The Age Factor in Hypercholesteremia and Atheromatosis in the Chick


The development of atherosclerosis in very young chicks challenges the concept that atherogenesis depends upon senescence. Instead, the age period, rather than age, seems to be the more significant factor in atherogenesis. This is so since the regulation of the plasma cholesterol level is shown to vary at different age periods. During the first two months of life of the chick, a resistance to hypercholesteremia and atheromatosis is seen. At the eighth week, corresponding to the time of puberty, the plasma cholesterol rises markedly, despite an unchanged dietary regimen. The resistance to vascular lesions disappears and atheromatosis develops rapidly over the next few weeks. This indicates that endogenous mechanisms dependent upon the age period are important factors in the tendency to hypercholesteremia and atherogenesis.

In an attempt to define the respective roles of age and aging in the susceptibility to hypercholesteremia and atheromatosis, we have recently studied the effect of a high cholesterol diet in the newly hatched chick. The very young chick was used because it was hoped in this way to eliminate as much as possible the effects of the aging process and of injuries to vessel walls which may occur in the course of the life of the animal.

Progressive formation of fibrous connective tissue and modifications of the ground substance of the arterial tree occur with increasing age. These facts have led to the concept that arteriosclerosis is a normal aging process superimposed on these basic changes. With aging of an animal, the arteries are exposed to successive noxious stimuli with consequent additive injury. The production of atheromatosis in very young animals therefore would give evidence concerning the necessity of vascular injury or senile metamorphosis of the vascular tissues as a precondition for the atherosclerotic process.

For these reasons we have attempted to produce atheromatosis by supplementing the diet of newly hatched chicks with cholesterol. In the course of the study, it was found that the age factor played an entirely unexpected role in the regulation of hypercholesterolemia and atherogenesis. A seasonal effect was also noted.

Methods

A total of 381 Hyline cockerels, one day old, were bought from a local distributor on two separate occasions. The first series of 166 chicks arrived in the laboratory Aug. 1, 1949, and was placed immediately on experimental diets. The animals were divided into a control group of 73 chicks which received normal starter mash and an experimental group of 93 chicks which received the same diet supplemented with 2 per cent commercial cholesterol (Armour) and 5 per cent cottonseed oil (diet 2CO). About 7 chicks from each group were sacrificed on arrival, and at 1, 2, 3, 5, 7, 10, 12, 15 and 26 weeks of age.

The second series of 142 chicks used in this experiment was received Feb. 21, 1950, and divided at once into two groups similar to those of the first series. Animals of the second series were sacrificed at 8, 15, and 26 weeks. Some of these birds have been continued on the diets for longer periods. Because of some differences in results between the August and the February experiments, certain data from the two groups will be discussed separately.

Blood was drawn for plasma cholesterol determinations at various intervals or at sacrifice. Chicks were examined postmortem for the presence of gross aortic atheromatosis and organ lipidosis. The general criteria for grading the degree of atheromatosis were those previously described. However, in this series emphasis is placed on the gross grading of the thoracic aorta. The values obtained in the gross grading of the abdominal aorta are not added to the thoracic

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aorta grades as heretofore. The gross specimens of the hearts and aortas were then stained with Sudan IV to bring out occult fatty infiltrations. The spleen, heart, liver and occasional other organs were examined microscopically in frozen sections using Sudan IV, or after fixing, paraffin embedding and staining with hematoxylin-eosin.

RESULTS

Effect of 2CO Diet on Growth in the Newly Hatched Chick

Since there were no significant differences in the rates of growth in the August and the February series, these are treated together. The normal and the 2CO chicks had approximately equal feed intakes and gained weight at approximately the same rate (table 1). These results show that the 2CO supplements had no notable deleterious effect on the growth of the animal.

### TABLE 1.—Weight Gains and Feed Intake in Series 2 for Both 2CO and Control Groups

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>Weight (Gm.)</th>
<th>Feed intake (Gm./week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>2CO</td>
</tr>
<tr>
<td>1</td>
<td>61</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>249</td>
<td>126</td>
</tr>
<tr>
<td>10</td>
<td>869</td>
<td>756</td>
</tr>
<tr>
<td>15</td>
<td>1730</td>
<td>1645</td>
</tr>
<tr>
<td>20</td>
<td>1966</td>
<td>1985</td>
</tr>
</tbody>
</table>

In earlier studies from this laboratory\(^3\)\(^4\) chicks on a diet containing 2 per cent cholesterol and 20 per cent cottonseed oil were shown to be dwarfed. Since the chicks in the present experimental groups also received 2 per cent cholesterol, stunting of growth is probably not due to the cholesterol intake. It is likely therefore that the effect was due to the larger amounts of oil (20 per cent) which had been used in the earlier experiments with the idea of enhancing cholesterol absorption. It is known that raw cottonseed oil contains gossypol, a toxic yellow dye,\(^5\) and it may have been that this compound was present in the oil used in earlier studies.

Plasma Cholesterol Levels at Various Age Periods

When the egg is laid, the egg white is nearly free of cholesterol; the yolk contains a cholesterol content of nearly 2 per cent which serves as building material during embryologic development. Little if any of the cholesterol is degraded during this period.\(^6\) The yolk is enclosed within the abdominal wall shortly before hatching. At this time the plasma cholesterol level is about 300 mg. per 100 cc. Examination within the first few days reveals the remainder of the yolk sac in the process of absorption. The liver is grossly fatty, containing much intra cellular sudanophilic material and numerous cholesterol crystals which are easily demonstrated by polarized light.

Ordinary Mash Diet. Chicks on the ordinary mash diet showed a rapid drop in plasma cholesterol levels from the natal 300 mg. per 100 cc. to an average of 90 mg. within the first week. No significant deviations from this value were observed throughout the 26 weeks of the experiment in this group (table 2).

### TABLE 2.—Plasma Cholesterol Levels (in mg. per 100 cc.) in Chicks on Regular Mash and 2CO Diets

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>Series 1</th>
<th>Series 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>2CO</td>
</tr>
<tr>
<td>0</td>
<td>334</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>98</td>
<td>340</td>
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<tr>
<td>5</td>
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<td>7</td>
<td>76</td>
<td>232</td>
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<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>85</td>
<td>505</td>
</tr>
<tr>
<td>12</td>
<td>91</td>
<td>820</td>
</tr>
<tr>
<td>15</td>
<td>66</td>
<td>872</td>
</tr>
<tr>
<td>20</td>
<td>86</td>
<td>822</td>
</tr>
<tr>
<td>25</td>
<td>95</td>
<td>262</td>
</tr>
</tbody>
</table>

2CO Diet. In contrast to the control group, the August chicks placed on the 2CO diet maintained a plasma cholesterol level at 300 mg. per 100 cc. for the first eight weeks of life (table 2).

At the eighth week of life, despite the fact that there was no change in dietary or other regime, the cholesteremia showed a remarkable spontaneous increase to an average of 800 mg. per 100 cc. The new level was maintained over the course of the next 12 weeks. At about the twenty-second week, with the dietary regime continuing as before, the plasma cholesterol level decreased spontaneously to an average level of 260 mg. per 100 cc.
The February series of chicks behaved similarly to the August series described above except that the cholesteremia for the first seven weeks ranged somewhat higher, about 500 mg. per 100 cc. (fig. 1). The average plasma cholesterol level increased to about 800 mg. per 100 cc. at the ninth week, and to 1460 mg. per 100 cc. at the tenth week. The values then leveled off at an average of about 1000 mg. per 100 cc. (table 2) until about the twenty-fourth week when they fell to an average of 600 mg. per 100 cc. Several chicks maintained high cholesterol values at this time (1000 to 1800 mg. per 100 cc.) but the general tendency was toward a marked reduction (as low as 290 mg. per 100 cc.). A progressively greater number of chicks exhibited lower cholesterol values following the 24 week age period. Some of these chicks have been continued on a 2CO diet for longer periods of time, as previous experiments have suggested that there may be a later endogenous elevation in the plasma cholesterol levels.

The remarkable changes in plasma cholesterol in the cholesterol-fed birds at 8 and at about 22 weeks, despite the unchanged dietary regime, strongly suggest that at these periods in the life of the chick, spontaneous changes occur in the endocrine and metabolic balance to influence the regulation of cholesteremia.

Data from Earlier Studies

Previous studies in this laboratory had shown unexplainable deviations in plasma cholesterol levels at various times during the course of the experimental work. These variations had been considered artefacts or to be due to unknown variations in feeding technic or sometimes attributed to technical error. It appeared advisable to review these data to determine if the unexpected variations could be related to the age of the animal.

Six groups of 2CO chicks with data which could be utilized for the present purpose had previously been studied in the laboratory. At the time of these experiments, we customarily purchased chicks at an approximate age of 3 to 5 weeks. For the purposes of the particular study under analysis at the time, some of the groups were kept in the laboratory for a week or more after arrival before the animals were placed on the 2CO regime. We therefore had available data on animals which were begun on the 2CO diet from 4 to 7 weeks of age.

An analysis of these records showed that regardless of the special experimental conditions being tested, a notable regularity could be seen in the pattern of the plasma cholesterol levels in five of the groups in that a marked rise in cholesteremia was seen at about the eighth week of life (table 3). These regimes, including ingestion of large amounts of thyroid powder or dinitrophenol or removal of the pancreas, had no significant effect on the appearance of the eight week effect. Two groups of 2CO chicks used as controls against these experiments also showed the hypercholesteremic response at about 8 weeks.

The Age Factor in Cholesteremia

In order to confirm and analyze the eight week phenomenon, the effect of the age at which the animals were placed on the 2CO diet was studied in a group of 28 chicks begun in February, 1950. These animals were divided into three groups. One of these groups was started on the 2CO diet at hatching, a second
was begun at 5 weeks, and the third group was placed on the 2CO diet at 7 weeks (fig. 2).

Eight animals placed on the 2CO diet at hatching showed an average plasma cholesterol of 524 mg. per cent at the third week of life and this value was maintained through the seventh week. In the eighth week, the average plasma cholesterol increased spontaneously to 840 mg. per cent; at the tenth week it was 1467 mg. per cent.

Eleven animals maintained on a plain mash diet for the first five weeks of life were begun on the 2CO diet at the fifth week. Within a week, the cholest eremia increased from the control values of about 90 mg. per 100 cc., to an average of 476 mg. per 100 cc.; at the tenth week of age (six weeks feeding) the cholest eremia averaged 1471 mg. per 100 cc.

The third group of 9 chicks was first given a normal mash diet for seven weeks and then placed on the 2CO diet. Within the first week of 2CO feeding the plasma cholesterol had risen to 644 mg. per 100 cc. At the tenth week of age (three weeks feeding) the average plasma cholesterol level was 1481 mg. per 100 cc.

Chicks maintained on normal mash had plasma cholesterols of about 90 mg. per 100 cc. throughout the entire 10 week experimental period.

These results demonstrate clearly that an endogenous change resulting in the upward regulation of the plasma cholesterol level occurs about the eighth week of life in the chick. This effect is independent of previous exposure to cholesterol or of the cholesterol level at 7 weeks. It is interesting to note that the eight week effect is not detected unless a hypercholesteremic stimulus is present, such as in chicks receiving a high cholesterol diet. No notable deviations of the plasma cholesterol level occur in chicks on a normal mash diet. This may account for the inability to evoke a hypercholesteremic response at various age intervals in the rabbit on a low cholesterol diet.3

Some time after the twentieth week, the plasma cholesterol unaccountably falls again (fig. 2). That this is not a permanent fall is indicated by previously published data on experiments carried on for 52 weeks, in which the plasma cholesterol rose again after the temporary reduction at around 20 weeks.

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**Table 3.** Plasma Cholesterol Levels (in mg. per 100 cc.) in Previous Experiments from this Department

<table>
<thead>
<tr>
<th>Regime begun at week</th>
<th>2CO</th>
<th>2CO</th>
<th>2CO dietrophenol</th>
<th>2CO thyroid</th>
<th>2CO pancreatectomy</th>
<th>2CO pancreatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at which observation made</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>496</td>
<td>155</td>
<td>432</td>
<td>246</td>
<td>199</td>
<td>970</td>
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<tr>
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<td>688</td>
<td>185</td>
<td>685</td>
<td>459</td>
<td>1288</td>
<td>1550</td>
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<tr>
<td>12</td>
<td>973</td>
<td>336</td>
<td>526</td>
<td>432</td>
<td>1140</td>
<td>1490</td>
</tr>
<tr>
<td>16</td>
<td>—</td>
<td>629</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>999</td>
<td>—</td>
<td>617</td>
<td>292</td>
<td>—</td>
<td>1815</td>
</tr>
<tr>
<td>21</td>
<td>—</td>
<td>974</td>
<td>—</td>
<td>—</td>
<td>2605</td>
<td>—</td>
</tr>
<tr>
<td>22</td>
<td>420</td>
<td>—</td>
<td>290</td>
<td>436</td>
<td>—</td>
<td>974</td>
</tr>
</tbody>
</table>

---

**Fig. 2.** Plasma cholesterol levels in three groups of baby chicks placed on 2CO diet at varying age periods: (--) were begun on 2CO diet at 1 day of age; (---) were begun at 5 weeks and (--.--.) at 7 weeks. Discussed in text.
Organ Lipidosis and Atheromatosis

Controls. Animals sacrificed on arrival at the laboratory (age 1 to 2 days) showed fatty livers but no arterial lipid infiltrations or atheromatosis, gross or microscopic. The fatty infiltration of the liver gradually disappeared and the liver took on a normal appearance over the course of the first two weeks in the animals on the plain mash diet.

In both the August and February animals receiving a normal mash diet, no thoracic, brachiocephalic or coronary lesions were observed at hatching.

In the grading system given below and in table 4, only the thoracic lesions are considered, since these are dependent upon cholesterol ingestion, while the abdominal lesions of the inter-renal region may occur in the absence of hypercholesteremia. Further, this inter-renal lesion is fundamentally a fibroptic process, with secondary lipid deposition when the animal is on a high cholesterol diet. By contrast, the thoracic lesions appear to be initiated as a result of intimal foam cell proliferation and this effect is closely correlated with cholesterol feeding and hypercholesteremia.

Gross lesions were seen in the abdominal aorta, below the renal arteries, at 12 weeks of age in these control animals. These were minimal lesions occurring in 3 of 15 animals, with an average grading of 0.5. The other 12 animals showed no gross lesions. Microscopic examination revealed the lesions to consist of slight thickenings of the intima with no lipid infiltration.

At 26 weeks, 6 of 15 control birds had abdominal aortic lesions averaging 0.75; moderate intimal thickening but no lipid infiltration was seen.

Cholesterol Enriched Diet (Table 4). In the group of animals begun in August 1949, no gross or microscopic lesions were seen through the time of the tenth week sacrifice. Beginning with the eleventh week, lesions were found in the thoracic aorta and in the brachiocephalic and coronary vessels in 2 of 4 birds. The percentage of animals with thoracic atheroma increased rapidly, and at 15 weeks of age all chicks autopsied were found to have atheromatosis.

The size and stage of development of the atheroma also progressed rapidly during this period, the average grade of the thoracic lesions being reported as 1.1 at 11 to 13 weeks, 2.1 at 15 to 18 weeks and 3.2 at 26 weeks. Despite extensive coronary atherosclerosis with virtual occlusion of many of the vessels, the myocardium showed no histologic damage.

At 26 weeks, large fibrotic plaques with calcium deposits, cartilage and bone formation were noted in the thoracic aorta. Fresh lipid deposits were seen marginally on the edge of these advanced lesions.

The series of animals begun on the 2CO diet in February (table 4) differed from that begun in August in that the cholesteremias were higher during the entire experimental period, and the tendency to atheromatosis was greater.

Most striking was the finding of gross thoracic atheroma graded as 0.9 in 2 chicks which died spontaneously at 5 weeks. Microscopically, several coronary arteries showed slight intimal lipid infiltration. Both brachiocephalic arteries showed large streaks of fatty infiltration in the intima and adjacent media. An interesting finding was marked splenic lipidosis with severe atheromatosis of the splenic arteries in these animals.

From the age of 8 weeks, all autopsied chicks of the February series had gross thoracic lesions and generalized atheromatosis. This became progressively more severe, being graded as 0.9 at 5 weeks, 1.4 at 8 weeks, 2.2 at 15 weeks and 3.6 at 26 weeks.

It can be seen from tables 2 and 4 that the February chicks did not show the resistance
to hypercholesteremia and atheromatosis which was seen during the first 8 weeks of life in the August chicks. The February chicks had earlier and more severe lesions early in life, although by the fifteenth week the degree of the lesions in the two groups was comparable (fig. 1).

These differences occurred despite the fact that the two series of animals were given the same diet at the same age periods. It may be that the summer chick is somehow different from the winter chick.

**Discussion**

Earlier studies from this laboratory demonstrated that the tendency to atherosclerosis may in general be correlated with the degree and duration of cholesterol feeding and therefore with the plasma cholesterol level. However, the present findings make it clear that endogenous factors dependent upon the age period of the animal must also be considered if the tendency to atheromatosis is to be assayed. This effect of age is apparent during at least four periods in the life of the chick.

Thus, the chick lives its entire three weeks of embryonic life in a cholesterol rich environment. At the time of hatching, the plasma cholesterol level is about 300 mg. per cent and cholesterol can be discovered in large amounts in the liver and in other abdominal organs. Yet no atheromatosis or arterial lipid infiltrations are observed at this time. Whether the absence of atheromatosis in the embryo despite hypercholesteremia is due to resistance to this process or to other factors remains to be determined.

The hypercholesteremia seen at hatching falls rapidly to about 90 mg. per cent during the first week of life and remains at this level for the rest of the life of the animal, provided that excess amounts of this sterol are not ingested.

When the newly hatched chick is placed on a diet supplemented with 2 per cent cholesterol and 5 per cent cottonseed oil, a maintained cholesteremia ranging about 300 to 500 mg. per 100 cc. is seen in the course of the next eight weeks. Even the feeding of much higher percentages of cholesterol, done in the course of other experiments, leads to no further increase in the cholesteremia in this age period.

It is during the first two months of life that we observed differences in the two series of experiments which were conducted. In our August series the plasma cholesterol level ranged about 300 mg. for the first two months. Serial studies up to the age of 7 weeks showed no lesions in the aortas or coronary arteries of these chicks. In the February group, however, a somewhat different course was seen in that the plasma cholesterol level ranged about 500 to 600 mg. per cent, and atheroma in the thoracic aorta, as well as in the brachiocephalic and coronary arteries were seen as early as 5 weeks of age. These lesions progressed and were moderately advanced by the time the animals were about 8 weeks of age. These seasonal variations are under further analysis.

At the eighth week of life of the chick, somatic changes manifest themselves in the beginnings of the rapid testicular growth corresponding to early puberty and the secondary rapid growth of the comb and changes in the feather patterns. There is no evidence in the normal chick fed a regular mash diet to suggest that there are any changes in cholesterol regulation. However, in the 2CO animals and in subsequent series receiving as little as 0.25 per cent cholesterol supplementation of the diet a change becomes apparent in a marked hypercholesteremia, levels approximating 1000 mg. per 100 cc. or more within the course of a week or so in the 2CO chicks.

The hypercholesteremia is maintained over the course of the next 12 weeks, a period of rapid somatic and testicular growth. During this period the tendency to atheromatosis increases markedly. This is seen in the fact that within four weeks after onset of 2CO feeding at the age of 8 weeks, the lesions and the plasma cholesterol levels are the same as in those animals receiving a cholesterol enriched diet from the time of hatching. The feeding of cholesterol during the first eight weeks is therefore much less effective in raising the plasma cholesterol level and in the production of atheroma than it is in the succeeding 12 weeks.

The degree of development of the lesions
was of the same order in the animals fed the 2CO diet since the seventh week of life, as in those begun on the diet immediately at hatching or at 5 weeks (table 4). Thus, despite the fact that the lesions began early in the group receiving 2CO since birth, the magnitude of the lesions in all groups was of the same order at the fifteenth week.

The occurrence of intimal proliferation, lipid infiltration and atheroma formation in chicks as young as 5 weeks of age argues strongly against the thesis that the arteriosclerotic process begins only on a site of pre-existing vascular injury or in an aging artery. Inasmuch as the chick may live as long as 20 years it can be seen that the 5 week period is but a very small part of the potential life of the animal. The development of atheromatosis during the second month of life can therefore not be attributed to a senility of the arterial tissues but must be considered as a pathologic process which may occur even in very young and presumably uninjured vessels.

The pathogenic role of increased cholesterol intake and hypercholesteremia is supported by the present results. The onset of the marked hypercholesteremia occurring at 8 weeks, followed by a rapid progression of lesions in the subsequent period further strengthens this argument. However, hypercholesteremia, per se, is not necessarily the only factor in atherogenesis, since the hypercholesteremia of the fetal period does not lead to arterial lipid infiltration and atheromatosis.

Despite the development of coronary lesions with a marked reduction in the lumen of the arteries in the chick, there have been no indications of significant myocardial injury. This protection of the myocardium against ischemia and necrosis may depend on the fact that the young chick myocardium is still capable of the elaboration of new vascular channels.

At the age of about 20 weeks the chick completes its normal growth and a second change in cholesterol balance is observed. The atherosclerotic process is considerably slowed down in its rate, and regression of lesions may occur at later periods in the life of the animal.

Our results clearly demonstrate that hypercholesteremia and atherosclerosis depend to a large extent upon the physiologic age of the animal. During certain periods in the life of the chick there is an increased tendency to hypercholesteremia and atherosclerosis, or perhaps a decreased resistance against this effect.

It is likely that these physiologic tides occur in animals other than the chick. For example, Pollack has published data which suggest that rabbits younger than one year are less susceptible to atherosclerosis than older rabbits.

The comparative infrequency of atherosclerosis in children on high cholesterol diets has been used as an argument against the thesis that cholesterol ingestion predisposes to coronary atherosclerosis. The present results suggest that this age period may be one similar to the prepubertal resistance to atherosclerosis in the chick. A review of the literature of xanthoma tuberosum shows that deaths have occurred in children with this disorder at the age of puberty (ages 10 to 15). Autopsy findings showed coronary atheromatosis. The tendency to xanthomatosis was probably present earlier in life, but did not become manifest in coronary artery disease until the age of puberty. This suggests the presence of mechanisms for the regulation of cholesteremia and atheromatosis in pubescent man similar to those seen in the chick at its pubertal age, 8 weeks.

In the literature, frequent occurrence of atherosclerosis in men in the fourth and fifth decades has been used in support of an aging concept in arteriosclerosis. On the basis of our present studies these results may be interpreted equally well as due to variations in the cholesterol tides depending on a changing endocrine balance, with a consequent decreased resistance to atherogenesis in this age period.

Rather than an aging of tissues, it appears that the physiologic period and the hormonal balance of the individual at a given time determines the tendency to atherosclerosis in the cholesterol-fed animal.

**Summary**

1. The problem of the relation of arterial aging and injury to the development of athero-
matosis was investigated by utilizing newly hatched chicks given a diet supplemented with 2 per cent cholesterol and oil (2CO).

2. Hypercholesteremia occurs in the chick during embryonic life. However, no atheromas were found in newly hatched chicks. This may be dependent on a specific resistance to atherogenesis during the prenatal period.

3. Atheromatosis was produced in the 2CO chick as early as the fifth week of life. These results cast doubt upon the concept that arterial aging and/or injury is a necessary precondition for the development of atherosclerosis.

4. The facility with which hypercholesteremia and atheromatosis developed depended in large part upon the age period of the 2CO chick. Chicks were found to be generally resistant to hypercholesteremia and atherogenesis during the first 8 weeks of life.

5. At about 8 weeks of age, corresponding to early puberty, a spontaneous increase in the plasma cholesterol occurs when the animals are on a cholesterol enriched diet.

6. Atherogenesis proceeds rapidly within the three to four weeks after the spontaneous rise in plasma cholesterol with the development of severe lesions by the twelfth week of life.

7. Spontaneous variations in the regulation of plasma cholesterol are also seen at about the twenty-second week, at the time of sexual maturation.

8. These experiments demonstrate that endogenous factors dependent upon the age period of the animal play a very important role in the regulation of cholesterol and atherogenesis in the cholesterol-fed chick.

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11. unpublished observations.
The Age Factor in Hypercholesteremia and Atheromatosis in the Chick

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