Atherosclerosis, the lipid-containing intimal lesion with marked fibrosis and calcification, morphologically similar to the human lesion, has been produced consistently in numerous animal species, mostly by feeding diets high in cholesterol and fat, with and without hormonal or other dietary manipulations. However, ulceration and thrombosis, the so-called "complicated" lesions so frequent in human atherosclerosis and so important in leading to morbidity and mortality, have not been predictably reproduced in animals prior to our own studies presented in preliminary fashion in 1958. Spontaneous ulceration of abdominal aorta lesions in old pigeons was described by Clarkson et al. Wakerlin, in 1951, described ulceration and thrombosis occurring in atherosclerotic lesions in hypertensive dogs on a high-cholesterol, high-fat diet with thiouracil. Constantinides, in 1961, produced ulcerated aortic and coronary lesions with thrombosis in rabbits fed a high-cholesterol, high-fat diet for two two-month periods alternating with three-month periods of normal, noncholesterol-containing diets and given high doses of vitamin A, Russell's viper venom, and norepinephrine just before they were sacrificed. The incidence of ulceration and thrombosis in Constantinides' series was rather low. Since our preliminary studies, we have developed a method involving dietary and hormonal modifications which lead to a predictable incidence of ulcerated atherosclerotic lesions. The ulcerated lesions were produced in the abdominal aorta and coronary arteries in cockerels by means of a high-fat, high-cholesterol, low-protein diet, combined with large oral doses of conjugated equine estrogens (Premarin), given during the continuation of the special diet or after the diet was replaced by a normal mash diet.

Methods

Seven series of experiments were carried out (S55, S56, S59a, S61, S62, S63, and S67) totaling 945 chicks. All were Hy-line cockerels obtained from a commercial hatchery and reared in a battery brooder from one day to five weeks of age, at which time they were transferred to regular tiered cages, 10 animals per tier. They were fed commercial chick-starter mash until the experiments were begun. They were placed on the atherogenic regimen from between six and one-half to nine weeks of age. The atherogenic ration in all birds contained 15 per cent protein. The reduction of the protein level from its usual 20 per cent level to 15 per cent was accomplished by substituting sucrose for mash. All series, except S62, received 1 per cent crystalline cholesterol. In S62, the cholesterol was derived from dried egg yolk, calculated to yield 1 per cent of the diet. All birds received 5 to 10 per cent cottonseed oil as the neutral fat, except that in both S61 and S62, one group of birds was fed butter instead of cottonseed oil at the 10 per cent level as the neutral fat. The atherogenic diet was started five to eight weeks before estrogen administration was begun. Estrogens were given as conjugated equine estrogens (Premarin) in the drinking water, at a dose level of 75 mg/bird/day for one to five weeks (table 1). During the period of estrogen treatment, the diet was unchanged in S55, S56, S61, S62, and one group of S59a. In the other group of S59a, the diet during estrogen exhibition was changed to a cholesterol-oil-free diet.
diet at the same low-protein level (15 per cent). In 55 and 56, the protein level was adjusted to 12.5 per cent in one group, and 25 per cent in the other, in order to determine the influence of the level of protein during estrogen administration. The lower level of protein was attained by proper substitution of sucrose for mash, and the high level was reached by adding soy protein (Drackett).

Birds were weighed at the start of the period of inducing lesions before Premarin was given (induction period), at the start of the period of treatment with Premarin (treatment period), and again at sacrifice. Weekly food intakes were recorded. At sacrifice, comb measurements were determined and the —r-r-r- (C/P) ratio was determined according to the method of Sperry and Webb.

The plasma lipid data and the data on the feminizing effect on the comb-index were summarized in table 2. Estrogen-treated birds gained significantly more weight than the controls, despite comparable food intakes. The feminizing effect on the comb-index was evident and more pronounced the longer the period of treatment.

The plasma lipid data and the data on the incidence and time course of the appearance of abdominal aorta ulceration are presented in table 2. Coronary atherosclerosis was evaluated from two frozen sections taken from each of two blocks from each heart and stained with Sudan IV and hematoxylin. The method has been described previously. Coronary involvement was determined by calculating the number of vessels with atheroma as a per cent of all vessels seen. Further examination was made on paraffin-embedded blocks of hearts in those cases in which frozen sections suggested ulcerated coronary lesions.

The incidence and time course of the appearance of abdominal aorta ulceration is presented in figure 1. From this it can be seen that ulcerated abdominal aorta lesions can be produced with some degree of predictability in cockerels. The data show that a prerequisite for ulceration is the induction of atherosclerotic plaques by means of a high-
ULCERATED ATHEROSCLEROTIC LESIONS

Summary of Physiological Data

<table>
<thead>
<tr>
<th>Groups</th>
<th>Therapeutic period, weeks</th>
<th>Sacrifice body weight Gm.</th>
<th>3 Weight* Gm.</th>
<th>Food intake Gm./bird/day</th>
<th>Comb Index†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>1450 ± 20</td>
<td>94 ± 16</td>
<td>105</td>
<td>59.4 ± 4.3</td>
</tr>
<tr>
<td>Estrogen</td>
<td>1</td>
<td>1532 ± 19</td>
<td>127 ± 16</td>
<td>120</td>
<td>46.4 ± 2.3</td>
</tr>
<tr>
<td>Control</td>
<td>2</td>
<td>1501 ± 15</td>
<td>144 ± 9</td>
<td>112</td>
<td>87.4 ± 3.1</td>
</tr>
<tr>
<td>Estrogen</td>
<td>2</td>
<td>1559 ± 18</td>
<td>198 ± 11</td>
<td>111</td>
<td>59.2 ± 2.0</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>1545 ± 18</td>
<td>198 ± 12</td>
<td>102</td>
<td>57.6 ± 2.2</td>
</tr>
<tr>
<td>Estrogen</td>
<td>4 to 5</td>
<td>1635 ± 20</td>
<td>278 ± 14</td>
<td>103</td>
<td>56.7 ± 1.0</td>
</tr>
<tr>
<td>Control</td>
<td>4 to 5</td>
<td>1610 ± 21</td>
<td>264 ± 17</td>
<td>114</td>
<td>77.8 ± 3.8</td>
</tr>
</tbody>
</table>

*Expressed as the weight gain from the onset of estrogen therapy to sacrifice.
†Product of the greatest height and greatest length of comb, each measured in centimeters.

chlesterol, high-fat, low-protein diet, followed later by high doses of estrogen. The source of dietary cholesterol can be crystalline cholesterol or egg yolk, the neutral fat cottonseed oil, or butter. Once the lesions were produced, the development of ulcers was independent of the diet during the period of estrogen treatment, regardless of whether the atherogenic diet was continued or replaced by regular mash diet, or whether the ration at this time was high or low in protein. Therefore, the data are summarized in a single composite tabulation (fig. 1).

MORPHOLOGICAL OBSERVATIONS

Grossly

The ulcerated lesions were found to occur anywhere in the abdominal (muscular) aorta, most frequently in the interrenal region. Sometimes a single ulcer was noted; often there were two or more. The ulcers were always longitudinally oriented. Figure 2 shows the gross appearance of such an aorta. Hemorrhages were frequently seen at the edges of the ulcer and on rare occasions gross dissection was observed (fig. 3). The base of the ulcer is either smooth with a denuded look, or new atheromatous yellow deposits are seen in it. The base can be narrow, slitlike, or can be broad, involving up to 75 per cent of the width of the aorta. The shape of the edge of the ulcer allows a classification into roughly three stages: (1) fresh—when the edge is elevated, undermined, ragged, and sharp; (2) healing—when the edge is elevated, rounded, and adhering to the ulcerated base; and (3) healed—when there is a gradual transition from a rounded edge to a shallow depression of the base. A gradual shading was noted between the healing and healed stages, so that these two stages are combined in the tabulation and evaluation.

Microscopically

The ulceration involves the media as well as the intima. The base of the fresh ulcer shows a clean, smooth surface consisting of a remnant of the media and the external elastic layer. Sometimes this external elastic layer...
FIGURE 2
(Irons appearance of ulcerated abdominal atherosclerotic plaques. Note the ragged overhanging edges, especially in the middle of the three ulcers. The adventitia in the ulcerated area always shows dense fibrous connective tissue and collagen. The edges of the fresh ulcer are overhanging and have fibrin and hemorrhage at their junction with the normal media and intima (fig. 4). The healing lesion is characterized by a rounded edge, somewhat resembling an amputation stump, with fibrous tissue from the bottom and the sides of the ulcer beginning to replace the defect (fig. 5). A further stage of healing is shown in figure 6. In the healed lesion, the surface and fibrous connective tissue replace the media. The direction of the cells is often perpendicular to the normal media (fig. 7). Sometimes healing is accompanied by calciﬁcation near the intima (fig. 8). New atheromata are seen to develop at the site of the ulcer. Figure 10 shows the microscopic appearance of an ulcerated dissecting lesion.

Hypercholesterolemia and Atherogenesis

<table>
<thead>
<tr>
<th>Therapeutic period weeks</th>
<th>Group</th>
<th>Number of birds</th>
<th>Plasma cholesterol mg. per cent</th>
<th>G/P</th>
<th>Coronary atherosclerotic incidence per cent</th>
<th>Per cent involvement</th>
<th>Thoracic aorta lesions incidence per cent</th>
<th>Grade</th>
<th>Abdominal aorta lesions incidence per cent</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ICO</td>
<td>53</td>
<td>1933 ± 93</td>
<td>2.41 ± 0.06</td>
<td>100</td>
<td>25.1 ± 1.7</td>
<td>100</td>
<td>2.59 ± 0.12</td>
<td>89</td>
<td>1.32 ± 0.10</td>
</tr>
<tr>
<td>RM</td>
<td></td>
<td>9</td>
<td>434 ± 60</td>
<td>1.25 ± 0.10</td>
<td>100</td>
<td>32.3 ± 0.6</td>
<td>100</td>
<td>2.76 ± 0.10</td>
<td>91</td>
<td>1.39 ± 0.12</td>
</tr>
<tr>
<td>ICO + estrogen</td>
<td>55</td>
<td>2697 ± 52</td>
<td>0.76 ± 0.04</td>
<td>98</td>
<td>25.2 ± 1.8</td>
<td>100</td>
<td>2.20 ± 0.08</td>
<td>94</td>
<td>1.36 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>RM + estrogen</td>
<td>9</td>
<td>1108 ± 94</td>
<td>0.61 ± 0.04</td>
<td>88</td>
<td>20.0 ± 4.0</td>
<td>100</td>
<td>2.22 ± 0.10</td>
<td>95</td>
<td>1.46 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>ICO + estrogen</td>
<td>153</td>
<td>1582 ± 64</td>
<td>2.21 ± 0.04</td>
<td>100</td>
<td>28.3 ± 0.9</td>
<td>100</td>
<td>2.55 ± 0.07</td>
<td>89</td>
<td>1.40 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>RM + estrogen</td>
<td>9</td>
<td>102 ± 49</td>
<td>4.19 ± 0.02</td>
<td>95</td>
<td>15.2 ± 0.8</td>
<td>100</td>
<td>2.68 ± 0.07</td>
<td>96</td>
<td>1.56 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>ICO + estrogen</td>
<td>167</td>
<td>1705 ± 38</td>
<td>0.83 ± 0.00</td>
<td>95</td>
<td>15.2 ± 0.8</td>
<td>100</td>
<td>2.68 ± 0.07</td>
<td>96</td>
<td>1.56 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>RM + estrogen</td>
<td>9</td>
<td>900 ± 81</td>
<td>0.46 ± 0.04</td>
<td>88</td>
<td>12.7 ± 2.8</td>
<td>99</td>
<td>2.41 ± 0.11</td>
<td>90</td>
<td>1.40 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>ICO + estrogen</td>
<td>142</td>
<td>1633 ± 67</td>
<td>2.30 ± 0.04</td>
<td>100</td>
<td>29.1 ± 1.1</td>
<td>95</td>
<td>2.55 ± 0.07</td>
<td>89</td>
<td>1.40 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>RM + estrogen</td>
<td>9</td>
<td>114 ± 10</td>
<td>0.46 ± 0.02</td>
<td>94</td>
<td>10.5 ± 0.6</td>
<td>99</td>
<td>2.41 ± 0.11</td>
<td>90</td>
<td>1.40 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>ICO + estrogen</td>
<td>156</td>
<td>1846 ± 37</td>
<td>0.60 ± 0.00</td>
<td>94</td>
<td>10.5 ± 0.6</td>
<td>99</td>
<td>2.41 ± 0.11</td>
<td>90</td>
<td>1.40 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>RM + estrogen</td>
<td>9</td>
<td>1010 ± 44</td>
<td>0.26 ± 0.01</td>
<td>78</td>
<td>4.5 ± 1.4</td>
<td>100</td>
<td>2.19 ± 0.11</td>
<td>91</td>
<td>1.59 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>ICO + estrogen</td>
<td>64</td>
<td>1782 ± 112</td>
<td>2.59 ± 0.07</td>
<td>100</td>
<td>31.8 ± 1.2</td>
<td>95</td>
<td>2.55 ± 0.07</td>
<td>89</td>
<td>1.40 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>RM + estrogen</td>
<td>18</td>
<td>120 ± 14</td>
<td>0.50 ± 0.02</td>
<td>94</td>
<td>12.5 ± 1.7</td>
<td>100</td>
<td>2.50 ± 0.10</td>
<td>98</td>
<td>1.81 ± 0.10</td>
<td></td>
</tr>
<tr>
<td>ICO + estrogen</td>
<td>86</td>
<td>1903 ± 59</td>
<td>0.59 ± 0.00</td>
<td>88</td>
<td>6.7 ± 0.7</td>
<td>100</td>
<td>2.50 ± 0.10</td>
<td>98</td>
<td>1.81 ± 0.10</td>
<td></td>
</tr>
<tr>
<td>RM + estrogen</td>
<td>17</td>
<td>875 ± 68</td>
<td>0.26 ± 0.02</td>
<td>82</td>
<td>5.5 ± 1.2</td>
<td>100</td>
<td>2.50 ± 0.10</td>
<td>98</td>
<td>1.81 ± 0.10</td>
<td></td>
</tr>
</tbody>
</table>

*Per cent involvement means per cent of vessels examined which showed lesions.
†In arriving at the mean grade of the group, all vessels were included; negative aortae were listed as zero and the total sum was divided by the number of birds examined.
‡ICO = 1 per cent cholesterol and oil as listed in table 1.
RM = regular mash.
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FIGURE 3
Dissecting aneurysm of the abdominal aorta from an ulcerated atherosclerotic lesion. Note the probe entering the dissection below. The clotted blood in the dissection is seen above through the thin aortic wall.

Thrombosis was observed rarely and inconsistently. Preliminary data indicate that thrombus formation may be slightly more frequent in butter-fed animals. This requires further study.

Ulceration of coronary arteries has also been observed (fig. 11). This occurred most frequently after only one week on estrogen treatment. However, due to the inability to observe the coronary lesions grossly and therefore, to choose proper sites for histological observation, a sequence of events in the coronary arteries comparable to the abdominal aorta was not possible. From table 3, it can be seen, however, that the healing of coronary lesions in all these experiments progressed as described previously.12

PATHOPHYSIOLOGICAL OBSERVATIONS
From figure 1, it can be seen that abdominal aorta ulceration on an atherogenic diet alone is rare. Following estrogen administration, a rather consistent pattern in the development of ulcers emerges. The incidence of ulcers is relatively small (7.8 per cent) after one week on estrogen, and all the ulcers observed were fresh. In the second and third weeks of estrogen therapy, the incidence of ulceration reaches a peak with the healing or healed stages becoming progressively more frequent (second week: 27.8 per cent ulcers—of these 71.4 per cent were fresh and 28.6 per cent healing; third week: 33.9 per cent ulcers—of
Further stage in the healing of an abdominal aorta ulcer. Hematoxylin-eosin. X 70.

these 44.6 per cent were fresh and 55.4 per cent were healing). In the fourth to fifth weeks, few fresh ulcers are found, but the number of healing or healed lesions is at a maximum (37.3 per cent ulcers—of these 12.9 per cent were fresh and 87.1 per cent healing and healed).

Discussion

It would appear from these results that ulceration of atherosclerotic lesions occurs during their healing process, which was initiated in these experiments by the administration of estrogen. In the aorta, this is the first evidence we have had of a healing process attributable to estrogen. It confirms the evidence of others\textsuperscript{13, 14} that estrogens do have an involutionary influence on atherosclerosis of the aorta as well as the coronaries. Fresh ulcers begin to appear within one week, increase in frequency during the second week and then tend to decrease in frequency thereafter. Whether fresh ulcers can occur after the fifth week of estrogen therapy remains to be determined.

The fresh ulcers quickly heal, so that the frequency of healing and healed ulcers in the second week of estrogen therapy approximately equals the number of fresh ulcers in the first week, and the number of such ulcers in the third week is approximately equal to the fresh ulcers in the second week. On this basis, it would appear that all of the healing ulcers in the second week had disappeared by the third week. In the fourth to fifth weeks, the healing and healed ulcers are in excess of the fresh ulcers found in the third week. However, the small number of birds observed in the fourth to fifth weeks makes quantitation at this time less secure. Thus, it would appear that under the conditions of these experiments, the appearance and disappearance of ulceration of atherosclerotic plaques is a matter of weeks.

Ulceration of atherosclerotic plaques is a common occurrence in man. This, together with superimposed thrombosis, transforms the silent vascular process into a manifest disease which approaches almost epidemic proportions in terms of morbidity and mortality.

It is generally accepted that ulceration represents a complication as the disease advances. The view has grown that this complication makes the disease more severe. However, some pathologists follow Meyer,\textsuperscript{15} who concludes that ulceration may well represent a partial (local) attempt at biological healing by the vascular wall. This view is based on a careful and detailed morphological study of human atherosclerosis. Two aspects of the process of ulceration merit further discussion: (1) Why

\textsuperscript{13} Meyer.\textsuperscript{15}
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FIGURE 8
Healed abdominal aorta ulcer. Orcein-van Gieson, X 70. Healing nearly complete with architecture approaching normal.

FIGURE 9
Healed abdominal aorta ulcer. Hematoxylin-eosin. X 170. The site of ulceration consists of newly formed media and atherosclerotic intima with a large calcium deposit (black in microphotograph).

does ulceration occur only in a lesion with a dense, hard, fibrous or hyaline cap overlying the soft atheromatous mass? (2) Why do some ulcers, but by no means all, lead to thrombosis?

Experimental work on this aspect of atherosclerosis is scanty. Besides our work, there are the reports of Wakerlin on the abdominal aortae of dogs, and of Constantinides on the aortae and coronary arteries of rabbits. In our experiments, ulceration occurred predominantly in the abdominal aorta at the site of the usual fibrotic spontaneous lesion which, in the presence of an atherogenic diet, becomes a site of predilection for lipid deposition, as described in our previous communications. Therefore, in our experiments on chicks, the same morphological pattern leading to ulceration is evident as in man and rabbit. In chicks, the ulceration is almost predictably triggered by estrogen administration superimposed on a lesion with a particularly soft core induced by the combination of a low-protein, high-fat, high-cholesterol diet.

How estrogens produce these changes is a matter of speculation at present. From the sequence of events in regression of coronary atherosclerosis, it seems probable that the disappearance of the lipid in the lesions is associated with absorption and transport to the adventitia. If this is true, it might be postulated that this would soften the center of the lesion, allowing the hard shell to crinkle and collapse under the influence of blood pressure and other mechanical factors acting on the vascular intima. However, estrogens are also known to influence the ground substance directly; therefore, the possibility of a mechanism operating via the ground substance cannot be excluded. It is even more likely that a combination of these factors may exist. What is true in the coronary arteries may apply equally to the abdominal aorta. In fact, the evolution is demonstrated better in this vascular bed, histologically. This is evidence that estrogens do have an effect on the atheroma of the aorta similar to that of the lesions in the coronaries.

It is interesting that ulceration does not occur with other types of mushy atheromata, but only in those with a hard cap. Could it be that the hard cap is sluggish in sinking down to fill in the potential space made available by the reabsorption of cholesterol? Perhaps this permits the pulsating stream within the blood vessel to rupture the cap, whereas the presence of a softer cap would permit adjustment to the streaming blood without rupture.

It is quite evident from our data that the
ulcers produced in cockerels are not an end-stage of the atherosclerotic process. Despite continuation of the atherogenic diet, the ulcers heal to form a scar. Microscopically, within the time limit of our study, the healing process produced a transformation of the vascular morphology at the site of the ulceration. But as mentioned above, it appears that an almost normal architecture can be rebuilt in a relatively short time if the ulcer does not penetrate too deeply. The evidence is insufficient to indicate whether or not ulcerated atherosclerotic lesions heal more slowly than nonulcerated lesions. The morphological feature of the healing and healed lesion further indicates that the reparative process proceeds from both edges and from the bottom of the lesion, making the lesion shallower, narrower, and shorter at the same time.

As mentioned before, thrombosis was rarely observed in our birds. Why thrombosis occurs in a given lesion and at a particular time is currently under study in our laboratory. Thrombosis cannot be attributed to speedy endothelialization, since Cotton et al.\textsuperscript{17} found that endothelialization of the intima in dogs occurs slowly over approximately a three-week period. Poole et al.\textsuperscript{18} found an even more protracted process in the rabbit. An ulcer represents something resembling an "open wound" in a vessel, so that the occurrence of thrombosis upon such a defect is not difficult to understand from our knowledge of blood-clot formation. It is, therefore, surprising that so many ulcers do not lead to thrombosis in the chick and man. Newer knowledge, so far still in its infancy, of thrombogenesis and thrombolysis hopefully will help to explain these puzzling problems.

**Conclusion**

Ulceration of atherosclerotic plaques in cockerels, as in man, has been observed only in those lesions showing a particular combination, viz., a dense fibrous cap overlying soft atheromatous deposits with or without necrosis. Pure atheromata without significant fibrosis have not been shown to ulcerate. It is, therefore, suggested that ulceration can occur not only by the progressive expansion of the atheromatous and necrotic mass under the fibrous layer until it ruptures through into the lumen, but also by shrinkage of the atheroma with collapse and rupture of the more rigid overlying tissue as a result of hemodynamic factors associated with the pulsating blood stream.

Our results have established several facts. Ulceration of atherosclerotic lesions is not an end-stage of atherosclerosis but a dynamic process with a distinct healing pattern. The
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appearance and evolution of these ulcers occur rather rapidly over a matter of weeks.

So far, thrombus formation has not been regularly produced in cockerels. Intensive studies of the factors predisposing to thrombosis, as well as of those which prevent its occurrence in the presence of an arterial ulceration before endothelialization develops, are of the utmost clinical importance.

Summary

1. Ulcerated abdominal aorta and coronary lesions have been produced in cockerels.
2. The prerequisite for ulceration is a lesion previously induced by a high-cholesterol, high-fat, low-protein diet, followed by the administration of large doses of estrogens.
3. The possible mechanisms leading to ulceration have been discussed.

Acknowledgment

We gratefully acknowledge the generous supply of cholesterol made available by Dr. E. Alpert of Merck and Company, and cottonseed oil by Mr. E. M. Deck of Anderson, Clayton and Company. Dr. J. B. Jewell, Ayerst Laboratories, generously supplied Premarin.

It is a pleasure to acknowledge the contribution of the technicians of the Institute's atherosclerosis research team: Miss Chizuko Kakita, Mrs. Charlene Thompson, Mrs. Geraldino Black, and Miss Boverley Carmen, Chemistry; Mrs. Dorothy Croom and Mrs. Jean Fogle, Histology; and Mr. William Jones, Physiology; and others.

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Production of Ulcerated Atherosclerotic Lesions in Cockerels
Ruth Pick, Louis N. Katz, Dolores Century and Philip J. Johnson

Circ Res. 1962;11:811-819
doi: 10.1161/01.RES.11.5.811

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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