struction is a feature, a colostomy is necessary. Whether or not it is permissible to apply this method of treatment to a younger patient, with an operable growth, is a question which we are not in a position to answer at present.

SUMMARY

1. A method of treatment of rectal carcinoma by diathermy fulgurization has been described and the limitations of the method indicated.

2. Fourteen patients who showed no evidence of extension of the growth beyond the rectum have been treated and 13 of these followed for periods from a few months up to ten years. In 10 the tumour appears to have been controlled by fulgurization alone; in the 3 others it was necessary to combine radiation therapy with fulgurization and the result was then satisfactory. A permanent colostomy was necessary in two patients.

3. There has been no mortality or serious morbidity attributable to the treatment.

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AN EXPERIMENTAL STUDY OF THE INTIMAL GROUND SUBSTANCE IN ATHEROSCLEROSIS*

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WHEN THE EXTENSIVE STUDIES made on the subject of atherosclerosis are reviewed, it is apparent that only the morphologic features form a basis common to all. These morphologic features are first of all a disturbance in the intercellular ground substance of the arterial intima at points of mechanical stress. Stainable lipids are then deposited in this altered ground substance.[1, 2, 3] Macrophages appear and phagocytose lipid, and capillary sinusoids arising from either the media or the arterial lumen invade the intima and may give rise to intimal hæmorrhage. Finally thrombosis may occlude the artery already narrowed by these processes.

As this earliest morphologic lesion is a disturbance of the intimal ground substance localized by mechanical stress, it seems logical to direct attention to the nature of this stress and then to its effect on ground substance. For this reason I have recently reviewed the physical principles that govern the load upon arteries and correlated them with the sites of atherosclerosis in experimental animals, in the human with vascular anomalies and finally in the common case with atherosclerosis.[4] I have already made a preliminary report of the experiments devised to selectively injure the ground substance at points where this kind of mechanical stress comes into force.[5]

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THE MECHANICAL FACTORS

From my study of the mechanical principles in atherosclerosis I concluded that the factor of importance is the degree of stretching of the artery.[4] Burton[6] has shown that the degree of stretching is related to the following four factors as outlined by Laplace's law: (1) Blood pressure. (2) Surrounding tissue pressure. (3) Radius of artery. (4) Curvature of curved artery. Counteracting this stretching are the structural components of the vessel wall.

EXPERIMENTAL ATHEROSCLEROSIS

The reproduction of atherosclerosis fulfilling the morphologic criteria has centred about increasing either the endogenous or exogenous cholesterol of the experimental animal. In these cholesterol-fed animals the localization of the atherosclerotic lesions may be influenced by the mechanical methods previously described,[4] or by direct injury to the artery such as freezing[7] or cauterizing.[8] These latter methods fail to simulate the circumstances existing physiologically. The same may be said of cholesterol feeding. Although the artery is not interfered with directly, the hypercholesterolæmia and the lipid deposits in the reticulo-endothelial system have no counterpart in man[9] except in such conditions as primary xanthomatosis, nephrosis, myxœdema and diabetes.[10]

Because the primary changes in atherosclerosis are morphologically of the intimal ground substance at points of mechanical stress, I have chosen experimental scurvy as the ideal means of reproducing these conditions. Wolbach[11] demonstrated that scurvy is a disease of the

ground substance, and it has been known for many years that stress localizes the lesions. Experimentally the lesions of scurvy may be localized by the stress of either compression[12] or stretching.[13] The stretching of the arterial wall by the hydrostatic pressure within its lumen is thus a stress suitable for localizing lesions. Where this stress is excessive the lesions will first appear.

Experimental atherosclerosis in scurvy. — The guinea pig is one of the few animals in which scurvy can be produced.[14] This animal is also acceptable for the study of atherosclerosis.[9] A total of 145 guinea pigs was divided with equal distribution of the sexes into the following dietary groups: (1) Chronic scorbutic diet. (2) Chronic scorbutic diet with oral ascorbic acid. (3) Chronic scorbutic diet with cholesterol and oral ascorbic acid. (4) Chronic scorbutic diet with cholesterol and intra-peritoneal ascorbic acid. (5) Acute scorbutic diet. (6) Acute scorbutic diet with oral ascorbic acid. (7) Acute scorbutic diet with cholesterol. (8) Acute scorbutic diet with oral ascorbic acid and cholesterol.

The chronic scorbutic diet consisted of "Baby Rabbit Pellets". The acute scorbutic diet consisted of "Rabbit Pellets". Both these feeds were obtained from Ogilvie Flour Mills, Montreal, and are known to be effective in producing scurvy.[15] I have produced typical lesions of scurvy in the bones and teeth of guinea pigs fed these diets.

Oral ascorbic acid was given in powder form, liberally sprinkled over the pellets. Intra-peritoneal ascorbic acid in a dose of 25 mgm. of "Redoxon" (Hoffmann LaRoche) was given twice a day for the first 19 days, then gradually increased so that by the end of 41 days, the dose was 100 mgm. twice a day.

Cholesterol dissolved in corn oil was impregnated into the pellets to supply about 500 mgm. of cholesterol per animal per day. All animals received vitamin E in the form of 5 mgm. of alpha tocopherol daily, because there is some evidence that it is deficient in this type of diet.[16] Animals dying of infection were excluded from the series.

The guinea pigs were killed at regular intervals over a period of from 12 to 41 days in each of the groups. After a specimen of blood was obtained by cardiac puncture for cholesterol determination, the animals were sacrificed by a blow on the head. The aorta was removed, fixed in 10% formalin and frozen sections from the arch and ascending portion were stained with Scharlach R for lipid. Sections were also obtained from the spleen as a representative of the reticulo-endothelial system.

The deposit of lipid in the arterial intima and the spleen was graded by an arbitrary system of plus signs:

1+: Earliest appearance of lipid.
2+: Moderate stippling of lipid.
3+: Intermediate between 2+ and 4+.
4+: Solid staining with lipid.

Plasma cholesterol levels were determined by a modification of the Liebermann-Burchard method; ten random samples were checked by the Sperry-Schonheimer technique and found to

TABLE I.

SHOWING THE RESULTS OBTAINED IN EACH OF THE DIETARY GROUPS

Diet	*Number of animals*	*Plasma cholesterol range*	*Average plasma cholesterol*	*Fat staining of spleen*	*Number of animals with atherosclerosis*	*Number of animals without atherosclerosis*	*Average degree† of atherosclerosis in those having it*
Chronic scorbutic	20	23 to 120 mgm. %	80.5 mgm. %	0	9	11	2.5+
Chronic scorbutic with oral ascorbic acid	22	26 to 106 mgm. %	53.5 mgm. %	0	0	22	0
Chronic scorbutic with oral ascorbic acid and cholesterol	18	41 to 270 mgm. %	162.0 mgm. %	3+	16	2	2.5+
Chronic scorbutic with intra-peritoneal ascorbic acid and cholesterol	18	85 to 301 mgm. %	179.4 mgm. %	2+	7	11	1.6+
Acute scorbutic	32	17 to 80 mgm. %	42.0 mgm. %	0*	19	13	2+
Acute scorbutic with oral ascorbic acid	16	23 to 77 mgm. %	40.0 mgm. %	0	0	16	0
Acute scorbutic with cholesterol	11	Not done	Not done	3+	11	0	2.6+
Acute scorbutic with oral ascorbic acid and cholesterol	8	Not done	Not done	3+	4	4	2+

*One animal in this group was found to have 1+ fat staining of the spleen. It is omitted in the representation of the figure as it was a solitary finding.

†Average obtained by dividing total of plus signs by the number of animals having lesions.

compare well. The table shows the results in the various dietary groups.

EXPERIMENTAL RESULTS

Acute and chronic scurvy were effective in producing lesions of the arterial intima indistinguishable from the lesions which have been described in early human atherosclerosis.[9] These lesions developed in as little as 15 days from the onset of the scorbutic diet. This represents a very short time when it is recalled that it takes about 12 days to produce ascorbic acid depletion in the guinea pig.[14] The lesions occurred at normal cholesterol levels and were unaccompanied by lipid deposits in the spleen.

Cholesterol feeding resulted in similar lesions with approximately the same rapidity but with hypercholesterolæmia and lipid deposits in the spleen. The combination of scurvy and cholesterol feeding was the most potent method of producing atherosclerosis, being effective in all the animals in which it was tried. Intraperitoneal ascorbic acid prevented the production of atherosclerosis of cholesterol feeding in 11 of 18 animals and the lesions in the remaining 7 were of minimum degree. None of the 38 control animals had atherosclerosis.

Fig. 1 shows a typical atherosclerotic lesion in a scorbutic guinea pig without cholesterol feeding.

COMPLICATIONS OF THE GROUND SUBSTANCE DISTURBANCE IN ATHEROSCLEROSIS

Once the lipid has been deposited in the altered ground substance certain other processes begin.

Intimal hæmorrhage.—Normally the intima receives its nourishment by diffusion from the arterial lumen and from the vasa vasorum which penetrate into the outer two-thirds of the media.[17] In atherosclerosis, dilated capillaries invade the intima from the vasa vasorum[18] and sometimes directly from the main arterial lumen.[19] These capillaries frequently rupture and produce intimal hæmorrhage.

In a recent study of intimal hæmorrhage in the lower limb arteries of 152 routine autopsies[5] the phenomenon was present 157 times in 55 of 123 cases exhibiting grossly visible atherosclerosis of these arteries. It was twice as common in men as in women, and was usually associated with hypertension and old age.

Intimal hæmorrhage may occlude the artery by its bulk[20] or by precipitating thrombosis.[21] It enlarges the plaque in which it occurs and probably propagates the deposition of lipid through a mechanism of further injury.[5] The following factors contribute to rupture of intimal capillaries:

1. The ectatic nature of these capillaries produces a high tension in their walls as calculated by Laplace's law.

2. The inter-endothelial cement of these capillaries is altered in a way similar to the alteration of the ground substance of the atherosclerotic plaque which they invade. They rupture like capillaries in scurvy.

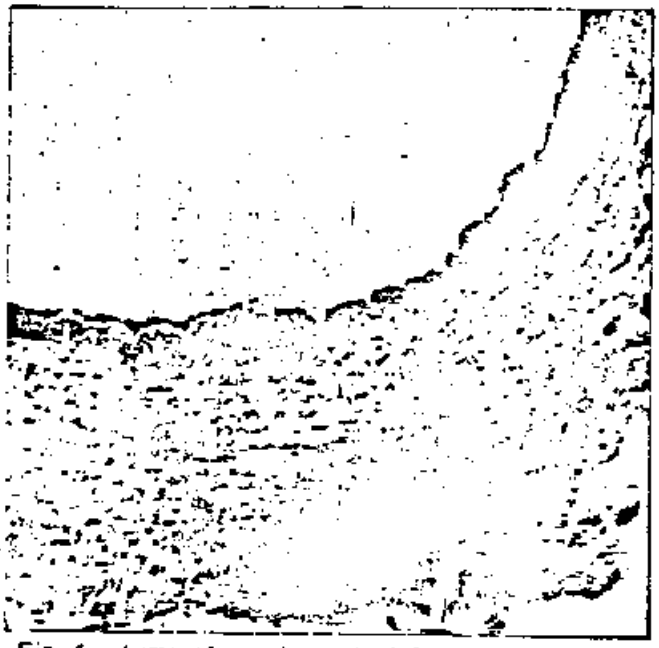

Fig. 1.—Aorta of a guinea pig fed the acute scorbutic diet alone. Note the deposit of stainable lipid filling the intima. This lesion occurred at a normal plasma cholesterol level and was unaccompanied by lipid deposit in the spleen. (Scharlach R.)

3. Those capillaries arising directly from the arterial lumen are exposed to high pressures.

Calcification.—Altered ground substance forms a medium which often calcifies.[22]

Thrombosis.—Chambers and Zweifach[23] demonstrated that injury to vascular endothelium results in the development of a stickiness of the inter-endothelial cement. Samuels and Webster[24] showed that platelets adhere along the lines of inter-endothelial cement when a vessel is injured. From this beginning, a thrombus is formed. In scurvy thrombus formation is common.[14] Aschoff and Koch[25] observed thrombosis of large veins in 33% of their autopsied cases of scurvy, and thrombosis of arteries has been reported in malnutrition.[26] It seems likely that the frequency of thrombosis in atherosclerosis is related to the altered ground substance of the intima and its endothelial lining.

THE RÔLE OF ASCORBIC ACID IN ATHEROSCLEROSIS

Previous studies of the bloodvessels in scurvy.—In human[27] and experimental[28] scurvy fat deposits occur in capillaries and small veins. Koch[29] observed hyaline degeneration and fat deposits in arteries in human scurvy. Widespread atherosclerosis and arterial thrombosis in young people was reported amongst fatal cases of malnutrition in prison camps.[26] Menten and King[30] produced "diffuse hyperplastic atherosclerosis" in scorbutic guinea pigs which had received sublethal doses of diphtheria toxin. The lesion described was medial proliferation. Bailey[31] produced a similar lesion with diphtheria toxin in normal guinea pigs.

The influence of ascorbic acid on the ground substance.—Scurvy is a disease of ascorbic acid deficiency with a resulting disturbance in the ground substance. I have shown that it is effective in producing lesions in guinea pig arteries which are morphologically identical with human atherosclerosis. Intra-peritoneal injection of ascorbic acid usually prevents and always greatly decreases the lesions of experimental cholesterol atherosclerosis. Thus ascorbic acid metabolism seems vital in the pathogenesis of atherosclerosis.

Morphologically the ground substance in scurvy assumes a watery appearance.[31] Chemically it has been shown that the glycoprotein which characterizes the normal ground substance undergoes depolymerization in scurvy.[32] There is a release of glycoprotein into the bloodstream.[33] When ascorbic acid is administered the normal state of the ground substance is quickly restored.[34] An increase in serum glycoprotein occurs under a variety of conditions including myocardial infarction, tumours,[35] infection and trauma.[36] It is noteworthy that ascorbic acid metabolism is disturbed under these and other circumstances including acute and chronic infection,[36] rheumatoid arthritis,[37] the toxæmia of diphtheria,[38] traumatic[39] and hæmorrhagic[40] shock, burns[41] and cold.[42] In one autopsy series[43] 20% of cases showed a condition of latent scurvy by chemical analysis of the tissues. One might speculate that in all these conditions in which ground substance is affected there would be a tendency towards atherosclerosis.

Atherosclerosis and infection.—The aorta was studied histologically for fat staining of the intima in 17 guinea pigs which had died of acute lobar pneumonia. These animals were drawn from the laboratory stock and had received a full diet including greens. They were noticeably sick for 24 to 36 hours and no bacteriological studies were made. Using the system of plus signs previously described for grading the fat staining, it was found that 6 of the 17 animals had some degree of lipid deposit in the intima. One of the lesions was 2+ and the remaining 5 were 1+. No plasma cholesterol determinations were made in this group. The depletion of ascorbic acid which occurs in infections is considered to be important in the deposition of lipid in the aortic intima of these animals.

Atherosclerosis and the thyroid.—Desiccated thyroid has been given to cholesterol-fed rabbits with resulting inhibition of atherosclerosis.[44] I have given 0.1 gm. of desiccated thyroid 3 times a week to 6 guinea pigs receiving the acute scorbutic diet previously described. These animals were fed 0.5 gm. of cholesterol in corn oil each day and a liberal supply of powdered ascorbic acid. Three of the 6 animals died on the 6th day, 2 of them exhibiting fat staining of the intima. The remaining 3 animals were killed on the 15th, 25th and 41st day respectively and all were found to have atherosclerosis. The average degree of lipid deposit was 2+.

In 5 animals fed the acute scorbutic diet alone, desiccated thyroid was given in the same dose as in the previous experiment, starting on the 13th day. In this way the effect of thyroid was studied in the animal just prior to the time of expected ascorbic acid depletion (about 12 days). Fat deposits were noted in the intima of 2 of the 5 scorbutic animals and the average lesions were 3.5+. Thus desiccated thyroid fails to inhibit atherosclerosis of cholesterol feeding or of scurvy in this small series. This might be expected as thyrotoxicosis increases the utilization of ascorbic acid.[45]

Atherosclerosis and cholesterol.—Much emphasis has been placed on cholesterol metabolism in atherosclerosis. Hypercholesterolæmia produces atherosclerosis in animals, but there is some information which suggests that it does so only after a preliminary injury of the intimal ground substance.[46] I have shown in two rabbits that cholesterol feeding produces a relative depletion of ascorbic acid (this animal can synthesize ascorbic acid) as measured by the intradermal dye injection method of Rotter[47] using the modification of Slobody.[48] This effect was also seen in cholesterol-fed guinea pigs receiving

ascorbic acid by mouth. This may possibly be the way in which cholesterol produces ground substance injury under conditions of hypercholesterolæmia. The accumulation of the lipid is probably also related to its overwhelming quantity under these circumstances.

Atherosclerosis and cortisone.—The administration of cortisone to cholesterol-fed rabbits inhibits atherosclerosis.[49] However cortisone fails to prevent or cure scurvy[50] or to decrease the hypersensitivity of the tuberculin test in BCG infected scorbutic guinea pigs.[51] In 5 guinea pigs fed the acute scorbutic diet for 12 days followed by intra-peritoneal injection of 2 mgm. of cortisone twice a day, atherosclerosis developed in 2, the average lesions being 3.5—. The plasma cholesterol levels in a group of 5 animals fed the same diet with 0.5 gm. of cholesterol in corn oil and liberal oral ascorbic acid were higher than in any other group studied. Despite cortisone, all 5 of these animals developed extensive atherosclerosis, the average lesion being 3.5+.

Phospholipid cholesterol ratio.—The ratio of cholesterol to phospholipid has been considered important in the pathogenesis of atherosclerosis. In alloxan diabetes in rabbits fed cholesterol the preservation of a normal phospholipid cholesterol ratio was considered responsible for the inhibition of atherosclerosis.[52] In a personal communication Maddoch[53] reported normal phospholipid cholesterol ratios in scorbutic guinea pigs. It is assumed that the atherosclerotic lesions in scorbutic guinea pigs occur without disturbance of this ratio.

Discussion

I conclude that ascorbic acid is essential for the maintenance of the ground substance of the arterial intima. Any factor disturbing ascorbic acid metabolism either systemically or locally results in ground substance injury with subsequent lipid deposit.

Local ascorbic acid depletion is additive to systemic depletion. Thus although scurvy produced by dietary deficiency of ascorbic acid is a systemic process, its manifestations are first apparent at sites where local stress produces additional depletion. Lesions are localized only at points where the sum of the systemic and local depletion exceeds the critical point necessary for the preservation of the ground substance. Infection of the gums thus produces manifestations of scurvy in the gums. Similarly mechanical stress localizes scorbutic lesions in bones, muscles, attachments of ligaments and in the blood vessels.

Local stress.—The local stress in atherosclerosis is the mechanical stretching of the arterial wall.[4] Just how it causes ascorbic acid depletion is obscure, but it is a factor constantly present to a greater or lesser degree.

There is some evidence that ascorbic acid is important in cell oxidation[55] but this is still not well established.[56] One theory might be that at points of greatest stretching the arterial wall does most work and here cell oxidation is greatest. If ascorbic acid is necessary for cell oxidation, local increased oxidation would be expected to result in local ascorbic acid depletion, and its resulting ground substance disturbance. The arterial wall is capable of respiration[57] and can synthesize[58] and oxidize[59] fatty acids, phospholipids and cholesterol. One objection to this theory is that the lesions are not located in the media where one would expect the most active oxidation to be taking place.

Another idea is that local stress acts in the same way as the stress depicted in the general adaptation syndrome of Selye. Certainly the general adaptation syndrome is accompanied by profound changes in ascorbic acid metabolism,[60] and these may be of a localized nature.

Systemic stress.—Atherosclerosis must not be considered as a disease of dietary ascorbic acid deficiency although it certainly seems to be true that such a dietary deficiency results in lesions identical with atherosclerosis. As previously mentioned, systemic depletion of ascorbic acid may follow the systemic stress of toxæmia, infections, tumours, rheumatic states, trauma, shock and cold. I have shown that cholesterol feeding has a systemic effect on ascorbic acid metabolism and that infection produces atherosclerosis in guinea pigs on a full diet and apparently only sick for a day or two.

Under certain circumstances it may be necessary to provide parenteral ascorbic acid to protect the ground substance.[54] The failure of cortisone to preserve the ground substance in ascorbic acid depletion suggests that ascorbic acid is the intermediary between the adrenal cortex and the ground substance. This idea is supported by the dramatic effect of parenteral ascorbic acid in the inhibition of experimental atherosclerosis of both scurvy and cholesterol feeding.

Summary and Conclusions

1. The mechanical stress important in the localization of atherosclerosis is a stretching of the arterial wall. This is influenced by arterial blood pressure, surrounding tissue pressure, radius of lumen, curvature of artery and arterial fixation.

2. This mechanical stress is counteracted by the components of the arterial wall.

3. This stretching force may be linked with the stress which localizes lesions in scurvy.

4. Ascorbic acid deficiency in guinea pigs produces atherosclerosis regardless of whether the scurvy is acute or chronic.

5. Atherosclerosis of scurvy occurs at normal cholesterol levels and without deposits of lipid in the reticulo-endothelial system. This form of atherosclerosis thus closely simulates the human form of the disease.

6. Intra-peritoneal ascorbic acid greatly inhibits atherosclerosis of cholesterol feeding in guinea pigs.

7. The ground substance disturbance associated with atherosclerosis is of major importance in the pathogenesis of arterial calcification, intimal hæmorrhage and of thrombosis.

8. Cholesterol feeding interferes with ascorbic acid metabolism in rabbits and in guinea pigs receiving oral ascorbic acid.

9. Acute infection in guinea pigs produces minimal atherosclerosis in about 33% of guinea pigs studied.

10. Thyroid and cortisone have no inhibitory effect on the atherosclerosis of cholesterol feeding in guinea pigs in a small series nor do they inhibit the atherosclerosis of scurvy.

11. Massive doses of parenteral ascorbic acid may be of therapeutic value in the treatment of atherosclerosis and the prevention of intimal hæmorrhage and of thrombosis.

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