethindrone—Norlutin.
Chlormadinone acetate—Lormin.

References

1. Tausk, M.: "Oral Contraceptives and the Incidence of Thrombosis," in Meyler, L., and Peck, H.M. (eds.): *Drug-Induced Diseases*, New York: Excerpta Medica Foundation, 1968, vol 3, pp 183-209.
2. Ask-Upmark, E.: "The Relationship between Thrombophlebitis, Thrombosis, Embolism and the Use of Oral Contraceptive Agents," in Meyer, L., and Peck, H.M. (eds.): *Drug-Induced Diseases*, New York: Excerpta Medica Foundation, 1968, vol 3, pp 211-217.
3. Dickey, R.P., and Dorr, C.H.: Oral Contraceptives: Selection of the Proper Pill, *Obstet Gynecol* 33:273-287 (Feb) 1969.
4. Fechner, R.E.: Atypical Leiomyomas and Synthetic Progestin Therapy, *Amer J Clin Path* 49: 697-703 (May) 1968.
5. Lipschutz, A.: *Steroid Hormones and Tumors*, Baltimore: The Williams & Wilkins Co., 1950.
6. Blaustein, A.; Shenker, L.; and Post, R.C.: The Effects of Oral Contraceptives on the Endometrium, *Int J Fertil* 13:466-475 (Oct-Dec) 1968.
7. Candy, J., and Abell, M.R.: Adenomatous Hyperplasia of the Uterine Cervix, *JAMA* 203:323-326 (Jan) 1968.
8. Taylor, H.B.; Irey, N.S.; and Norris, H.J.: Atypical Endocervical Hyperplasia in Women Taking Oral Contraceptives, *JAMA* 202:636-639 (Nov) 1967.
9. Govan, A.D.T.; Black, W.P.; and Sharp, J.L.: Aberrant Glandular Polypi of the Uterine Cervix Associated With Contraceptive Pills: Pathology and Pathogenesis, *J Clin Path* 22:84-89 (March) 1969.
10. Kyriakos, M.; Kempson, R.L.; and Konikov, N.F.: A Clinical and Pathologic Study of Endocervical Lesions Associated With Oral Contraceptives, *Cancer* 22:99-110 (July) 1968.