Focal Lipid Lesions in Blood Vessels due to Erythrocytes and Platelets

Experimental Observations on Goats and Rabbits
By P. J. Barnard, M.D., and D. H. Thompson, F.R.C.S. (Eng.)

In 1946 and subsequently, Duguid presented evidence derived from human material that thrombosis might cause, not merely complicate, atherosclerosis. This was an independent revival of Rokitansky’s original Auflagerung (incrustation) hypothesis. Duguid considered erythrocytes a source of lipid in atherosclerosis. In 1936, Clark and associates had suggested that atherosclerosis arose by deposition of fibrin-staining masses from the bloodstream, but this aroused little interest at the time. Corroboration of Duguid’s hypothesis, also on human material, has not been wanting, but support from animal work was not obtained when fibrin or blood clot was used. In 1962, Hand and Chandler found that thrombi, as distinct from fibrin and blood clot, evoked lesions containing lipid in the pulmonary arteries of rabbits. Friedman and Byers were unable to confirm this but found instead that thrombi in arteries of rabbits induced lesions resembling human atherosclerosis only in the presence of hypercholesterolemia.

Experiments on goats and rabbits, planned to gather further evidence on the lipogenic effects of blood corpuscles on the vascular system, will be described herein. Several blood constituents were separately introduced either into isolated segments of systemic vessels or into the pulmonary arteries or into both. The constituents used were whole blood clot, plasma, a concentrate of platelets in saline, packed erythrocytes, red cell sludge, and thrombi. By “sludge” is meant the stroma and envelopes remaining after washed erythrocytes had been hemolyzed and the free pigment largely removed. Thrombi consist mainly of platelets aggregated in flowing blood. They have an orderly structure of platelet columns thinly ensheathed by fibrin. Spaces between the columns are occupied by neutrophils and erythrocytes. Clots, by contrast, form in stagnant blood, and consist of a fibrin-mesh containing large numbers of rather evenly distributed erythrocytes. The number of platelets present in clots are few compared to thrombi. Sludge was used because it was thought that by this means red cell lipid, in a concentrated form, would be presented to the vascular intima.

Methods

Segments of the common carotid artery and jugular vein on the same side, each segment 2 to 3 cm long, were isolated between silk ligatures in goats, but only the jugular veins were used in rabbits. Branches were ligated. Full-grown goats and rabbits of mixed breeds and both sexes were employed for experiments using vascular segments, and for the embolic experiments. The number of animals in each experiment, its duration, and the blood preparation used are summarized in table 1 for vascular segments and table 2 for embolic material.

Vascular Segments Used (Table 1)

Goats (Experiments 1 to 8)

Experiment 1. After ligation, the segments were emptied by syringe and washed out with normal saline solution. This was done to assess damage from ligation alone.

Experiment 2. Arterial ligation was begun distally and venous ligation proximally to obtain segments distended with blood. It was thought the blood might stay fluid and so permit evaluation of the effect of stagnant but unclotted blood of vessel walls.

Experiment 3. A thrombin solution was injected into ligated segments that were full of blood, as

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in experiment 2, to ensure clotting, so that the effect of whole blood clot could be studied.

**Experiment 4.** Autogenous plasma was injected into segments that had been washed out with normal saline.

**Experiment 5.** Platelets concentrated as described by Weissbach\textsuperscript{17} and suspended in normal saline were injected into washed segments.

**Experiment 6.** Theuffy coat was removed from centrifuged heparinized blood, and the erythrocytes were washed three times in normal saline. Each animal's own packed erythrocytes were then introduced into segments previously washed out with saline.

**Experiment 7.** Empty vascular segments were filled with red cell sludge, made as follows: The plasma anduffy coat were removed from heparinized blood, after which the erythrocytes were washed three times in normal saline. The packed cells were frozen and thawed repeatedly to complete hemolysis, the resulting sludge being washed twice with normal saline to remove most of the free hemoglobin. Four goats received autogenous sludge, one received sludge from another goat, and the rest, sludge from human blood.

**Experiment 8.** Thrombi were prepared by the method of Hand and Chandler,\textsuperscript{14} except that blood was withdrawn into disposable plastic syringes from whence it was dispensed in 1.0-ml amounts into polythene tubes of the requisite size. Each thrombus was 2 mm in diameter and about 5 mm long. Thrombi were introduced into empty segments of the jugular veins through slits made in their walls, each slit being excluded when the final ligature was placed. For introduction into empty carotid segments, thrombi were chopped up fine with a safety razor blade; 0.2 ml of saline was added, and the whole was drawn up into a Luer-type syringe. The nozzle was inserted through a slit in the arterial wall, the contents were injected, and the mural wound excluded by ligature.

**Rabbits (Experiments 9 and 10)**

**Experiment 9.** Human red cell sludge was introduced into isolated segments of jugular veins in rabbits.

**Experiment 10.** Autogenous thrombi prepared as for goats were isolated in segments of the jugular veins of rabbits.

**Pulmonary Emboli (Table 2)**

**Goats (Experiment 11) and Rabbits**

*(Experiments 12 and 13)*

**Experiment 11.** Twenty autogenous thrombi were loaded into plastic tubing of the same caliber as that in which they were prepared, and with use of saline, were injected via slits made in the jugular veins of goats. A week later a further similar dose was given. Thrombi were dipped

### Table 1

<table>
<thead>
<tr>
<th>Segments of Carotid Arteries (C) and Jugular Veins (J) of Goats (G) and Rabbits (R)</th>
<th>C No.</th>
<th>G No.</th>
<th>J No.</th>
<th>Empty</th>
<th>Blood</th>
<th>Clot</th>
<th>Plasma</th>
<th>Platelets</th>
<th>Erythrocytes</th>
<th>Sludge</th>
<th>Thrombi</th>
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Table 2

Pulmonary Embolic Experiments on Goats (G) and Rabbits (R)

<table>
<thead>
<tr>
<th>Experiment</th>
<th>G or R</th>
<th>Type of emboli</th>
<th>Time elapsed at killing, weeks; no. of animals for each lapse of time</th>
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<tbody>
<tr>
<td>11</td>
<td>G</td>
<td>Thrombi</td>
<td>2 2 1 2 1 1 1 1 1 10</td>
</tr>
<tr>
<td>12</td>
<td>R</td>
<td>Sludge</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>R</td>
<td>Thrombi</td>
<td>3 2 3 3 3 3 1 1 18</td>
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into decolorizing charcoal suspended in normal saline to facilitate subsequent identification of lesions in the lungs, in those animals which were to live longer than 3 weeks.

Experiment 12. Red cell sludge from human blood was injected into the marginal ear veins of rabbits. Daily injections of 0.6 ml were given to each animal for 21 days. The lungs were examined 7 days after the final injection. Preliminary trials on five rabbits had shown that sludge was arrested in capillaries, arterioles, and small muscular arteries, and that sludge did not persist in the lungs for longer than 30 minutes.

Experiment 13. Three autogenous thrombi were injected via the jugular veins of each rabbit, and the lungs subsequently examined (table 2). For animals intended to live longer than 3 weeks, thrombi were predipped in a saline suspension of charcoal.

Additional Methods

Goats were anesthetized intravenously with atropine and pentobarbital sodium; rabbits, with the barbiturate only. None of the animals were given dietary supplements of lipid. Aseptic precautions were observed. In experiments with thrombi, fragments were removed and examined microscopically to confirm that platelet aggregates were present. When fixed, the lungs were cut into slices about 2 mm thick and examined with a magnifying glass to help recognize lesions. Sections were stained with hematoxylin and eosin, by the Weigert-van Gieson method and by the Perls method for iron. Frozen sections were stained with Sudan black B and a mixture of Sudan III and IV, and for cholesterol and its ester, the Schultz method was applied.18 The amount of lipid found in any lesion with the stains used here, was scored arbitrarily from 0 to ++ +, as was the concentration of foamy cells (lipophages).

Ten normal goats and 10 rabbits, living on the same foodstuffs as the experimental animals served as controls.

Results

Vascular Segments Used (Table 1)

Goats (Experiments 1 to 8)

Experiment 1. In this experiment empty jugular and carotid segments had been prepared. One arterial and two venous segments had remained empty. In these there was slight circumferential intimal fibrosis. There was no stainable lipid. Lumina of the other segments contained organizing intimal fibrosis. There were deposits of hemosiderin, and collagen had formed. Sudanophilic material had accumulated mostly within macrophages (lipophages). These lipophages reacted less strongly to the Schultz method, and this suggested a smaller content of cholesterol than of sudanophilic material.

Experiment 2. Jugular and carotid segments had been ligated when full of blood in this experiment. In none had the blood remained fluid. The changes found resembled those of the next experiment.

Experiment 3. Carotid and jugular segments in which clotting had been assured by injection of thrombin displayed well-advanced organization, with recanalization of variable extent, and transmural vascularization. There were deposits of hemosiderin, and collagen had formed. Sudanophilic material had accumulated mostly within macrophages (lipophages). These lipophages reacted less strongly to the Schultz method, and this suggested a smaller content of cholesterol than of sudanophilic material.

Experiment 4. Two carotid segments filled with plasma exhibited organization extending some distance into the plasma, but there was no significant sudanophilia. The rest contained organizing blood derived from transmural capillaries and resembled the lesions of experiment 3.

Experiment 5. Of segments filled with platelet-rich saline, two veins showed slight circumferential intimal fibrosis as in experiment 1. There was only a trace amount of sudanophilic material. The other segments contained organizing blood clot.

Experiment 6. The segments of this experiment, which had received packed red cells, again resembled those of experiment 3.
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except that production of hemosiderin was greater, sudanophilia was more pronounced, and Schultz-positive material was present in greater amount. There was no lipid in lesions 6 weeks old or older.

Experiment 7. Segments filled with sludge suffered changes like those filled with packed cells, except that there was more sudanophilia, scored as +++ instead of ++, and Schultz-positive material, scored as + in place of the + for packed cells. This applied to lesions 2 and 3 weeks old. Two further lesions containing lipid were found at 6 weeks, but none thereafter. In these two lesions lipophages were more compactly aggregated than in those 3 weeks old. The remaining segments exhibited intimal fibrosis or canalized lumina only.

Experiment 8. With regard to production of lipid, the lesions resulting in segments filled with thrombi differed in no histological essential from those attributable to sludge (fig. 1). Hemosiderin, however, was negligible in amount as was expected from the far smaller red cell content of thrombi. Thrombi, like sludge, either shrank in size and became covered with endothelium, to create eccentric intimal lesions, or they underwent canalization. Segments examined after 1 and 3 weeks (4 in all) contained macrophages loaded with engulfed platelets and lipid. Vacuolated or multinucleated lipophages were common. Similar cells were found in lesions due to packed red cells or sludge. There were compact lipophage collections in two of four segments harboring thrombi 6 weeks old. The remaining segments, as for sludge, exhibited intimal fibrosis and recanalized lumina only.

Rabbits (Experiments 9 and 10)

Experiment 9. Sludge isolated within the jugular veins of rabbits underwent the same changes as those in the similar experiment (no. 7) on goats (fig. 2). Only one lipophage-containing lesion was found after 3 weeks, from a segment 8 weeks after the introduction of sludge.

Experiment 10. Thrombi isolated within the jugular veins of rabbits were transformed like those of experiment 8 on the goat (figs. 3 and 4).

Pulmonary Emboli (Table 2)

Goats (Experiment 11) and Rabbits (Experiments 12 and 13)

Experiment 11. Thromboemboli within the pulmonary arteries of goats underwent the
Figure 3

Jugular vein of a rabbit 4 weeks after filling with thrombi. There is unorganized thrombotic material (A) and accumulations of lipophages (B). Elsewhere (as at C), masses of lipophages are being canalized. Rabbit; experiment 10; Weigert-van Gieson stain; × about 65.

The same fate as those confined to segments of carotid arteries and jugular veins of experiments 8 and 10 (fig. 5). Thrombi 1 and 3 weeks old resembled thrombi of those experiments in that collections of lipophages were prominent. Lesions more than 3 weeks old in goat lungs were hard to find even with the aid of charcoal marking. This was probably because the small emboli used were scattered through a large volume of tissue, even if only the lower lobes, where most emboli impacted, are considered. Though the goats each received 40 thromboemboli, the lesions subsequently identified averaged only a tenth of this number per animal. It is not known whether lesions merely escaped notice, or whether the thrombi had disintegrated without causing visible damage. A similar difficulty was encountered in the thromboembolic experiment on rabbits. Of the 30 lesions older than 3 weeks found in the goat lungs, only four contained aggregated lipophages. Of these, three were 6 weeks old, and one was 12 weeks old. The remaining lesions took the form of eccentric intimal fibroelastosis or fibrosis, or of lipid-free canalized tissues.

Experiment 12. This experiment in which sludge was used repetitively as embolic material elicited no lesions, apparently because sludge was cleared too quickly for pulmonary arteries to suffer any noticeable harm.

Experiment 13. Whole thrombi produced changes in the elastic pulmonary arteries of rabbits no different from those of embolic material.

Figure 4

Detail from figure 3 showing lipophages from region near B; Weigert-van Gieson stain; × about 290.

Figure 5

Elastic pulmonary artery containing a plaque 12 weeks old resting on an intraluminal septum. The pale region represents aggregated lipophages; the dark region, charcoal particles. Goat; experiment 11; Weigert-van Gieson stain; × about 25.
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Figure 6

Elastic pulmonary artery 6 weeks after thromboembolism. The black deposits are charcoal; the rest comprises a collection of lipophages. In this lesion the media is thin and occupied by a focus of lipophages above A. Rabbit; experiment 13; Weigert-van Gieson stain; × about 65.

experiment 11 on goats (fig. 6). At 2 and 3 weeks (two and three animals, respectively), the organization of thromboemboli was again characterized by accumulation of lipophages. At 4 and 6 weeks, compact lipophage collections were found in five lesions, the rest were devoid of lipid. In these last lesions and all others more than 6 weeks of age, only intimal fibrosis and recanalized lumina were encountered.

General Comment on Results

In lesions 3 weeks old or less, lipophages were commonly seen in the medial and adventitial coats. The lipophages were accompanied by small infiltrates of lymphocytes admixed with lesser numbers of neutrophils and a few plasma cells. In lesions older than 3 weeks, however, lipophages were usually confined to the intima or intraluminal septa, leukocytic infiltrates had largely disappeared, and there was variable increase of adventitial fibrous tissue. Aggregates of lipophages did not last longer than 6 weeks except in a few instances in which such aggregates persisted up to 12 weeks. These observations applied to goats as well as to rabbits and whether sludge or thrombi were used. No compact collections of lipophages were seen in lesions due to clots, and those associated with packed erythrocytes were comparatively small. Packed erythrocytes, however, were used only in goats, and the number of experiments carried out were fewer than for sludge and thrombi.

Internal elastic laminae, particularly in lesions beyond the third week, were commonly thickened, split, or reduplicated. At the third week, the media was generally intact except for the presence of lipophages, leukocytic infiltrates, and transmural capillaries. In older lesions, mural capillarization was also common, as was atrophy of smooth muscle, with or without fibrosis, especially opposite eccentric liposclerotic nodules or plaques in veins.

Cross sections of lesions due to thrombi 2 to 3 weeks of age, whether in vessels of the neck or in the lungs, had a distinct yellow tinge, which confirmed the similar observation of Hand and Chandler\(^\text{14}\) with regard to pulmonary arteries.

Discussion

In these experiments on goats and rabbits, packed or hemolyzed red cells and platelets led to accumulations of lipophages in focal lesions of systemic and pulmonary blood vessels. Arteries and veins responded to these cells in a similar way. Erythrocytes and platelets did not stain for lipid in the fresh state, sudanophilia and Schultz-positive lipid appearing only in the presence of organization. Liberation of lipid from erythrocytes and platelets was probably due to phagocytic action since extracellular lipid was scanty. From the heavy staining with Sudan black B, it seemed likely that phosphatide was an important constituent of the lipid,\(^\text{15}\) which was expected since red cells and platelets are known to be rich in fatty substances including phospholipid.\(^\text{14}\) The lipid associated with sludge and thrombi was about equal in amount; it was greater than that from packed

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cells and greater still than that from whole blood clot.

Intraluminal hemorrhage from transmural or luminal capillaries sometimes complicated interpretation of the lesions. Nevertheless, it was concluded that thrombi had the same lipogenic effect as sludge. This statement is founded on the study of lesions, selected for the absence of hemorrhage, and hemosiderin except in small amounts. Friedman and Byers\textsuperscript{15} found no evidence that thrombi were themselves lipogenic, and they suggested that leakage of cholesterol-rich plasma from newly formed vessels in organizing thrombi contributed the lipid.\textsuperscript{16} The lipid-bearing lesions described and illustrated arose in animals not given supplements of fat in any form, nor were arterial lesions found in control animals living on the same diet. That preferential accumulation of noncorpuscular lipid took place as a consequence of intimal reaction is an untenable alternative. Embolic experiments using whole blood clot have not caused persistent lipid-containing lesions, even though this substance elicits intimal organization as great as that associated with thrombi.\textsuperscript{11, 13} It might be argued also that the red cells present in thrombi, and not platelets, were the source of lipid in experiments using thrombi. This is highly improbable since clots, which contain many more erythrocytes than do thrombi, fail to induce lesions containing aggregates of lipophages like those illustrated herein. The amount of available lipid in small clots, compared to packed cells or sludge of similar volume, is presumably insufficient for the purpose. It has been further suggested that though platelets might provide a direct source of lipid, it is also possible that they enhance lipid deposition in arteries by interfering with fat transport and metabolism, since platelets contain an antilipase.\textsuperscript{19}

No assertion is made that atherosclerosis of human type has been reproduced in these goats and rabbits. Much hinges on the meaning of the word “atherosclerosis.” If it means that accumulations of lipid were found embedded in fibrous tissue, then these experimental lesions fit the term. If “atheros” (porridge), the pultaceous matter containing lipid found in advanced lesions, is an essential element of the disease in man, then they do not fit the term. The same applies to cholesterol “clefts,” which were absent from the lesions of these goats and rabbits. These experimental lesions were not progressive or permanent; lipid became concentrated in collections of macrophages which persisted for 12 weeks at the most. Human atherosclerosis is generally regarded as steadily advancing in severity and extent, but there is no proof that this need be so. In these experiments, lipid in corpuscular form was presented on solitary occasions to the vascular intima, a circumstance hardly calculated to promote progressive disease.

The early onset and severity of atherosclerosis in diabetes, nephrosis, and xanthomatosis has been a persuasive argument that extracellular lipid plays the paramount pathogenetic role in atherosclerosis. Though conditions like diabetes mellitus are special instances of disturbed lipid metabolism, lipid disorders are also commonly found in atherosclerosis, not complicated by other diseases. Since atherosclerosis is typically focal, localizing factors must be conceded a place in pathogenesis as much for the thrombogenic as for the metabolic hypothesis. High blood pressure in the systemic circuit and the injurious effects of turbulent blood flow on intima are generally accepted localizing factors.\textsuperscript{19} Metabolic theory holds that lipid is transported into the intima by seepage or by macrophages, or that the lipid is synthesized locally.\textsuperscript{16} It can be postulated that repetitive platelet encrustation on repeatedly damaged areas of intima at sites of turbulence will in time lead to substantial accumulation of fatty material and eventual atherosclerosis. This has the advantage of simplicity over the metabolic hypothesis, in that it explains at the same time, the presence of thrombi and how lipid can be delivered to restricted regions of the intima. Thrombin adsorbed onto the surface of thrombi might also account for clots, where these are present as well. It is pertinent
to recall here that the occlusive masses which "complicate" atherosclerosis are thrombi, not clots.

Much confusion has resulted from the use, without definition, of the word "thrombosis," which has been applied indifferently to clots, aggregates of platelets, and even to deposits of fibrin. Fibrin is not productive of lipid in experimental lesions.\textsuperscript{13} Because, as has been shown herein, red cells are a substantial source of lipid, it is probable that as a constituent of thrombi or in the presence of clots in addition, they add to the total lipid released by intimal reaction because of thrombi. Apart from surface clots, particularly in ulcerated atherosclerotic lesions, hemorrhage from fragile capillaries into plaques is a not uncommon feature of advanced human disease. The cholesterol "cles" of old hematomas elsewhere than in the vascular system are a reminder of the large lipid store in red blood cells.

The thrombi used in these experiments did not provoke lipid-containing lesions of solely nodular type, but this need not militate against their possible participation in atherosclerosis. Atherosclerosis envisages a process whereby nodules or plaques slowly encroach on the lumen. Ultimately a large thrombus produces complete occlusion. The thrombi used in these experiments were big enough to cause occlusion at the start, which can explain the frequency of canalized lumina. Recanalization and hemorrhage from transmural or intimal capillaries are also features of human atherosclerosis, especially when the lesions are thick.

These experiments confirm those of Hand and Chandler\textsuperscript{14} and support the hypothesis that atherosclerosis may be thrombogenic in origin. In other words, thrombosis may cause as well as complicate atherosclerosis. Nevertheless, noncorpuscular lipid and other factors undoubtedly play a prominent part,\textsuperscript{20-22} the complexities of atherosclerosis going beyond what any single hypothesis today can claim. Regardless of how atherosclerosis might arise, were it not for thrombosis, there would be a startling drop in the morbidity and mortality ascribed to this disease. This statement is based on everyday necropsy experience. Elderly persons in Western societies, almost without exception, harbor advanced atherosclerosis, yet most die from unrelated causes. Intensified efforts to elucidate the interrelationship between lipids and thrombosis, rather than atherosclerosis as such, therefore should be made. It has been demonstrated for example that hyperlipemia inhibits thrombolysis.\textsuperscript{23} It has been found also that the risk of thrombosis in atherosclerotic disease can be disclosed and measured by determining the activity of anti-Willebrand factor and factor VIII, and that linolenic acid protect against platelet aggregation.\textsuperscript{24} This latter finding has been confirmed by Kerr and associates,\textsuperscript{25} who also observed that irreversible platelet aggregation occurred in the presence of sphingomyelin and lyssolecithin. The metabolic and thrombogenic hypotheses need not be mutually exclusive, and indeed it might be that corpuscular and noncorpuscular lipids reinforce the effects of another.

**Summary**

Experiments on goats and rabbits living on a normal diet demonstrated that the lipid associated with organizing thrombi became concentrated in fibrosed focal lesions of blood vessels. The lipid that appeared during organization of lysed erythrocytes underwent changes similar to those of lipid in thrombi. From this it was concluded that what red cells there were in the thrombi contributed to the total lipid present. These observations are pertinent to the pathogenesis of atherosclerosis, because they help to explain the thrombosis characteristically associated with this disease, and how lipid can be delivered to restricted regions of the arterial intima.

**References**


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