ISSN 1682-8356
ansinet.org/ijps

INTERNATIONAL JOURNAL OF

POULTRY SCIENCE

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International Journal of Poultry Science 3 (11): 671-684, 2004

The Relation Between Diet, Plasma Cholesterol and Atherosclerosis in Pigeons, Quails and Chickens

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Abstract: A literature survey was conducted to determine the relationship between plasma cholesterol concentrations and the severity of diet-induced atherosclerosis in pigeons, quails and chickens. A direct relationship was found between plasma cholesterol and atherosclerosis as induced by cholesterol feeding. In general, dietary polyunsaturated fatty acids versus saturated fatty acids lowered plasma cholesterol concentrations in the three avian species

Key words: Atherosclerosis, cholesterol, diet, pigeons, quails, chickens

Introduction

The composition of the diet is a major determinant of plasma cholesterol concentrations and thus also affects atherogenesis as has been demonstrated in humans and various animal species (Brousseau *et al*., 1995; Consensus Conference, 1985; Grundy, 1986; Kurushima *et al*., 1995; Rudel *et al*., 1990). Avian species such as pigeons, quails and chickens have been widely used as experimental animals in atherosclerosis research. In this paper, we review the effect of dietary cholesterol and fat on plasma cholesterol levels and the development of atherosclerosis in pigeons, quails and chickens.

Experimental avian species

Pigeons: Spontaneous atherosclerosis probably occurs in all breeds of pigeons, but the prevalence varies widely between breeds. White Carneau (WC) pigeons develop atherosclerosis easily without dietary manipulation, while both Show Racer (SR) and Racing Homer (RH) pigeons have a low incidence of atherosclerosis (Lofland, 1965; Prichard, 1965). The most prominent lesions occur at the bifurcation of the thoracic aorta into the celiac axis and abdominal aorta (Lofland, 1965; Prichard, 1965). Microscopically visible lesions can already be observed in birds of one week old (Prichard, 1965). Santerre *et al*. (1972) reported that little difference exists between WC and SR pigeons up to one year of age, but after that the severity of atherosclerosis increased much more in WC pigeons. Grossly visible atherosclerosis appears after 9-12 months in WC pigeons. The incidence increases from 30% at 1 year to 100 % at 3-4 years (Prichard *et al*., 1964). Prichard (1965) reported that in WC pigeons, at 4 years of age, nearly 10% of the thoracic aorta surface in all birds is covered with plaques. The incidence of coronary atherosclerosis is 70% in WC pigeons aged 1 through 12 years. In SR pigeons, the incidence of aortic atherosclerosis is 15% after 7 years (Prichard *et al*., 1964). Feeding cholesterol markedly enhances the rate of development, the severity and the extensiveness of atherosclerosis in pigeons (St. Clair, 1983). The location of cholesterol-induced atherosclerosis is similar to that of spontaneous atherosclerosis (Lofland, 1965).

Quails: Japanese quails are susceptible to both spontaneous and diet-induced atherosclerosis (Shih, 1983). Wexler (1977) reported that both male and female quails develop atherosclerosis at 2 years of age. Atherosclerosis can easily be induced by feeding cholesterol (Morrissey and Donaldson, 1977a; Shih, 1983). However, between the different studies reported in literature a large variation is seen in both time needed to develop atherosclerosis and amount of cholesterol needed. The development time ranges from 10-15 weeks to 9-28 months (Morrissey and Donaldson, 1977a; Ojerio *et al*., 1972; Radcliffe and Liebsch, 1985; Shih, 1983; Shih *et al*., 1983; Smith and Hilker, 1973) and the amount of cholesterol used in the different studies differs from 0.5 to 5.0 % (Hammad *et al*., 1998; Morrissey and Donaldson, 1977a; Ojerio *et al*., 1972; Smith and Hilker, 1973; Toda and Oku, 1995; Wu and Donaldson, 1982). There is also a large inter-individual variation in plasma cholesterol level and development of atherosclerosis in response to dietary cholesterol (Chapman and Day, 1976; Smith and Hilker, 1973). To be able to detect small differences between test and control animals and to reduce the number of animals needed, populations with genetic uniformity have been created (Chapman and Day, 1976). Several lines of either susceptible or resistant quail have been produced in the past through selection on the basis of development of cholesterol-induced atherosclerosis (Bacon *et al*., 1988; Chapman and Day, 1976; Inoue *et al*., 1995; Shih *et al*., 1983). Japanese quail have also been selected for plasma cholesterol response after

injection of adrenocorticotropin. The high response line (HL) has been shown to be susceptible to cholesterol-induced atherosclerosis (Hammad *et al.*, 1998; Siegel *et al.*, 1995). The susceptible quails have a more uniform response to dietary cholesterol and develop atherosclerosis more rapidly with lower levels of dietary cholesterol needed (Inoue *et al.*, 1995; Shih *et al.*, 1983).

Chickens: In 1942, Dauber and Katz (1942) successfully induced atherosclerosis in chickens by feeding diets with 2.5-5.0% cholesterol dissolved in cottonseed oil. Since then, chickens have been used intensively in the investigation of experimental atherosclerosis. Horlick and Katz (1949) found that the first lesions developed within two weeks of feeding 1.0-4.0% cholesterol. Chickens do not only develop cholesterol-induced atherosclerosis, but also spontaneous atherosclerosis. Dauber (1944) reported spontaneous atherosclerosis in chickens examined at a commercial farm. Gross intimal lesions were found in 41-45% of all animals examined. The earliest lesions appeared at 5-6 months of age. Masegi *et al.* (1993) reported spontaneous coronary atherosclerosis in broilers at 60 days of age, while Orita *et al.* (1994) found lesions in the aorta as early as at 30 days of age. In 500-day old layers, the incidence was 45%. Induced lesions resemble the spontaneous ones (Horlick and Katz, 1949).

Dietary cholesterol and plasma cholesterol level: When no cholesterol is added to the diet, plasma cholesterol levels in pigeons range from 5.92 to 13.5 mmol/l (n=51; 8.23 ± 1.80) (Barakat and St. Clair, 1985; Bell *et al.*, 1979; Clarkson *et al.*, 1962; Clarkson and Lofland, 1967; Lofland *et al.*, 1961; Ray and Young, 1978; Young, 1974). In quail, they range from 3.25 to 16.04 mol/l (n=67; 6.64 ± 2.32) (Chamberlain and Belton, 1987; Hammad *et al.*, 1998; McClelland and Shih, 1988; McCormick *et al.*, 1982; Morrissey and Donaldson, 1977ab; Ojerio *et al.*, 1972; Radcliffe and Liebsch, 1985; Siegel *et al.*, 1995; Smith and Hilker, 1973; Toda and Oku, 1995; Wu and Donaldson, 1982; Yuan *et al.*, 1999; Yuan *et al.*, 1997;). In chickens, plasma cholesterol concentrations range from 1.41 to 5.40 mol/l (n=49; 2.88 ± 0.90) (Allen and Wong, 1993; Castillo *et al.*, 1994; Ho, 1976; Horlick and Katz, 1949; Horlick *et al.*, 1949; Moss and Benditt, 1970; Narayan and Calhoun, 1976; Rodbard *et al.*, 1953).

When cholesterol is fed to pigeons, plasma cholesterol increases in both susceptible and resistant strains. Lofland *et al.* (1961) reported a large inter-individual variation in response of plasma cholesterol to dietary cholesterol in WC pigeons. There have been some controversial reports on the effect of strain on plasma cholesterol. Young (1974) reported that feeding a cholesterol-free diet for 6 and 12 weeks resulted in significantly higher plasma cholesterol levels in WC pigeons when compared to SR pigeons. This strain effect was not seen when cholesterol was added to the diet or when the cholesterol-free diet was fed for more than 12 weeks. Patton *et al.* (1975) only found a strain difference when 0.5% cholesterol was added to the diet, but not with the addition of 0.2% cholesterol. WC pigeons had significantly higher plasma cholesterol during the first 12 weeks of feeding 0.5% cholesterol, but the effect was not seen at 14 weeks. On the other hand, some authors have reported that plasma cholesterol levels in resistant strains were higher than in susceptible pigeons. Barakat and St. Clair (1985) found higher levels in resistant pigeons from the first month of feeding throughout the 6 months of the experiment. Ray and Young (1978) found that plasma cholesterol levels in SR pigeons reacted more quickly to dietary cholesterol than that in WC pigeons. During 6 and 9 weeks of feeding, plasma cholesterol levels were higher in SR pigeons. However, at 12 weeks the significant strain difference in plasma cholesterol was reversed, WC pigeons now having higher levels. However, most authors have found no difference between strains of pigeons (Bell *et al.*, 1979; Clarkson and Lofland, 1961; St. Clair, 1983). It appears that the reported strain differences in response to dietary cholesterol are mainly due to an effect of feeding duration.

In quails, different lines have been created through genetic selection. Although the animals were exclusively selected on the basis of the development of atherosclerosis, plasma cholesterol levels in response to dietary cholesterol have also been influenced (Shih *et al.*, 1983). Susceptible quail have higher levels when compared to random-bred animals, whereas resistant animals have lower levels (Chapman and Day, 1976; Hammad *et al.*, 1998; Shih *et al.*, 1983; Siegel *et al.*, 1995; Wu and Donaldson, 1982). There appears to be a lower threshold for the amount of dietary cholesterol that is needed to increase plasma cholesterol levels. Yuan *et al.* (1999) reported that 0.05% dietary cholesterol did not result in an increase in plasma cholesterol, whereas Siegel *et al.* (1995) found no effect of feeding a diet containing 0.1 % cholesterol.

Kakita *et al.* (1972) studied the relation between dietary cholesterol and plasma cholesterol in chickens. It appeared that the increase in plasma cholesterol corresponded with the increments in dietary cholesterol up to 2.0%. When more than 2.0% cholesterol was fed, the authors noticed a drop in plasma cholesterol. They hypothesized that this could be due to liver damage, which would result from the overload of dietary cholesterol.

As mentioned above, not only genetic factors influence the response of plasma cholesterol to dietary cholesterol but also the duration of the experimental period. When a cholesterol-free diet is fed, plasma cholesterol appears to be constant over time in all three

avian species (Barakat and St. Clair, 1985; Horlick and Katz, 1949; Horlick *et al.*, 1949; Morrissey and Donaldson, 1977a; Moss and Benditt, 1970; Ray and Young, 1978; Rodbard *et al.*, 1953; Velleman *et al.*, 1998; Wagner, 1978; Wu and Donaldson, 1982). However, when cholesterol is added to the diet, plasma cholesterol increases over time to eventually reach a plateau when a new steady state in cholesterol metabolism is reached (Horlick and Katz, 1949; Morrissey and Donaldson, 1977a). The effect of feeding period is somewhat variable, depending on the amount of cholesterol fed. Clarkson and Lofland (1967) fed different levels of cholesterol to WC pigeons. They found no difference in plasma cholesterol when either 0 or 0.05% cholesterol was added to the diet. Addition of 0.1% cholesterol caused a significant increase in plasma cholesterol, and plasma cholesterol stayed constant after the initial rise in the first month. When 0.25% cholesterol was added to the diet, plasma cholesterol increased during 9 months. Feeding 0.5% cholesterol resulted in a sharp increase during the first 3 months, after this time plasma cholesterol remained fairly constant. Addition of 1.0% dietary cholesterol caused a similar increase in plasma cholesterol as did 0.5% cholesterol until 9 months, after which plasma cholesterol showed a sharp increase. Wagner and Clarkson (1977) fed 0.5% cholesterol to WC pigeons. They found a rapid incline in plasma cholesterol during the first two months to over 50.3 mmol/l, followed by a small decline at 4 months. After 4 months, plasma cholesterol showed a small increase until it reached a plateau value of approximately 37.7 mmol/l. Patton *et al.* (1975) also reported an increase in plasma cholesterol over time when cholesterol was added to the diet. The increase was clearly visible when 0.5% cholesterol was added to the diet, but not when 0.2% cholesterol was fed.

Morrissey and Donaldson (1977a) fed 1.0% cholesterol to random-bred quail. Plasma cholesterol concentrations reached a maximum level of approximately 62.8 mmol/l within the first month after which there was a small decline in plasma cholesterol to eventually reach a plateau at 6-10 weeks of about 44.3 mmol/l. Shih *et al.* (1983) found that feeding 0.5% cholesterol to SUS quail increased plasma cholesterol during 9 weeks, whereas feeding either 0.25% cholesterol to SUS quail and RES quail or 0.5% to RES quail resulted in a maximum level at 3 weeks, followed by a small decline in plasma cholesterol. The maximum level of plasma cholesterol was 22.3 and 15.9 mmol/l when 0.25% cholesterol was fed to SUS and RES quail, respectively, and 21.6 mmol/l when 0.5% was fed to RES quail. Smith and Hilker (1973) tested the effect of different diets on plasma cholesterol and they found that the effect of the feeding period differed between the experimental treatments. The length of time an experimental diet was fed had a marked effect on plasma cholesterol in some treatments, while other diets showed no consistent pattern. Velleman *et al.* (1998) also reported a significant influence of time on plasma cholesterol in quail. They found an increase in plasma cholesterol in the first two weeks, followed by a decline at 4 weeks, after which a plateau was reached of approximately 37.7 mmol/l.

Katz *et al.* (1958) found that the degree of hyperlipemia paralleled with the percentage and amount of dietary cholesterol intake when 0.25-2% cholesterol was fed in combination with 5.0% cottonseed oil. Horlick and Katz (1949) tested the effect of different levels of dietary cholesterol on plasma cholesterol level. All animals receiving cholesterol showed an immediate and marked increase in plasma cholesterol. Feeding 0.5% cholesterol resulted in a slight tendency to raise plasma cholesterol to a maximum average of 19.4 mmol/l. Addition of 1.0% cholesterol to the diet caused an upward trend in plasma cholesterol for 15 weeks, with a sharp dip to 19.3 mmol/l at 9 weeks. A maximum average value of 64.8 mmol/l was reached. When 2.0% cholesterol was added to the diet a high average of 72.4 mmol/l was reached at 7 weeks, followed by a sharp decline to 25.2 mmol/l at 9 weeks. After that, plasma cholesterol showed a secondary rise to 56.7 mmol/l at the end of the experiment. When 4.0% cholesterol was fed, a maximum of 38.7 mmol/l was reached in 3 weeks and again a steady decline was seen to 26.5 mmol/l at 9 weeks, followed by a rise in plasma cholesterol. When 2.0 or 4.0% cholesterol was added to the diet, the same degree of lipidemia was produced as by feeding 1.0% cholesterol. When compared to feeding 1.0% dietary cholesterol, which showed an upward trend during the experiment, the feeding of 2.0% resulted in a steep initial rise that flattened out. Feeding 4.0% cholesterol also produced also a steep initial rise, followed by a plateau and finally a fall in plasma cholesterol. Jones and Dobrilovic (1969) reported a steep initial rise of plasma cholesterol during the first 5 weeks when cholesterol was added to the diet, and a slight fall in the second 5 weeks.

In summary, it appears that the duration of the experimental period influences the plasma cholesterol level in all three avian species. The effect of time depends on the amount of cholesterol fed. The effect of dietary cholesterol depends on the strain or breed used. We calculated the linear relation between dietary cholesterol and plasma cholesterol for pigeons, quail and chickens. With help of literature data regression formulas have been calculated (Table 1). The linear correlation coefficient for pigeons, quail and chickens is 0.80 (Fig. 1), 0.37 and 0.58, respectively. Strain of animal used and the duration of the experimental period were not included in the regression equations. It appears that there is a direct relation between dietary cholesterol and

Table 1: Regression formulas for the relationships between dietary and plasma cholesterol an plasma cholesterol and atherosclerosis as calculated with literature data on pigeons, quail and chickens

Species	Y	X	Number		R^2	Intercept±SE/ P-value	Slope ± SE/ P-value
			Data points	Experiments			
Pigeon	Aortic atherosclerosis	Plasma cholesterol	42	8	0.29	-0.65±2.6/0.800	0.46±0.11/0.000
	Coronary atherosclerosis	Plasma cholesterol	21	4	0.50	-0.96±1.9/0.622	0.26±0.06/0.000
	Plasma cholesterol	Dietary cholesterol	151	10	0.64	9.0±0.9/0.000	43.5±2.7/0.000
Quail	Atherosclerosis	Plasma cholesterol	95	11	0.46	1.8±3.4/0.605	1.2±0.1/0.000
	Plasma cholesterol	Dietary cholesterol	186	18	0.14	12.9±1.1/0.000	5.6±1.0/0.000
Chicken	Atherosclerosis	Plasma cholesterol	71	15	0.26	16.9±3.2/0.000	0.85±0.17/0.000
	Plasma cholesterol	Dietary cholesterol	128	23	0.34	4.8±1.2/0.000	7.1±0.9/0.000

plasma cholesterol, the relationship being strongest in the pigeons.

Dietary cholesterol and atherosclerosis: Feeding cholesterol results in the induction of atherosclerosis. The time of onset and the severity of the induced-atherosclerosis are influenced by the amount of cholesterol fed. In pigeons, aortic atherosclerosis is usually graded as aortic atherosclerotic index, i.e. the percentage of aortic surface covered by streaks and plaques (Clarkson *et al.*, 1973; Lofland *et al.*, 1966). For example, Clarkson *et al.* (1973) reported that feeding 0.5% cholesterol during 12 months resulted in an index of 29%. Clarkson and Lofland (1967) tested the effect of different levels of cholesterol on the development of both aortic and coronary atherosclerosis in WC pigeons. They found no difference when either no cholesterol or 0.05% cholesterol was fed. When 0.1% cholesterol was added to the diet, atherosclerosis was not seen at 6 months, but it had developed after 1 year, and with 0.25% added it developed after 6 months. At 1 year, the extent of atherosclerosis was significantly increased when compared to 6 months. Feeding 0.5 and 1.0% resulted in the same degree of atherosclerosis at 6 months, whereas after 12 months significantly more atherosclerosis was seen in the animals fed 1.0% cholesterol. This reflects the higher levels of plasma cholesterol at 9 months after feeding 1.0% cholesterol when compared to feeding 0.5%. The increases in coronary atherosclerosis generally paralleled the increased levels of dietary cholesterol. In some birds fed 0.05% cholesterol, coronary atherosclerosis was seen at 1 year. None of the control animals developed the disease. The authors stated that it should be possible to produce the desired level of plasma cholesterol or extent of atherosclerosis by selection of the level of dietary cholesterol. Furthermore, from the results of their study it becomes clear that the effects of dietary cholesterol are a function not only of the amount fed but also of the duration of feeding. This was also shown by St. Clair (1983), who reported that plaques developed after feeding cholesterol for 3 weeks. In the next ten weeks, there was a strong increase in atherosclerosis index, from approximately 4 to 48% at 13 weks. The development of cholesterol-induced atherosclerosis is not only influenced by the amount of cholesterol fed, but also by the strain of pigeons that is used. Clarkson and Lofland (1961) fed the same diet to three different strains of pigeons. They found that the atherosclerotic index was markedly affected by the added cholesterol in WC pigeons (index 22.4), whereas RH pigeons were only slightly affected (index 0.27). The AK pigeons were intermediate in their response (index 4.1). Patton *et al.* (1975) also found a significant difference in aortic atherosclerosis between the breeds. However, the authors did not find a breed effect on the development of coronary atherosclerosis, and neither did Lofland (1965). When 0.5% cholesterol was fed, WC pigeons had a prevalence of 29.4 and RH pigeons of 25.6. On the other hand, Clarkson and Lofland (1961) did find a significant difference in the prevalence of coronary atherosclerosis between RH and WC pigeons when 1.0% cholesterol was fed. The RH pigeons were found to be resistant whereas the WC pigeons showed a marked increase in the development of atherosclerosis. Although both aortic and coronary atherosclerosis are induced by dietary cholesterol, no correlation can be found between the development of the two (Clarkson and Lofland, 1961; Clarkson *et al.*, 1962). This suggests that the two sites are independent of each other in their susceptibility to atherosclerosis. It might reflect differences in the fundamental mechanisms leading to the production of atherosclerosis in the aorta and the coronary arteries (Clarkson *et al.*, 1962).

When quails are used as experimental animals, the induction of atherosclerosis depends on the duration of the feeding period, the line of quail used and the amount of added cholesterol. Due to genetic selection, quail lines have been produced that develop atherosclerosis more rapidly with less cholesterol needed. Chapman and Day (1976) described the production of SEA (= Susceptible to Experimental Atherosclerosis) quail. When the breeding program was started, the incidence of atherosclerosis was 48% after feeding 2.0%

Table 2: Effect of fat source on plasma cholesterol levels in pigeons

Author	Dietary cholesterol level (%)	Dietary fat		Duration of feeding (weeks)	Plasma cholesterol (mmol/l)
		Fat source	Level (%)		
Lofland *et al.*, 1966	-	Margarine	30	60	9.0
	0.035	Butter	30	60	10.6
	0.035	Crisco	30	60	13.1
	0.035	Corn oil	30	60	12.0
Lofland *et al.*, 1961	0.25	Corn oil+5% protein	10	36	22.4
	0.25	Coconut oil+5% protein	10	36	41.7
	0.25	Corn oil+15% protein	10	36	24.4
	0.25	Coconut oil+15% protein	10	36	46.1
	0.25	Corn oil+30% protein	10	36	35.4
	0.25	Coconut oil+30% protein	10	36	62.8
Prichard *et al.*, 1968	-	Butter	30	104	7.9
	-	Control	-	104	8.5

cholesterol for 15 weeks. The mean score for the atherosclerosis was 29. The fourth generation of genetic selection had an incidence of 99% and a mean score of 76. Shih *et al.* (1983) reported that through genetic selection not only the severity of atherosclerosis was increased but also the time of onset shortened. SUS (= Susceptible) quail developed atherosclerosis in 8 weeks, whereas random bred quail needed 12 weeks. Besides the line of quail used, the duration of the experimental period also influences the severity and incidence of atherosclerosis. Hoekstra *et al.* (1998) reported the development of atherosclerosis in all birds fed 1.0% cholesterol, with a mean score of 2.22 at 4 weeks, 2.95 at 8 weeks and 3.69 at 12 weeks. McCormick *et al.* (1982) found the first lesions at 3 weeks, and the incidence increased to 100% at 12 weeks in SEA quail after feeding 1.0% cholesterol. Shih *et al.* (1983) mentioned that in SUS quail the incidence and severity increased linear in time when either 0.25% or 0.5% cholesterol is added to the diet. In RES (= Resistant) quail, atherosclerosis only develops within 9 weeks when as much as 0.5% cholesterol is added to the diet. The incidence is higher at 6 weeks than at 9 weeks. Smith and Hilker (1973) reported that the damage to the arteries becomes more intense with increased time. This is also mentioned by Fann *et al.* (1989).

The development of atherosclerosis has also been studied in chickens. Dauber and Katz (1942) found lesions in all 6 birds that were fed 2.5-10.0% cholesterol for more than 10 weeks. Furthermore they mentioned that cholesterol feeding induced microscopically visible intimal changes after 42 days and grossly visible lesions after 49 days. Horlick and Katz (1949) reported that both incidence and severity of atherosclerosis increased when more cholesterol was added to the diet. The first lesions became visible after 1.5-2 weeks of feeding cholesterol. The incidence and severity increased with increased duration of feeding (Horlick and Katz, 1949). Katz and Stamler (1953) reported that with dietary cholesterol varying from 0.25 to 2.0% cholesterol in combination with 5.0% cottonseed oil both time of onset and severity and incidence of lesions paralleled with the percentage of dietary cholesterol intake. Rose and Balloun (1969) found that cholesterol-induced atherosclerosis develops more rapidly in the abdominal aorta than the thoracic aorta. This was also seen by Fisher *et al.* (1959). This is in contrast to Horlick and Katz (1949), who found that lesions in the abdominal aorta tended to occur somewhat later and were less advanced.

Thus, feeding cholesterol induces atherosclerosis in the three different avian species. The severity and incidence of the induced atherosclerosis depends on the amount of cholesterol fed, on the duration of feeding, on the strain or line of animal used, and on the location of the atherosclerosis.

Dietary cholesterol and lipoprotein profile: Barakat and St. Clair (1985) investigated the effect of feeding cholesterol on lipoprotein profile in WC and SR pigeons. The distribution of cholesterol among the lipoproteins was similar in both breeds when the cholesterol-free diet was fed, 75-80% of total cholesterol being transported in HDL particles and 20-25% in LDL particles. Plasma VLDL-cholesterol levels were too low to detect. The addition of 0.5% cholesterol to the diet resulted in a significant shift in lipoprotein profile. The absolute amount of HDL-cholesterol did not change, but there was an increase in both LDL and VLDL-cholesterol. LDL particles now carried about 50% of total cholesterol, whereas VLDL particles were responsible for 25% in WC pigeons and 50% in SR pigeons. SR pigeons had significantly higher plasma cholesterol levels, which was due to the higher levels of VLDL-cholesterol. Langelier *et al.* (1976) found that when a

Table 3: Effect of fat source on plasma cholesterol in quail

Author	Dietary cholesterol level (%)	Dietary fat		Duration of feeding (weeks)	Plasma cholesterol (mmol/l)
		Fat source	Level (%)		
Chamberlain and Belton, 1987	-	Control (SEA)	-	36	5.2
	-	Fish oil (SEA)	8.6	36	6.2
	-	Lard (SEA)	8.6	36	5.1
	-	Control (RB)	-	36	5.9
	-	Fish oil (RB)	8.6	36	5.5
	-	Lard (RB)	8.6	36	5.7
Smith and Hilker, 1973	-	Control	-	36	7.6
	0.5	Control + cholesterol	-	36	4.8
	-	PUFA	16	36	7.3
	0.5	PUFA + cholesterol	16	36	9.5
	-	SFA	16	36	9.6
	0.5	SFA + cholesterol	16	36	47.8
Siegel *et al.*, 1995	-	Control (HL)	-	18	7.7
	0.1	Cholesterol (HL)	-	18	6.8
	-	Corn oil (HL)	4.0	18	5.7
	-	Coconut oil (HL)	4.0	18	6.7
	-	Control (LL)	-	18	4.7
	0.1	Cholesterol (LL)	-	18	3.7
	-	Corn oil (LL)	4.0	18	5.1
	-	Coconut oil (LL)	4.0	18	5.3
	-	Control (CL)	-	18	4.2
	0.1	Cholesterol (CL)	-	18	4.6
	-	Corn oil (CL)	4.0	18	4.4
	-	Coconut oil (CL)	4.0	18	4.3
Toda and Oku, 1995	-	Control	-	12	5.2
	2	Corn oil	15	12	28.6
	2	Palmitic fatty acids	15	12	27.4
	2	MCT	15	12	8.6
	2	Coconut oil	15	12	14.1
	2	Palm kernel oil	15	12	12.4
Yuan *et al.*, 1999	-	Control	-	9	5.2
	0.05	Beef tallow	6.0	9	6.8
	0.5	Beef tallow	6.0	9	35.6
	0.05	Beef tallow	12.0	9	7.5
	0.5	Beef tallow	12.0	9	41.9
Yuan *et al.*, 1997	0.05	Beef tallow	5.0	9	7.2
	0.05	Butter	5.0	9	6.7
	0.05	Soyabean oil	5.0	9	5.7
	0.5	Beef tallow	5.0	9	62.6
	0.5	Butter	5.0	9	59.1
	0.5	Soyabean oil	5.0	9	49.7

SEA = Susceptible to Experimental Atherosclerosis; RB = Random Bred; CL = Control Line; HL = High responder Line; LL = Low responder Line

cholesterol-free diet was fed, 71.7% of total cholesterol was transported by HDL. Furthermore, they found no VLDL-cholesterol. This was also described by St. Clair (1983), who furthermore mentioned that feeding cholesterol increased both VLDL and LDL-cholesterol. Breed effect on lipoprotein profile has been studied, both by Jensen *et al.* (1978) and Lofland and Clarkson (1960) who found no significant differences between WC and SR pigeons.

Studies have also been conducted with quails and chickens to identify changes in lipoprotein profile due to cholesterol feeding. In these two species, HDL is also the main transport vehicle for cholesterol when a cholesterol-free diet is fed (Allen and Wong, 1993;

Table 4: Effect of fat source on plasma cholesterol in chickens

Author	Dietary cholesterol level (%)	Dietary fat		Duration of feeding (weeks)	Plasma cholesterol (mmol/l)
		Fat source	Level (%)		
Cembrano *et al.*, 1967	1.8	Safflower	9.0	17	19.8
	1.8	Coconut	9.0	17	18.4
Dauber and Katz, 1943	-	Control	-	30	4.0
	2.0	Cholesterol	-	30	38.7
	-	Cottonseed oil	20.0	30	4.8
Stamler *et al.*, 1950a/ Katz and Stamler, 1953	-	Control	-	15	2.7
	-	Cottonseed oil	5.0	15	2.1
Stamler *et al.*, 1957a/ Katz *et al.* 1958	0.5	Cottonseed oil	5.0	NG	5.4
	0.5	Crisco	5.0	NG	6.5
	0.5	Cottonseed oil	5.0	NG	5.0
	0.5	Lard	5.0	NG	5.0
Stamler *et al.* 1957b/ Katz *et al.* 1958	1.0	Cottonseed oil	10.0	5	31.5
	1.0	Oleic acid	10.0	5	21.2
	1.0	Olive oil	10.0	5	16.0
	1.0	Neofat	10.0	5	24.5
	1.0	Chicken	10.0	5	17.9

NG = not given in literature

Hammad *et al.*, 1998; Hermier and Dillon, 1992; Kruski and Narayan, 1976; Nagata *et al.*, 1997; Narayan and Calhoun, 1976; Oku *et al.*, 1993; Radcliffe and Liebsch, 1985; Wu and Donaldson, 1982; Yuan *et al.*, 1998). Hammad *et al.* (1998) studied lipoprotein profile in different lines of quail. They found that 70% of total cholesterol was transported as HDL-cholesterol. Wu and Donaldson (1982) mentioned that HDL-cholesterol represented 79-84% of total cholesterol in quail. When a cholesterol-free diet is fed to quails, most authors report low or non-detectable levels of VLDL-cholesterol (Nagata *et al.*, 1997; Oku *et al.*, 1993; Wu and Donaldson, 1982; Yuan *et al.*, 1998). However, Hammad *et al.* (1998) found that 14-20% of total cholesterol was carried as VLDL-cholesterol. Furthermore, they found that addition of 0.5% cholesterol to the diet resulted in a decrease in plasma VLDL-cholesterol and an increase in LDL-cholesterol, which now was responsible for 62% of total cholesterol. Other authors mentioned an increase in plasma VLDL-cholesterol, thus becoming the major lipoprotein, when cholesterol is added to the diet (Nagata *et al.*, 1997; Oku *et al.*, 1993; Radcliffe and Liebsch, 1985; Wu and Donaldson, 1982). Nagata *et al.* (1997) reported that 46-54% of total cholesterol is recovered in VLDL + chylomicrons. Oku *et al.* (1993) found that 76% of lipoprotein cholesterol was carried by VLDL particles, and Wu and Donaldson (1982) mentioned that 40-44% of total cholesterol is transported as VLDL-cholesterol. In their report, Hammad *et al.* (1998) give an explanation for the different response in lipoprotein profile. They did not determine VLDL-cholesterol, but they calculated it with the help of the following formula: VLDL-cholesterol (mmol/) =TG (mmol/l) / 2.2 (Friedewald *et al.*, 1972). The authors speculated that the difference in outcome is related to direct determination versus calculation. No change in HDL-cholesterol is usually observed when cholesterol is fed to quail (Hammad *et al.*, 1998; Oku *et al.*, 1993; Radcliffe and Liebsch, 1985).

When cholesterol is added to the diet of chickens, a sharp increase in VLDL-cholesterol (Hermier and Dillon, 1992; Jones and Dobrilovic, 1969; Kruski and Narayan, 1976; Narayan and Calhoun, 1976) and LDL-cholesterol (Allen and Wong, 1993; Jones and Dobrilovic, 1969; Kruski and Narayan, 1976; Narayan and Calhoun, 1976) can be seen. Kruski and Narayan (1973) reported that VLDL-cholesterol represented 77 % of total cholesterol when cholesterol is added to the diet. Hermier and Dillon (1992) found that the increase in VLDL-cholesterol was accompanied by an increase in IDL and a decrease in LDL. In contrast to investigations with pigeons and quails, many authors have found a decrease in plasma HDL-cholesterol when cholesterol was added to the diet (Hermier and Dillon, 1992; Kruski and Narayan, 1973; Narayan and Calhoun, 1976). Only Allen and Wong (1993) found no change in HDL when a cholesterol-rich diet was fed.

Thus, HDL is the major cholesterol carrier in the examined avian species when they are fed a cholesterol-free diet. However, inclusion of cholesterol in the diet results in a significant shift in lipoprotein profile that is similar for all three species. Both VLDL-

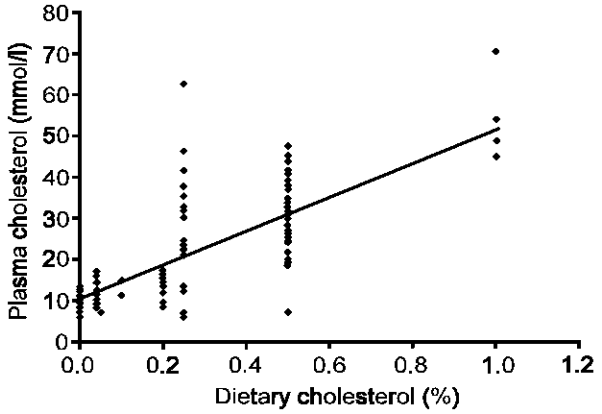

Fig. 1: The relationship between dietary and plasma cholesterol levels in pigeons

Data points (n=151) are groups means and are taken from 10 publications (Barakat and St. Clair, 1985; Bell *et al.*, 1979; Clarkson *et al.*, 1973; Clarkson and Lofland, 1967; Lofland *et al.*, 1966; Lofland *et al.*, 1961; Patton *et al.*, 1975; Ray and Young, 1978; Wagner, 1978; Young, 1974)

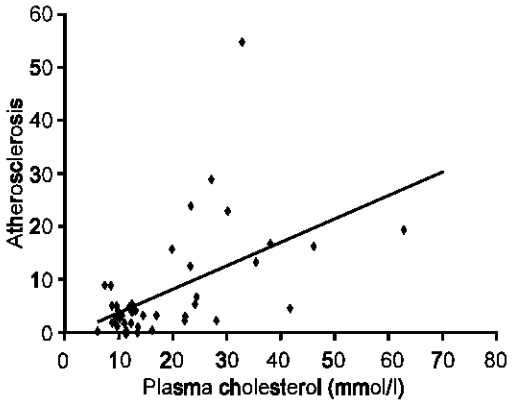

Fig. 2: The relationship between plasma cholesterol and aortic atherosclerosis in pigeons

Atherosclerosis index is defined as the percentage of aortic surface covered by streaks and plaques.
Data points (n=42) are group means and are taken from 7 publications (Clarkson *et al.*, 1973; Lofland *et al.*, 1966; Lofland *et al.*, 1961; Patton *et al.*, 1975; Ray and Young, 1978; Wagner, 1978; Young, 1974)

cholesterol and LDL-cholesterol increases, VLDL becoming the main cholesterol transport vehicle, while there is no change in HDL-cholesterol for pigeons and quail. Chickens show a small decrease in plasma HDL levels when cholesterol is added to the diet.

Dietary fat and plasma cholesterol levels: The effect of dietary fat amount and composition on plasma cholesterol has been investigated in pigeons, quails and chickens (Tables 2-4). The results from the different

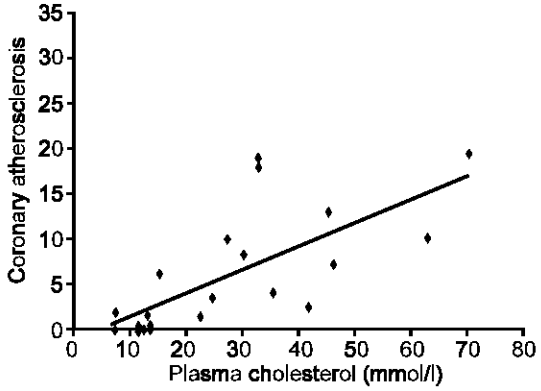

Fig. 3: The relationship between plasma cholesterol and coronary atherosclerosis in pigeons

Prevalence of coronary atherosclerosis is defined as percent of the arteries seen which contained atherosclerotic plaques.
Data points (n=21) are group means and are taken from 4 publications (Clarkson *et al.*, 1973; Clarkson and Lofland, 1967; Clarkson *et al.*, 1962; Wagner, 1978)

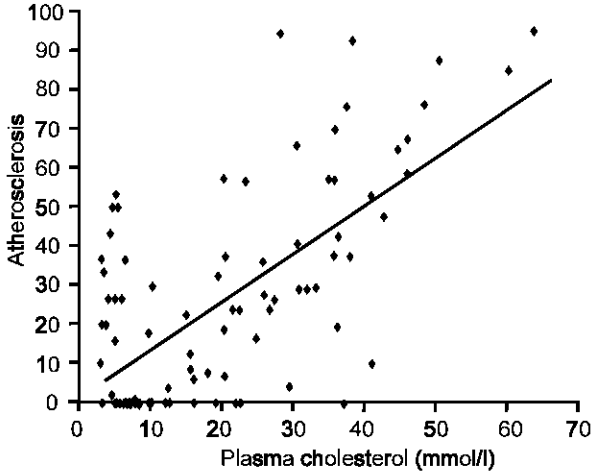

Fig. 4: The relationship between plasma cholesterol and aortic atherosclerosis in quail

Atherosclerotic scores in literature were converted into values on a 0-100 scale, where 0 = no atherosclerosis, 100 = severe atherosclerosis.
Data points (n=95) are group means and are taken from 11 publications (Chapman and Day, 1976; Hammad *et al.*, 1998; Hoekstra *et al.*, 1998; McClelland and Shih, 1988; McCormick *et al.*, 1982; Shih *et al.*, 1983; Siegel *et al.*, 1995; Wu and Donaldson, 1982; Yuan *et al.*, 1999; Yuan *et al.*, 1998; Yuan *et al.*, 1997)

studies can be controversial. Lofland *et al.* (1966) tested the effect of different fat sources in a diet with no or 0.035% added cholesterol and they did find a fat effect on plasma cholesterol, but there was a highly significant interaction with protein level. The effect of the dietary fat source depended on protein source and level. Prichard

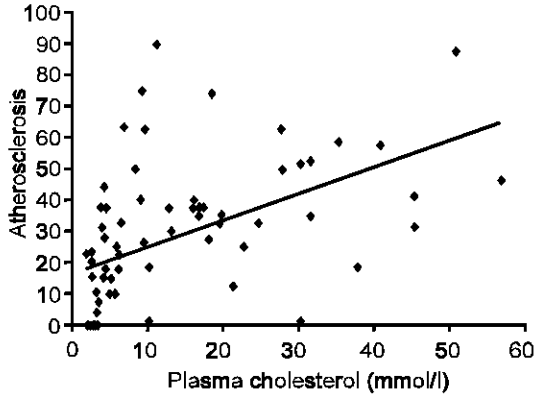

Fig. 5: The relationship between plasma cholesterol and aortic atherosclerosis in chickens

Atherosclerotic scores in literature were converted into values on a 0-100 scale, where 0 = no atherosclerosis, 100 = severe atherosclerosis.
Data points (n=71) are group means and are taken from 15 publications (Cembrano *et al.*, 1967; Griminger and Fisher, 1986; Horlick and Katz, 1949; Horlick *et al.*, 1949; Katz and Stamler, 1953; Katz *et al.*, 1958; Stamler and Katz, 1950; Stamler *et al.*, 1950a,c; Stamler *et al.*, 1957a,b; Stamler *et al.*, 1958a,b; Rodbard *et al.*, 1953; Rodbard *et al.*, 1950; Rose and Balloun, 1969)

et al. (1968) fed 30% butter for 24 months to WC pigeons, without cholesterol added to the diet. No effect on plasma cholesterol was seen. However, when Lofland *et al.* (1961) compared the effect of feeding 10% coconut oil with feeding 10% corn oil in combination with a diet containing 0.25% cholesterol, they found that feeding corn oil resulted in significantly lower plasma cholesterol levels, but only when cholesterol was added to the diet.

The effect of dietary fat has also been tested in quails (Table 3). Smith and Hilker (1973) used a variety of diets with or without 0.5% added cholesterol. The diets rich in saturated fatty acids significantly increased plasma cholesterol levels. Furthermore, they found that in the presence of dietary cholesterol polyunsaturated fatty acids exhibited a lowering effect on plasma cholesterol levels. Yuan *et al.* (1999) fed either 6.0 or 12.0% beef tallow to susceptible quail in combination with a low and a high-cholesterol diet. They did not find an effect on plasma cholesterol. In a previous study, Yuan *et al.* (1997) reported a significant influence of dietary fat on plasma cholesterol. They tested the effect of three different fat sources in combination with a low and high-cholesterol diet. On the high-cholesterol diet, feeding 5.0% soybean oil resulted in significantly lower plasma total cholesterol levels and a decrease in cholesterol content of all lipoproteins when compared to feeding either beef tallow or butter. No influence of dietary fat on plasma cholesterol was seen in absence of dietary cholesterol. Siegel *et al.* (1995) tested the effect of 4.0% coconut oil and corn oil in CL, LL and HL quail. They did not find an effect on plasma cholesterol. Toda and Oku (1995) also investigated the effect of different fat sources on plasma cholesterol levels. They found that feeding fat sources rich in medium chain fatty acids resulted in significantly lower plasma cholesterol levels then when fat rich in either linoleic acid or saturated fatty acids was fed. Sadi *et al.* (1996) reported that feeding a fat source rich in linoleic acid or oleic acid resulted in higher plasma cholesterol levels when compared to feeding a fat source rich in either α-linolenic acid or γ-linolenic acid. Finally, Chamberlain and Belton (1987) tested the effect of fish oil in combination with a cholesterol-free diet. They found that when 8.6% fish oil was fed, plasma cholesterol levels were significantly higher in SEA quail than when 8.6% lard was fed. No significant effect was found in random-bred quail. Feeding fish oil did resulted in a decrease in plasma TG and VLDL levels in random-bred quail, but not in SEA quail. The different responses to dietary fish oil indicate that genetic factors play an important role in the development of atherosclerosis.

The results in studies with chickens are also variable (Table 4). For example, Cembrano *et al.* (1967) did not find a difference in plasma cholesterol when either 9.0% safflower oil or 9.0% coconut oil was fed in combination with 1.8% cholesterol. Furthermore, the addition of 5 or 20% cottonseed oil to a cholesterol-free diet did not change plasma cholesterol levels (Dauber and Katz, 1943; Stamler *et al.*, 1950a). Katz *et al.* (1958) reported that little or no influence on hypercholesterolemia was seen when either a fat source rich in saturated fatty acids or rich in unsaturated fatty acids was fed. This was also mentioned by Stamler *et al.* (1957b), who tested the effect of various amounts of corn oil on the development of atherosclerosis. However, Worcester and Bruckdorfer (1978) did find a significant increase in plasma cholesterol when 10% coconut oil was added to the diet in combination with 0.5% cholesterol when compared to feeding maize oil. Stamler *et al.* (1957b) also reported a significant influence of dietary fat on plasma cholesterol, the levels being highest when cottonseed oil was fed and lowest when olive oil was fed.

Thus, it appears that the effect of dietary fat is most clear when hypercholesterolemia induced by dietary cholesterol is present. If no cholesterol is added to the diet, no consistent effect of dietary fat is seen. When cholesterol is present in the diet, it appears that unsaturated fatty acids and medium chain fatty acids are responsible for lower levels of plasma cholesterol in the three avian species when compared to saturated fatty acids.

Dietary fat and atherosclerosis: Some research has been conducted to identify the effect of dietary fat source on the development of atherosclerosis in avian species.

In a study with WC pigeons, Clarkson *et al.* (1962) found that feeding 10% corn oil in combination with 0.25% cholesterol resulted in significantly less coronary atherosclerosis when compared to feeding coconut oil. Lofland *et al.* (1961) presented the effects on aortic atherosclerosis from the same experiment. They found that dietary fat appeared to influence the atherosclerotic index to a slight degree. These results suggest a stronger influence of dietary fat on plasma cholesterol than on the severity of aortic atherosclerosis. Prichard *et al.* (1968) did not find an effect of feeding 30 % butter during 24 months on either the atherosclerotic index or the prevalence of coronary atherosclerosis. The butter-fed group had a slightly higher aortic index. However, there were significant differences in the appearance of coronary atherosclerosis between the butter and the control group. The butter group had a significantly higher degree of luminal narrowing and the plaques contained significantly less stainable fat. Butter may lead to an increase in plaques size without an increase in fat. Lofland *et al.* (1966) fed four different fat types to WC pigeons. They only found a smaller degree of aortic atherosclerosis in the margarine-fed group. The diet containing margarine was cholesterol-free, whereas the other three diets contained 0.035% cholesterol. The difference in degree of atherosclerosis was probably due to this small amount of cholesterol. No effect was found for coronary atherosclerosis, but the animals were probably too young to develop significant coronary atherosclerosis.

The effect of dietary fat has also been tested in quail. Yuan *et al.* (1997) fed three different fat sources in combination with a high and low-cholesterol diet. They did not find an effect of the different diets on the development of atherosclerosis, but they saw an effect on plasma cholesterol between the fat sources in the high-cholesterol diets. Smith and Hilker (1973) tested the effect of a variety of diets on the development of atherosclerosis and found that feeding a diet rich in polyunsaturated fatty acids protected against the development of atherosclerosis when compared to feeding a diet rich in saturated fatty acids. Yuan *et al.* (1999) reported that high levels of beef tallow only resulted in an increase in aortic atherosclerosis when it was fed in combination with a high-cholesterol diet. It is interesting that the level of beef tallow did not influence plasma cholesterol, but there was a significant effect on plasma TG levels. Siegel *et al.* (1995) tested the effect of different diets on the development of atherosclerosis in CL, LL and HL quail during 8 weeks. They found that feeding 4.0% coconut oil resulted in a significant increase in atherosclerotic lesions when compared to the control group or the group fed 4.0% corn oil. No difference was found between the cholesterol and coconut-fed groups. Sadi *et al.* (1996) fed different fats and oils in combination with 2.0% cholesterol. They reported that perilla oil, which is rich in α-linolenic acid, and primrose oil, which is rich in γ-linolenic acid, were less atherogenic than fat sources rich in linoleic acid and oleic acid. A corresponding effect of these fat sources was seen on plasma cholesterol levels. Toda and Oku (1995) also tested the effect of different fat sources on the development of atherosclerosis in combination with 2.0% cholesterol. They found that a fat source rich in medium chain fatty acids is less atherogenic than a fat source rich in palmitic acid and linoleic acid, and that linoleic acid was as atherogenic as palmitic acid. The effect of fish oil was investigated, both in absence and in combination with dietary cholesterol (Chamberlain and Belton, 1987; Chamberlain *et al.*, 1991; Fann *et al.*, 1989). When a cholesterol-rich diet was fed for 15 weeks, 10% fish oil resulted in significantly less atherosclerotic lesions when compared to feeding beef tallow (Fann *et al.*, 1989). Since atherosclerosis developed in the fish oil-fed group, fish oil may only delay and not prevent the development of the disease in SEA quail. When no cholesterol was added, the incidence of fatty streaks were significantly higher when either feeding 8.6% fish oil was compared to feeding 8.6% lard (Chamberlain and Belton, 1987) or when feeding 2.0% fish oil was compared to feeding 2.0% olive oil (Chamberlain *et al.*, 1991). It is likely that another substance in fish oil than n-3 polyunsaturated fatty acids is responsible for the higher atherogenecity. A possible explanation is the fact that fish oil contains more cholesterol than lard, thus that there was a difference in cholesterol content between the two experimental diets (Chamberlain and Belton, 1987; Fann *et al.*, 1989).

The effect of feeding coconut oil was tested in chickens. Both Cembrano *et al.* (1967) and Worcester and Bruckdorfer (1978) found that feeding coconut oil in combination with dietary cholesterol resulted in significantly more aortic atherosclerosis when compared to feeding either safflower oil or maize oil. However, only Worcester and Bruckdorfer (1978) reported a significant change in plasma cholesterol level. Cembrano *et al.* (1967) used 2.0% cholesterol and Worcester and Bruckdorfer (1978) 0.5%. Stamler *et al.* (1957b) found that feeding 10% oleic acid in combination with 1.0% cholesterol resulted in a significantly lower incidence of aortic atherosclerosis when compared to feeding cottonseed oil. Again, no effect on plasma cholesterol was found.

Thus, it appears that dietary fat can influence the development of atherosclerosis. However, dietary fat only exerts an effect when cholesterol is added to the diet, thus modifying the response of cholesterol-induced atherosclerosis. The effect of fat source on plasma cholesterol and on the development of atherosclerosis is not always the same. Therefore, it is possible that at least a part of the effect of dietary fat on atherosclerosis

is not mediated through plasma cholesterol. It appears that saturated fatty acids stimulate the development of atherosclerosis when compared to unsaturated fatty acids. Furthermore, it seems that both n-3 polyunsaturated fatty acids and medium chain fatty acids are less atherogenic than linoleic and oleic acid.

Plasma cholesterol in relation to atherosclerosis: When cholesterol is added to the diet, both plasma cholesterol levels and the degree of atherosclerosis increase. Therefore, we tried to establish a relation between plasma cholesterol concentrations and the degree of atherosclerosis in the experimental avian species. First of all, the regression equation between plasma cholesterol and either aortic or coronary atherosclerosis has been calculated with the help of literature data on pigeons. All data were included; no selections were made for strain and period of feeding. The linear correlation coefficients were 0.54 and 0.71 for aortic and coronary atherosclerosis, respectively (Table 1). The correlation is higher for coronary atherosclerosis, suggesting that the development of aortic and coronary atherosclerosis are independent of each other. This was also described by Clarkson and Lofland (1961), who found no correlation between the two types of atherosclerosis. Moreover, Patton *et al.* (1975) stated that the mechanisms controlling coronary and aortic atherosclerosis could be different in one breed and similar in another, since RH pigeons developed as much coronary atherosclerosis as WC pigeons.

The correlation was also calculated for plasma cholesterol levels and aortic atherosclerosis for quails and chickens. Again, strain and duration of feeding were not included. The linear correlation coefficients were 0.68 for quail and 0.51 for chickens (Table 1). The literature data were also used to create Fig. 2-5. The correlation found for quails resembles the one found by Yuan *et al.* (1998), who found a correlation of 0.62. For chickens, several authors have mentioned that no or just a weak correlation could be found between plasma cholesterol and the development of atherosclerosis (Cembrano *et al.*, 1967; Dauber and Katz, 1943; Horlick and Katz, 1949).

The correlation coefficients are significant, but not very high. A possible explanation is given by Kakita *et al.* (1972). They studied the relation between plasma cholesterol and coronary atherosclerosis in chickens. The presence of a lower threshold was discussed, since no coronary atherosclerosis appeared to develop when plasma cholesterol levels below 2.0-2.5 mmol/l were present. The increment was highest with plasma cholesterol levels from 2.5-10.1 mmol/l. When plasma cholesterol was transformed into their logarithmic values, a higher linear correlation was found (r = 0.52) then when actual values were used.

In conclusion, it appears that there is a direct relation between plasma cholesterol and the degree of atherosclerosis, the relation being strongest for plasma cholesterol and coronary atherosclerosis in pigeons and plasma cholesterol and aortic atherosclerosis in quails.

Conclusion: The major conclusion of this literature review is that plasma cholesterol concentrations and the degree of atherosclerosis are directly related in pigeons, quails and chickens. The data also indicate that fats rich in polyunsaturated fatty acids lower plasma cholesterol when compared to fat rich in saturated fatty acids.

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