EXPERIMENTAL VENOUS AND ARTERIAL THROMBOATHEROSCLEROSIS: A COMPARATIVE STUDY*

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Received for publication September 30, 1961

IN an earlier study (Friedman, Byers and Pearl, 1960) we described and compared the early response of the inferior vena cava with that of the aorta of the normal rabbit to experimentally induced thrombotic processes. Both types of vessels exhibited a prompt intimal hyperplasia leading to a thrombosclerotic plaque within a few weeks. However, it was observed that the intimal reaction of the inferior vena cava was accompanied by a far richer supply of new arterioles and capillaries than could be detected in the corresponding arterial intimal reaction.

Neither type of vessel, however, in the normocholesteraemic animal exhibited a process that became thromboatherosclerotic (*i.e.* contained detectable lipid after staining with Sudan IV). However, when rabbits were made hypercholesteraemic by feeding of excess cholesterol and cottonseed oil in a second study, it was found (Friedman and Byers, 1961) that the arterial intimal hyperplasia resulting from the intra-aortic induction of a thrombus quickly accumulated an excess both of lipid and cholesterol. The responsibility for such early and continued accumulation was found (Friedman and Byers, 1962) to lie chiefly in two phenomena: an abnormal permeability or "leaking" of the newly developed capillaries accompanying the hyperplastic tissue, and an abnormal retention or sequestration of such exuded lipid materials probably by intimal cell pinocytosis or phagocytosis. Frequent haemorrhage of intimal vessels also probably contributed to the escape of lipoproteins from the blood plasma into areas of sequestration.

Since it already had been observed that similar to the artery, the vein also developed an hyperplastic intimal response accompanied by newly formed vessels, it was thought to be of interest to determine the nature of the thrombus-induced plaque developing in the inferior vena cava of the rabbit fed excess cholesterol and cottonseed oil. For control and comparative purposes, plaques also were induced in the aorta of these same rabbits.

MATERIALS AND METHODS

A. *Effect of feeding of cholesterol and cottonseed oil upon venous and arterial thrombosclerotic plaques.*—(Throughout this paper, plaques resulting from spiral insertion into the vessels of normocholesteraemic rabbits will be referred to as thrombosclerotic plaques, and those resulting from spiral insertion into the vessels of hypercholesteraemic rabbits as thromboatherosclerotic).

* Aided by Grants from the Life Insurance Medical Research Fund, The National Institutes of Health (H-119), American Heart Association, Sacramento County Heart Association, Contra Costa County Heart Association, and Humboldt County Heart Association.

Thirty-seven healthy young male rabbits were anaesthetized with Nembutal and a thrombus was induced in both the inferior vena cava and abdominal aorta by means of the magnesium alloy spiral as described in previous studies (Friedman *et al.*, 1960). Following the operation, the rabbits were given a diet consisting of Wayne rabbit chow enriched with cholesterol (2 per cent) and cottonseed oil (2 per cent). Ten animals were killed at the end of 1 month ; 9 at the end of 2 months, and 6 at the end of 3 months. The remaining surviving rabbits thereafter were fed ordinary rabbit chow. Two of these surviving rabbits were killed at 5 and the remaining 3 rabbits at 8 months after thrombus induction (or 2 and 5 months respectively after resumption of ordinary feeding). Seven rabbits died during the course of the experiment either because of the obstructive effects of the 2 thrombus-induced plaques, or because of the ill effects of the excess cholesterol feeding. Serum for cholesterol analyses (Friedman and Byers, 1962) was obtained from each rabbit at the beginning of the experiment and at death. Additional samples were obtained at the end of 3 months from those rabbits allowed to survive a longer period.

At autopsy, the entire aorta and the abdominal portion of the inferior vena cava of each rabbit was opened and inspected for possible atherosclerosis. The plaque formations in both types of vessels also were located, studied and compared. After sections were taken for histological study, these plaques were removed and analyzed for their total cholesterol content (Friedman and Byers, 1959).

B. *Effect of intravenous injection of Evans blue upon venous and arterial thrombosclerotic plaques.*—Twenty-two rabbits which 28 days previously had received a magnesium alloy spiral in both the inferior vena cava and abdominal aorta were given 10·0 mg. of Evans Blue by intravenous injection. The rabbits were brought to autopsy 24 hr. later and the plaque areas in both the aorta and inferior vena cava were inspected for areas of dye extravasation or densification. These rabbits had ingested ordinary Wayne laboratory chow throughout the experimental period.

C. *Effect of intravenous injection of a colloidal suspension of carbonyl iron upon venous and arterial thrombosclerotic plaques.*—Twenty-three rabbits that 25 days earlier had received a coil in both the inferior vena cava and abdominal aorta were injected intravenously with 1·0 ml. of a suspension containing 0·3 mg of colloidal carbonyl iron particles (approx. diam. : 3 μ) twice a day for 3 days. These rabbits were killed 24 hr. following the last injection, the plaque areas inspected for gross iron deposits and then sections including the underlying vessel wall were obtained, stained with Berlin blue and examined for possible microscopic areas of iron deposit.

RESULTS

A. *Evolution of venous and arterial thromboatherosclerotic plaques in rabbits during and after ingestion of excess cholesterol*

Description of morphological changes.—From the onset, it was observed both grossly and histologically that the thrombus induced plaque developing in the inferior vena cava differed considerably from that developing in the aorta of the same animal. Grossly, both types of plaques became covered with intimal tissue within the first 7–14 days, but the venous plaque resembled a sausage or rope-like structure and was usually anchored to the subjacent vein only at its ends, in contrast to the aortic plaque which from the first week usually became adherent along its entire length to the aortic intima. The plaques generally continued to exhibit this difference in form and attachment throughout the period of feeding excess cholesterol (Fig. 1), and also during the period when such feeding was discontinued (Fig. 2). The venous plaque also was observed at all stages to present the appearance of a richly growing, pliable and quite soft papilloma-like process rather than that of a dense, semi-fibrotic scar-like structure (as did its aortic counterpart from the 3rd–4th week on). Then, too, as previously described before, (Friedman and Byers, 1961) whereas almost all of the aortic plaques 2 months of age or over exhibited a necrotic core filled with a liquid rich in lipid,

EXPLANATION OF PLATES

FIG. 1 : Rabbit W-728.—Thromboatherosclerotic plaques from the inferior vena cava (right) and aorta (left) of a cholesterol-oil fed rabbit 3 months after insertion of spiral into aorta and vena cava. The aortic plaque is in 3 segments due to incision of aorta at autopsy. The atherosclerotic involvement of these aortic segments is easily discernible. Note the greater size and the scar-like appearance of the aortic plaques in contrast to the thinner, tubular, softer-appearing venous plaque. See Fig. 11 and 12 for microscopic views of these plaques.

FIG. 2 : Rabbit W6-732.—Thromboatherosclerotic plaques from inferior vena cava (right) and aorta (left) of a rabbit 8 months after insertion of the spiral and 5 months after cessation of a 3 months' period of cholesterol-oil feeding. Both venous and aortic plaques appear to have diminished in size. The dense, scar-like structure of the aortic plaques persists.

FIG. 3 : Rabbit 344.—Venous thromboatherosclerotic plaque from a cholesterol-oil fed rabbit 4 weeks after insertion of spiral into inferior vena cava (H. and E × 200). A basal area of hyperplastic intimal tissue immediately below the thrombus mass (not shown) is shown. The vascularity of this area is composed chiefly of small arteries and arterioles with well-developed walls as shown above. Such well-developed vessels were rarely, if ever, seen in the basal areas of the aortic plaques.

FIG. 4 : Rabbit 344.—Aortic thromboatherosclerotic plaque from the same rabbit whose venous plaque is shown in Fig. 3 (H. and E. × 200). A basal area of hyperplastic intimal tissue immediately above the media is shown. The vascularity of this area always appears to consist of separated, thin-walled capillaries as illustrated here, or masses of thin-walled sinusoidal channels (compare with Fig. 8).

FIG. 5 : Rabbit T-2-23.—Areas of the inferior vena cava (right) and aorta (left) of a rabbit injected with Evans blue prior to autopsy. These areas had sustained thrombosclerotic plaques (4 weeks old) which had been removed prior to photography. The 3 dark streaks on the aorta outline the areas occupied by plaque segments and have been formed by the extravasation of the Evans blue dye. Such basal extravasion of dye does not occur in that part of the vena cava which had been subadjacent to the plaque.

FIG. 6 : Rabbit W15-353.—Thrombosclerotic plaques (4 weeks old) from the inferior vena cava (right) and aorta (left) of a rabbit injected twice daily with colloidal iron for 3 days immediately prior to autopsy. The deposition of iron just beneath the respective surfaces of each type of plaque is quite easily seen. See Fig. 7 and 15 for microscopic views of these plaques.

FIG. 7 : Rabbit W15-353.—Photomicrograph of aortic plaque shown grossly in Fig. 6 (Berlin blue × 80). Iron particles can be seen upon and just below the hyperplastic intimal tissue encircling the thrombus. Same iron localization is present in the adventitia. Usually, considerable iron also is found just above the internal elastic membrane in the basal area of the plaque.

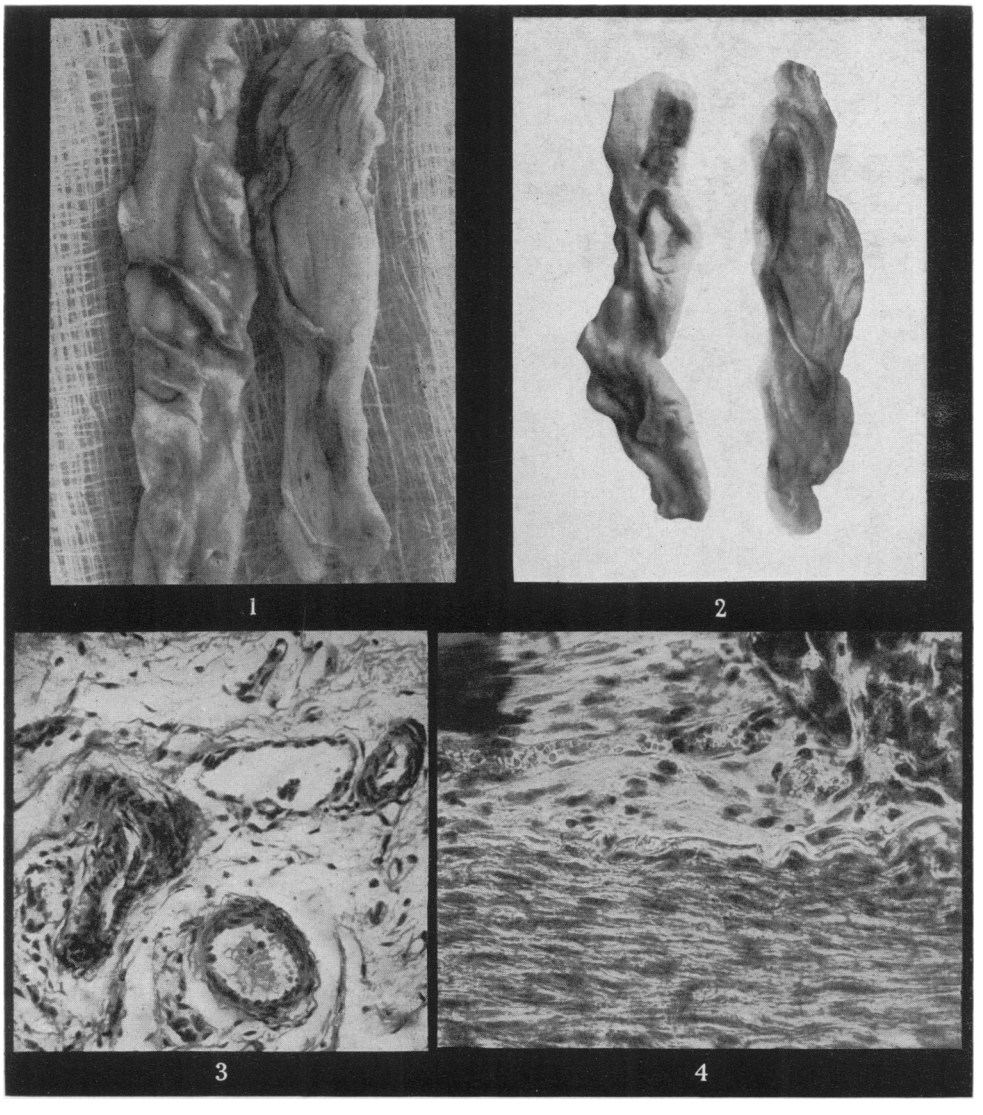
FIG. 8 : Rabbit 341.—Developing aortic thromboatherosclerotic plaque in a cholesterol-oi fed rabbit 28 days after intraortic insertion of spiral. (Berlin blue × 400). Dilated sinusoids filled with red blood cells (yellow) can be seen immediately contingent to a partially disorganized media. Note the presence of iron (blue) at the base of the plaque. This rabbit had received injections of colloidal iron prior to death.

FIG. 9 : Rabbit 342.—Developing venous thromboatherosclerotic plaque from a cholesterol-oil fed rabbit 28 days after insertion of spiral into vena cava (Sudan IV × 60). Compared with the aortic plaque of the same animal (Fig. 10), this venous plaque exhibits a central, orderly accumulation of cells almost all of which contain abundant deposits of Sudan staining material. The intracellular site of Sudanophilia affords a purplish red colour to the plaque rather than the reddish-brown afforded the aortic plaque (Fig. 10) by its extracellular deposits of Sudan staining lipid. The new peripheral intimal tissue encircling the thrombus remains relatively free of Sudanophilia. At this stage, both types of plaques are more nearly the same size than at later stages.

FIG. 10 : Rabbit 342.—Developing aortic thromboatherosclerotic plaque from the same rabbit whose venous plaque is shown in Fig. 9 (Sudan IV × 60). The Sudanophilia (reddish-brown) can be seen to involve the basal areas of the plaque, but the more peripheral thrombus encircling portions of new intimal tissue are free of the stain. Note that the portions of the aorta not subjacent to the plaque are free of Sudanophilia.

FIG. 11 : Rabbit W6-728.—Venous thromboatherosclerotic plaque from a cholesterol-oil fed rabbit 3 months after insertion of spiral into inferior vena cava (Sudan IV × 60). The essentially cellular structure of the central portion of the plaque remains and the Sudanophilia remains primarily intracellular accounting for the purple rather than reddish-brown

(*cont. on p.* 201.)



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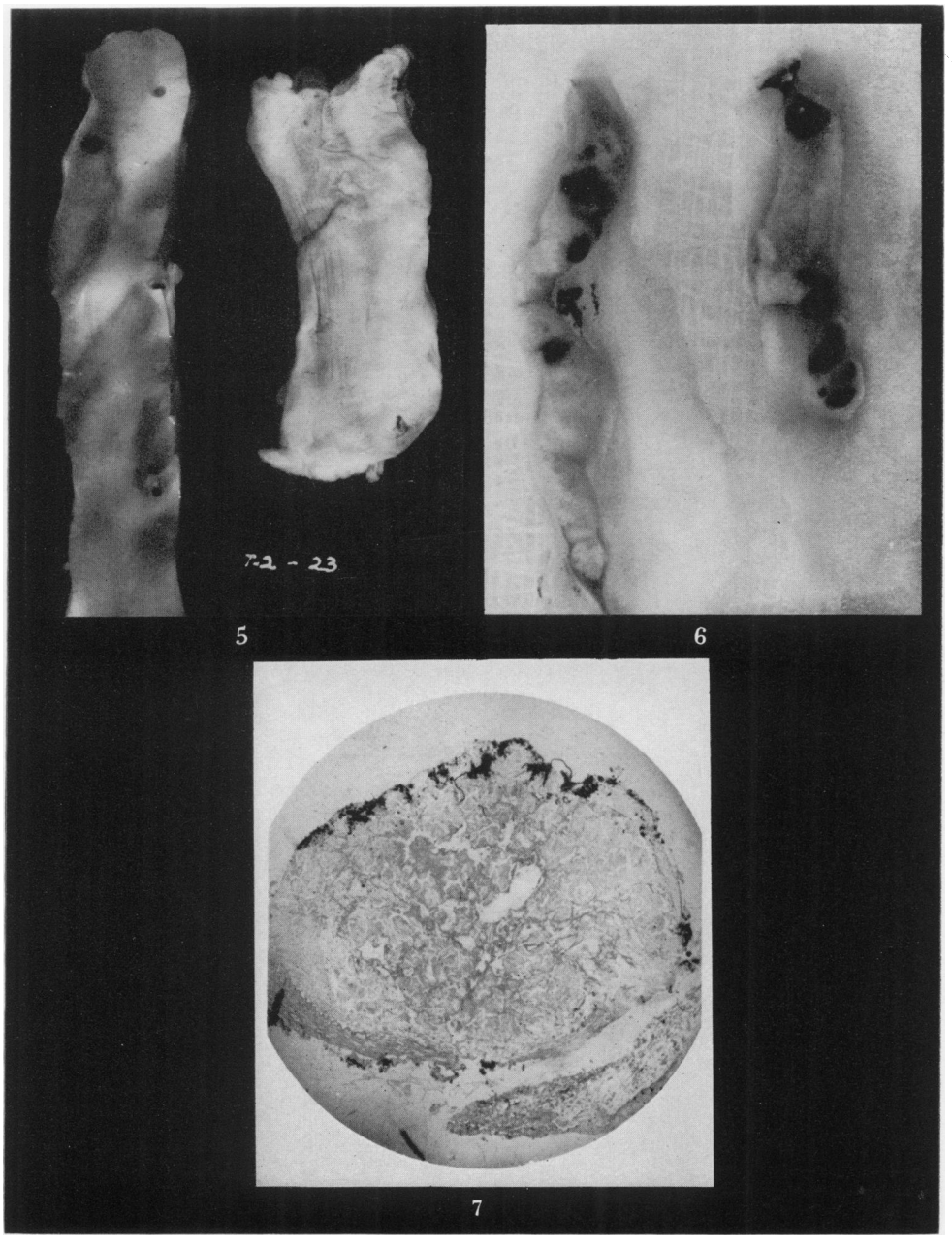

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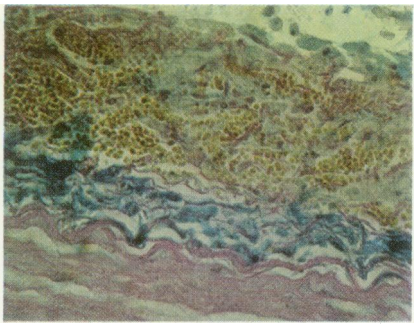

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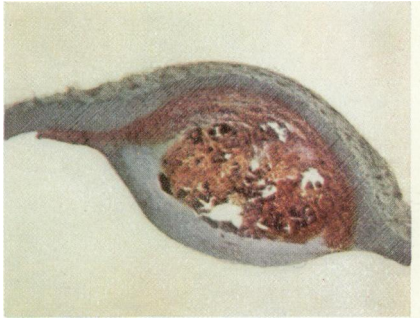

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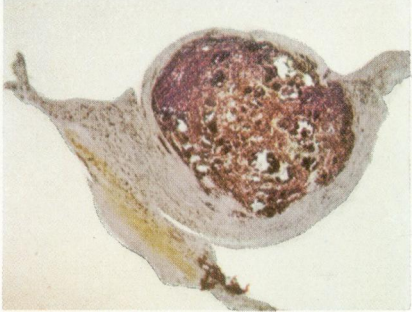

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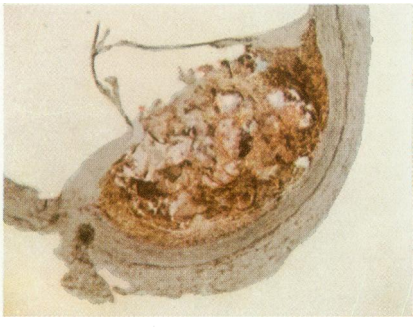

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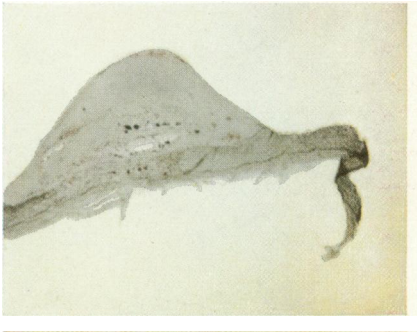

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only a few of the venous plaques showed similar degeneration. Finally, the venous plaques after the first month were not as large as the aortic plaques, and they also appeared to regress more rapidly than the aortic plaques following the return of the experimental animals to the stock diet. Indeed, venous plaques regressed so rapidly that it was rather difficult to find the site of the venous plaque in 2 of the 3 rabbits killed 8 months after initial thrombus induction (*i.e.* 5 months after stopping the feeding of excess cholesterol).

Upon histological examination of both types of plaques 4 weeks after induction of the thrombus, we were impressed with the marked difference in vascularity between the 2 kinds of plaques. The venous plaques almost always exhibited well developed small arteries and arterioles in the basal area (Fig. 3) whereas only dilated capillaries (Fig. 4), or sinus-like complexes of very thin-walled vessels (Fig. 8), were found in the analogous area of aortic plaques. Venous plaques also invariably displayed many arterioles and capillaries rather uniformly distributed throughout the total cellular mass, including the thrombus encircling limbs of hyperplastic intimal tissue. But rarely could a blood vessel be observed in the more peripheral intimal extensions of aortic plaques. These dissimilarities in structure and distribution of vessels are stressed here because we believe that they account for the differences observed after dye and iron injections to be described below.

The venous plaques at 4 weeks (Fig. 9) usually showed complete encirclement of the original thrombus by limbs of hyperplastic intimal tissue. In addition, there was an extensive, confluent and orderly cellular infiltration and replacement of the interior of the thrombotic process. Invariably, these central cells contained large quantities of Sudan staining material, but the peripheral encircling limbs of intimal tissue usually remained devoid of stain indicating that the lipid within the central cells was not being derived from that present in luminal blood, but

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(*cont. from p.* 200.)

colour. Note in comparison with the aortic plaque (Fig. 12) that the venous plaque is much smaller, more polypoid in structure and has a remarkably narrow layer of intimal tissue encircling the total process. This latter tissue, however, remains relatively Sudan-free.

FIG. 12: Rabbit W6-728.—Aortic thromboatherosclerotic plaque from the same rabbit whose venous plaque is shown in Fig. 11 (Sudan IV × 60). Here the basal Sudanophilia with the thick fibrous, partially hyalinized tissue forming the top of the plaque is clearly shown. Note, however, that this latter tissue contains almost no Sudanophilia. The central portion of the plaque shows remnants of metallic salts (purple). The thinning of the subjacent media shown here occurs in almost all of these plaques.

FIG. 13: Rabbit W6-730.—Venous plaque from a rabbit 8 months after insertion of spiral into inferior vena cava and 5 months after cessation of an initial period of cholesterol-oil feeding for 3 months (Sudan IV × 60). A diffusely thickened, lipid-free segment of the inferior vena cava has now replaced what was undoubtedly 5 months previously, a thromboatherosclerotic plaque, as shown in Fig. 11.

FIG. 14: Rabbit W6-730.—Aortic plaque from the same rabbit whose venous plaque is shown in Fig. 13 (Sudan IV × 60). This plaque now shows almost no Sudanophilia. Heavy scar-like tissue is observed in place of the lipid-rich tissue observed in the plaque of the animal sacrificed immediately after 3 months of cholesterol feeding (Fig. 12).

FIG. 15: Rabbit W15-353.—Developing venous thrombosclerotic plaque from a normocholesteraemic rabbit 28 days after intraortic insertion of spiral (Berlin blue × 60). This rabbit had received 6 injections of colloidal iron during the 3 days immediately preceding autopsy. Iron deposition (blue staining) is rather diffusely distributed in plaque. A small accumulation of iron also can be seen in the adventitial tissue.

from lipid present in the blood of the adventitia derived capillaries supplying the central area of the plaque. Haemorrhage was never found in any part of the venous plaques either after one month or later.

The aortic plaques of these same animals at 4 weeks also usually exhibited complete encirclement of the original thrombus by hyperplastic intimal tissue, but the central penetration of the thrombus by basal hyperplastic tissue was usually disordered and irregular (Fig. 10). Sudanophilia, as previously described, (Friedman and Byers, 1961) again was seen in these plaques and mostly in the basal area. But whereas the Sudanophilia was entirely intracellularly disposed in the venous plaque, it was largely extracellularly distributed in aortic plaques. Finally, haemorrhages (Table) were of frequent occurrence in these aortic plaques both at 1 and 2 months after thrombus induction. Such haemorrhages occurred in the basal central and lateral areas—that is, in only those areas where blood vessels could be detected as described above.

The venous and aortic plaques examined 2 months after thrombus induction and cholesterol-oil feeding continued to exhibit the above described differences (Table). In addition, the venous intimal tissue encircling the total mass was thinner and less fibrous than analogous tissue of the aortic plaque. Also, at this time areas of necrosis frequently were observed in the central area of most aortic, but in none of the venous plaques.

Both varieties of plaques when examined 3 months after thrombus induction continued to exhibit differences. At this time, the venous plaques (Fig. 11) were still composed of a papilloma-like mass of cells containing Sudanophilic material surrounded by a thin peripheral rim of encircling intimal tissue. Usually, too, the total process was considerably smaller than that seen in the aorta. The aortic plaque in contrast (Fig. 12) exhibited a far thicker peripheral rim of partially hyalinized, Sudan-free tissue and great masses of extracellular lipid in its base and central portion. Areas of rarefaction in the latter area were almost always observed.

The 2 venous and aortic plaques obtained from rabbits 2 months after cessation of the high cholesterol feeding (or 5 months after induction of the thrombus) showed far less intense Sudanophilia staining. The venous plaques had become smaller, and the usually observed central cellular tissue had shrunk and was partially replaced by dense connective tissue. The aortic plaques too had shrunk somewhat and the central area of the plaque was almost completely replaced by fibrous, hyaline tissue still containing diffusely, but not densely, deposited Sudanophilic materials.

The 3 venous and aortic plaques that had been *in situ* for 8 months (or an additional 5 months after cessation of high cholesterol feeding) showed marked loss of Sudanophilia and diminution in size. Two of the venous plaques had practically disappeared (Fig. 13) to be replaced by rather vague, relatively Sudan-free connective tissue fibres with some hyalinization. The remaining venous plaque showed a small amount of Sudanophilic tissue in a small whorl-like mass of connective tissue. Although each of the 3 aortic plaques showed at least a trace of the dye, its concentration was strikingly less (Fig. 14) than that seen in the plaques of animals killed 3 months after thrombus induction and at the height of their diet induced hypercholesteraemia. The central, semi-cellular, frequently partially necrotic mass earlier observed in the aortic plaques had now been replaced by dense fibrous tissue.

TABLE.—*Comparison of Some of the Characteristics of Venous and Aortic Thromboatherosclerotic Plaques*

Number of rabbits		Average serum cholesterol (mg./100 ml.)	Cholesterol content (g./100 g.)		Aortic plaques					Venous plaques				
			Aorta	Vein	Wt. (dry) (g.)	Number with Sudan	Number with haemorrhage	Cholesterol content (g./100 g.)	Plaque/aorta cholesterol ratio	Wt. (dry) (g.)	Number with Sudan	Number with haemorrhage	Cholesterol content (g./100 g.)	Plaque/vein cholesterol ratio
	A. *One month after insertion of spiral*													
10		194*	0·45	..	0·016	10	4	2·41	5·3	0·010	7	0	1·73	..
	Range:	(129–240)	(0·36–0·51)	..	(0·010–0·020)			(1·44–3·81)		(0·008–0·012)			(1·57–2·10)	
	S.E. of mean:	±11·2	±0·143	..	±0·001			±0·254		±0·001			±0·127	
	B. *Two months after insertion of spiral*													
9		483*	1·20	0·62	0·018	9	3	5·60	4·7	0·006	7	0	3·85	6·2
	Mean:	(195–839)	(0·40–4·24)	(0·39–0·94)	(0·008–0·038)			(3·51–12·42)		(0·004–0·009)			(2·46–10·12)	
	S.E. of mean:	±12·4	±0·295	±0·07	±0·001			±1·16		±0·001			±0·82	
	C. *Three months after insertion of spiral*													
6		956*	2·52	1·64	0·014	6	0	19·61	7·8	0·008	6	0	11·71	7·1
	Range:	(702·1427)	(1·24–3·29)	(1·03–2·27)	(0·005–0·033)			(15·18–25·32)		(0·003–0·015)			(6·36–17·62)	
	S.E. of mean:	±32·49	±0·10	±0·21	±0·001			±1·65		±0 ·001			±1·42	
	D. *Five months after insertion of spiral*													
2		223†	2·27	1·70	0·015	2	0	10·91	4·8	0·004	2	0	9·39	5·5
	Range:	(280–366)	(0.74–3·8)	(0·75–2·64)	(0·013–0·016)			(5·72–16·1)		(0·002–0·005)			(7·23–11·55)	
	E. *Eight months after insertion of spiral*													
3		45‡	1·52	0·49	0·006	3	0	4·70	3·1	0·003	1	0	1·84	3·7
	Range:	(42–50)	(1·14–2·04)	(0·35–0·68)	(0·003–0·008)			(2·71–7·37)		(0·002–0·003)			(1·70–1·99)	

* Average serum cholesterol calculated as mean of initial and terminal levels of serum cholesterol.
† Average serum cholesterol calculated as mean of serum cholesterol levels at 3 and 5 months respectively.
‡ Serum cholesterol level at time of death. These animals, however, had been observed to have a normo-cholesteremic level when bled 3 months earlier.

Description of changes in cholesterol content.—As the Table demonstrates, both venous and aortic plaques of only one month's duration contained far more cholesterol than respective venous and aortic segments adjacent to the plaque areas. In short, such plaques had become atherosclerotic (*i.e.* exhibiting Sudanophilia and cholesterol deposit in the hyperplastic intimal mass) even though the average serum cholesterol (Table) of the rabbits was not above that commonly found in man. Moreover, as the period of hypercholesteraemia continued, each type of plaque continued to accumulate cholesterol so that at the end of the 3 months period of feeding cholesterol, relatively tremendous amounts of cholesterol were found in both types of plaques. Five months following the cessation of the cholesterol diet, however, both varieties of plaques were found to have lost relatively large amounts of cholesterol.

It was of interest, however, that although the venous plaques were considerably smaller than their aortic counterparts, both during and after the hypercholesteraemic period, nevertheless, their cholesterol content per gram of dry tissue was found (Table) to be not much less than that of the aortic plaques during and for a time after the feeding of excess cholesterol. This quantitative similarity confirms that which we previously pointed out (Friedman and Byers, 1961)—namely, that the cholesterol sequestration found in the aortic plaque could not be due solely to haemorrhage since no haemorrhage ever appears to occur in venous plaques.

B. *Permeability of blood vessels of venous and arterial thrombosclerotic plaques to Evans blue dye and colloidal iron*

When the 22 rabbits that had received an injection of Evans blue dye were autopsied, considerable difference was observed in the effect of such injection upon venous and aortic plaques. Thus, none of the venous plaques ever exhibited extravasation of the dye in the central and lateral basal portions of the plaque lying immediately upon the media (Fig. 5), whereas 20 of the 22 aortic plaques showed a dense accumulation in these areas (Fig. 5). On the other hand, 9 of the 22 venous plaques displayed a diffuse condensation of the dye throughout its central and peripheral portions—a phenomenon seen in only 2 of the 22 aortic plaques. In other words, excess dye appeared to accumulate only at the base of the aortic plaques but in the central and peripheral portions of the venous plaques.

The findings at autopsy of the rabbits injected with colloidal iron were in some respects similar and in others, in contrast to the findings following injection of Evans blue. On gross inspection, 14 of the 23 venous plaques of 28 days of age showed iron deposition which usually (12 instances) was just beneath the surface of the peripheral intimal tissue (Fig. 6) or distributed diffusely through the plaques. But significant basal deposition was observed in only 3 of the 23 plaques. Twenty of the 23 aortic plaques of these same animals also revealed grossly discerned deposits of iron. Although this iron was most often observed in the basal areas of the plaques (16 instances), it also was observed in 11 instances to be deposited immediately below the peripheral intimal tissue (Fig. 6).

Microscopic examination of 20 sets of these plaques in general confirmed the gross observations. Thus, iron accumulation was observed in 19 of the venous and in an equal number of aortic plaques. Iron particles tended to be more diffusely distributed (14 instances) in the central and superficial aspects of the

venous plaques (Fig. 15) although it was not unusual to find some iron at the base of the plaque (5 instances) and even in the adventitial area (4 instances). In the aortic plaques, iron tended to be chiefly accumulated (Fig. 8) in the basal areas, but it was also quite frequently found (11 instances) upon and just beneath the peripheral intimal tissue encircling the thrombus (Fig. 7).

DISCUSSION

In an earlier study (Friedman and Byers, 1961) we found that the new adventitia-derived capillaries accompanying the arterial hyperplastic intimal tissue responding to the deposition of an experimentally induced thrombus exhibited profound " leaking " of triglyceride and cholesterol moieties. These latter substances spilled in abundance, then were sequestered in part by their intracellular ingestion by hyperplastic intimal cells. This then appeared to be the mechanism by which the thrombosclerotic plaque quickly evolved into a thromboatherosclerotic one. The cholesterol deposit found in such plaques then arose from a transmedial, not a transintimal source of blood.

The present studies suggest that essentially the same mechanism is in play to account for the lipid and cholesterol deposition found in the venous thromboatherosclerotic plaque. For just as the new capillary of the arterial plaque was found to be abnormally permeable, so too was the capillary of the venous plaque ; and just as the arterial hyperplastic intimal cell was found to be phagocytic, so again was the analogous type of venous cell. Unlike the arterial thromboatherosclerotic plaque, however, the venous plaque never exhibited haemorrhage. Perhaps it is the occurrence of this latter phenomenon in the arterial plaque that accounts for the frequent and sometimes massive extracellular deposition of lipid. The absence of such excessive haemorrhagic escape of lipid in the venous plaque perhaps allows the orderly, almost exclusive, intracellular ingestion and retention of that excess lipid which may have escaped from a vessel not fragmented but only abnormally permeable.

The presence, however, of almost as much lipid (as judged by intensity of Sudanophilia) and cholesterol in the venous as in the arterial thromboatherosclerotic plaque spelled out plainly enough that extensive deposition of these substances could occur with just simple " leaking " of the new capillaries. In short, haemorrhage did not appear to be the *sine qua non* of the mechanism responsible for excess lipid and cholesterol deposition in thromboatherosclerotic plaques of either type.

If the hyperplastic intima and capillaries of the venous plaque exhibited these properties in common with their arterial counterparts, nevertheless, the arterial plaque differed quite markedly from the venous one. The arterial plaque from the very first appeared tougher and larger. On microscopic examination also, the fibrous and hyaline transformation of the new aortic intimal tissue covering the original thrombus appeared far more developed than that seen in the venous plaque. The latter, both upon gross and microscopic examination, resembled a polyp far more than it did a scar. The marked difference in the calibre and distribution of the blood vessels in these respective types of plaques we believe was responsible for the differences noted at the site of dye extravasation. Finally, regression of the venous plaque was far more marked than that observed in the aortic plaque.

The cause(s) of the differences in response on the part of the inferior vena cava and the aorta to an induced thrombus remain to be determined. Possibly they stemmed from the gaseous and pressure differences existing in the blood flowing in veins and arteries ; possibly they were the result of intrinsically determined differences in tissue response. It is of considerable interest to us, however, that irrespective of these differences and also irrespective of the rare spontaneous involvement of the inferior vena cava by any atherosclerotic process in the cholesterol fed rabbit, nevertheless, the venous intimal response to a thrombus was almost as lipid and cholesterol-laden as that of the arterial intima.

SUMMARY

Experimental thromboatherosclerosis was produced in segments of the inferior vena cava and abdominal aorta of the same rabbit by initial induction of a thrombus followed by feeding of excess lipid.

The venous plaque differed from the arterial plaque in (*a*) the calibre and distribution of its vasculature, (*b*) absence of haemorrhage, (*c*) exclusive intracellular deposition of lipid, (*d*) its smaller size, (*e*) the comparative scarcity of fibrous and hyaline changes in the newly developed intimal tissue, and (*f*) its more rapid rate of regression with loss of lipid and cholesterol following cessation of cholesterol feeding.

The venous plaque resembled, however, the aortic plaque in (*a*) the early ingrowth of hyperplastic intimal tissue into and about the thrombus with disorganization of the media subjacent to the thrombus, (*b*) the presence of phagocytic intimal cells, and (*c*) excessive permeability to or " leaking " of lipid from the newly formed capillary vessels accompanying the hyperplastic intimal tissue.

The role of excessive capillary permeability and intimal phagocytosis in the accumulation of lipid and cholesterol in these plaques is discussed.

We wish to express our thanks to Burroughs Wellcome and Company for underwriting the cost of colour reproductions published with this study and we gratefully acknowledge the technical assistance of Clarence Omoto, Warren Hayashi and Betty Tsai Wang.

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