SOME NEWER APPROACHES TO THE PROBLEMS OF ARTERIOSCLEROSIS

PART II - EXPERIMENTAL THERAPEUTIC APPROACH TO THE PROBLEMS OF ATHEROMATOSIS

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Herbivorous animals such as rabbits and guinea pigs were found to be easily susceptible to atheromatosis following the feeding of cholesterol. Cats and dogs until recently were found refractory. Fox [1] discovered that birds developed spontaneously with advancing age, atherosclerosis closely resembling that found in humans. Dauber [2] emphasized the great frequency with which aortic atheroma were present in chickens over 6 months of age. We demonstrated in our laboratory high blood and tissue total cholesterol and cholesterol esters in old hens, especially in the high egg producing (Texas A. and M.) white leghorn stock. It would seem, therefore, that omnivorous domestic fowl of this type would be a most suitable animal for the study of spontaneous atherosclerosis. Chickens normally ingest animal cholesterol-containing foods. We chose three year old white leghorn hens for the study of the effects of decholesterolemia and atheromatosis. Young pullets and cockerels were chosen from the same stock for the study of the effect of these agents on experimentally induced hypercholesterolemia and atheromatosis in the tissues.

Anitschkow [3] demonstrated that the feeding of cholesterol in oil to rabbits produced marked atherosclerotic changes. Murata and Kataoka [4] in 1918 discovered that the administration of thyroid extract along with the cholesterol prevented the atheromatosis of the aorta. This was confirmed by Liebig [5]. Turner and Khayat, and Meeker, Kesten and Jobling [6] found that potassium iodide prevented the usual hypocholesterolemia in aortic atheromatosis in normal animals fed cholesterol. If the thyroid gland was removed the potassium iodide did not have its prophylactic action. Page and Bernhard 7.ª, noted that administration of di-iodide of ricinsterolic acid decreased atheromatosis

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but actually caused elevation of the blood cholesterol suggesting a tissue receptivity factor. Eberhard [7.b] found that alcohol fed to rabbits along with cholesterol produced greater hypercholesterolemia but less atheromatosis. Bruger et al.[8] found that sex hormones inhibited hypercholesterolemia and atheromatosis in normal female rabbits fed cholesterol but not after castration. Duff and McMillan found that the alloxan diabetes in spite of hyperlipemia limited sharply the atheromatosis in cholesterol fed rabbits.

Allan and his associates [9] discovered the beneficient effects of feeding of fresh pancreas in the clearing and prevention of fat deposition in the liver of depancreatized dogs. Fisher [10] demonstrated the effectiveness of dried pancreas, Hershey [11] used crude lecithin for the same purpose, Chaikoff and Kaplan [12] prepared a litotropic fraction AR extract of the pancreas which they found had lipotropic properties. Dragsted et al. [13] named his extract ‘’lipocaic” and Wolffe et al. [14] called his extract ‘’lipolysin”. Best and Huntsman’s [15] selection of choline as the lipotropic factor initiated many further and generally confirmatory studies. Huber, Broun and Casey [16] found that the lipocaic was effective in the prevention of deposition of lipids in the aortic subintima of rabbits fed cholesterol. Kersten and Silbowitz [17] reported that soya lecithin similarly delayed but did not prevent hypercholesterolemia and atheromatosis in rabbits.

Our *experimental results* with choline, methionine and inositol on naturaly occurring hypercholesterolemia and subintimal atheromatosis

EFFECTS OF CHOLINE INOSITOL AND METHIONINE ON BLOOD TISSUE LIPIDS

	Blood cholesterol mg/100ml		Livid PO_4	Tissue cholesterol mg/100					
				Aorta		Heart		Liver	
	Total	Esters		Total	Esters	Total	Esters	Total	Esters
Control series	274 8	166	06	230	1762	275	223	340	240
36 old mens	SD± 39	± 19	± 27	± 41	± 204	± 71	± 19	± 65	± 24
Choline 20	174	121		190		205		236	
3&A 28-72 days	SD± 25	± 108		± 292		± 203		± 93	
Choline 26	179	144	101	165	83	198	147	249	210
W&S 10-64 days	SD ± 24	± 92	± 18	± 50	± 24	± 57	± 19	± 57	± 256
Control series	195	147	107	253	188	233	172	303	223
20 old mens	SD ± 18	± 20	± 2	± 50	±47	± 48		± 50	± 38
Inositol 23	184	135	118	201	155	166	129	253	191
30-68 days	SD ± 19	± 16	± 19	± 38	± 44	± 37		± 55	± 43
Methionine 23	138	95	166	156	102	135	91	276	169
36-57 days	SD ± 25	± 24	± 4	± 21	± 21	± 19	± 13	± 94	± 63

S.D. Standard Deviation S&A Summer & Autumn W&S Winter & Soring

Table 1 - Hypercholesterolemia and the effects of lipopropic agents in old hens. The data in these tables were assembled and statistically treated by John W. Chriss, M.D. and Paul M. Sims, M. D. Fellows in Cardiovascular Research under the H. H. Weinert Fund.

in old hens, Texas A. & M. white leghorn, high producing stock, may be shown in Table 1. In comparison with the two series of 26 old hens control, the 26 old hens placed on choline chloride 0.5 gram daily, showed some reduction of the cholesterol levels of the blood in the aorta, heart muscle, and liver. A similar series of 3-year old hens given 0.5 gram of inositol, showed less but still some decholesterolizing effect. In other series of the same stock, methionine 0.4 gram dose, had seemingly considerable decholesterolizing effect.

It was found that young birds of the same Texas A. & M. white leghorn stock at growing mash, impregnated with cholesterol in oil, in preference to the mash itself. They were started on doses of 0.5 gram a day in 5 cc. cotton seed oil, showing rapid rises and high lipid levels until about the 40th day, and grew normally. The cholesterol level dropped off some in most birds. After 40 days of treatment of cholesterol in oil, all birds showed gross evidences of atheromatosis in the aorta coronaries. The livers were also very fatty. All the tissues had increased contents of cholesterol and cholesterol esters. The control series and various experimental studies are shown in Tables 2, 3, 4 and 5. In these series, after about 40 days we halved the dose of cholesterol to 0.5 grams in 5 cc. of oil every other day. This brought the blood levels down to a third of what they had been. The addition of 0.5 gram of inositol or 0.5 gram choline and 2 cc. Kumbacha was apparently not significant when given from the beginning.

BLOOD AND TISSUE STUDIES ON YOUNG COCKERELS
FED CHOLESTEROL AND VARIOUS DECHOLESTERIZING AGENTS

			Blood		Treat	Change	Final Blood		Heart		Liver		Aorta		
Group	Treat.	Days	Total	Esters	Days	Drug	Total	Esters	Total	Esters	Total	Esters	Total	Esters	Grade
F-6	Cholest 0.5/0	44	1579 ±407	264 ±5/0	112 ±68 off chol	No Chol Inositol 0.5/0	175 ±65	75 ±60	356 ± 67	103 ± 75	800 ± 67	203 ± 52	602 ±108	254 ±141	0
G-6	Cholest 0.5/0	44	1632 ±241	1225 ±388	114 ±70 off	No Cholest Kumbacha 2cc/0	170 ± 31	60 ± 26	314 ± 62	97 ± 35	1028 ± 547	205 ±154	648 ± 241	407 ± 275	0
H-6	Cholest 0.5/0	44	1395 ± 417	1001 ±478	114 ± 70 off	No Cholest Choline 0.5/0	169 ± 38	71 ± 11	273 ± 107	78 ± 48	612 ± 208	253 ± 198	342 ± 133	156 ± 64	0
I-5	Cholest 0.5/0	44	1604 ± 406	1291 ± 507	116 ± 72 off	No Cholest No Drug	143 ± 20	61 ± 11	324 ± 37	128 ± 82	878 ± 72	193 ± 84	447 ± 101	173 ± 68	0
J-5	Cholest 0.5/0	44	1807 ±194	1398 ±242	108 ± 72	No Cholest No Drug	159 ± 18	65 ± 16	303 ± 55	75 ± 23	748 ± 88	305 ± 24	565 ± 80	187 ± 84	1 17
K-14	Cholest 0.5/0	46	1400 ±280	901 ±343	112 ± 72	No Cholest No Drug	155 ± 24	59 ± 14	334 ± 42	103 ± 56	810 ± 109	218 ± 30	456 ± 61	164 ± 55	0

Table 2

In three other groups the addition of the drugs after the discontinuance of the cholesterol feeding on the 44th day seemed to have no definite effect on the return to normal levels in the blood and tissues in 70 days of treatment. The cholesterol levels in the tissues were still high after the decholesterolizing agents were used, with the exception of the series in which choline was used, were brought to the normal. Four other series, in which the cholesterol 0.5 gram in 5 cc. of corn oil daily was maintained, one given no drug, another given 2.5 gram daily choline, another 2.5 gram

BLOOD AND TISSUE STUDIES ON YOUNG COCKERELS FED CHOLESTEROL & VARIOUS DECHOLESTERIZING AGENTS

Group	Treat	Days	Blood Total	Blood Esters	Treat Days	Treat Drug	Final Blood Total	Final Blood Esters	Heart Total	Heart Esters	Liver Total	Liver Esters	Aorta Total	Aorta Esters	Grade
L-25	Chol 0.5 gm. Day	56	589 ± 285	330 ± 189	68	0	525 ±190	257 ±133	480 ± 77	290 ± 83	3820 ±1002	2320 ±1462	690 ±486	210 ±294	i - ii
M-12	Chol. 0.5 gm Choline 2.5 gms.	66	379 ±102	184 ± 92	77	0	395 ±157	171 ±97	403 ± 67	176 ± 86	2389 ±968	1148 ±650	579 ±176	171 ±127	0
N-10	Plain Food only	56	219 ± 28	68 ± 18	78	0	172 ±41	57 ±32	368 ±90	125 ±78	754 ±137	209 ±114	340 ±43	66 ±49	0
O-12	Chol 0.5/0 inositol 2.5 CM	66	326 ±80	134 ±104	74	0	359 ±157	142 ±96	393 ± 58	212 ±86	1931 ±1006	1003 ±798	428 ±152	170 ± 72	i
P-13	Choles 0.5/0 Choline 2.5 gm inositol 2.5 gm	72 74 78			76	0	460 ± 938	209 ±184	433 ± 111	177 ± 91	2630 ±1730	1207 ± 777	598 ±176	191 ±86	i

Table 3

BLOOD AND TISSUE STUDIES ON YOUNG COCKERELS FED CHOLESTEROL & VARIOUS DECHOLESTERIZING AGENTS

Group	Treat	Days	Blood Total	Blood Esters	Treat Days	Treat Drug	Final Blood Total	Final Blood Esters	Heart Total	Heart Esters	Liver Total	Liver Esters	Aorta Total	Aorta Esters	Grade
A-20	Growena	48	214 ± 57	87 ± 47	68 to 112	No Drug Control	175 ± 35	40 ± 27	386 ±179	134 ± 69	749 ±196	241 ±163	454 ±163	166 ± 72	0 in all
B-20	Growena Chol 0.5 gms	40	968 ±512	577 ±435	66 to 112	Cholest 0.5 q 5/0	324 ±114	122 ± 96	715 ±315	449 ± 297	1890 ±1199	992 ± 825	1113 ±555	640 ± 394	i - iii
C-10	Cholest 0.5 gm Inos as gms	40	1193 ±470	804 ±465	67	Chol 0.5/ 5/0	485 ± 314	248 ± 212	692 ± 266	443 ± 104	1575 ±1008	978 ±1108	1243 ± 413	798 ± 561	i - ii
D-10	Chol 0.5/0 Kurobache 20 cc/0	40	1435 460	920 401	67	Chol 0.5/ 20	446 ± 322	224 ± 118	847 ± 234	592 ± 224	1072 ±664	1178 ± 677	1653 ± 506	1140 ± 362	i ii
E-10	Cholest 0.5/0 Choline 0.5/0	40	1502 459	1047 400	70	Chol 0.5/ q 20	442 ± 155	167 ± 85	684 ±178	440 ± 31	1604 ± 430	865 ± 208	1292 ± 282	826 ± 274	i - ii
F-6	Cholest 0.5/0	40	1579 ±407	1264 ± 519	112 -68 CH	Chol inos 0.5/0	175 ± 65	75 ± 60	356 ± 67	103 ± 75	800 ± 67	203 ± 52	602 ± 108	254 ± 141	0

Table 4

daily inosital, the combination of the two drugs and a group of controls on plain food, showed lower values in general in the blood and in the tissues of those on drugs, but the standard deviations were too high.

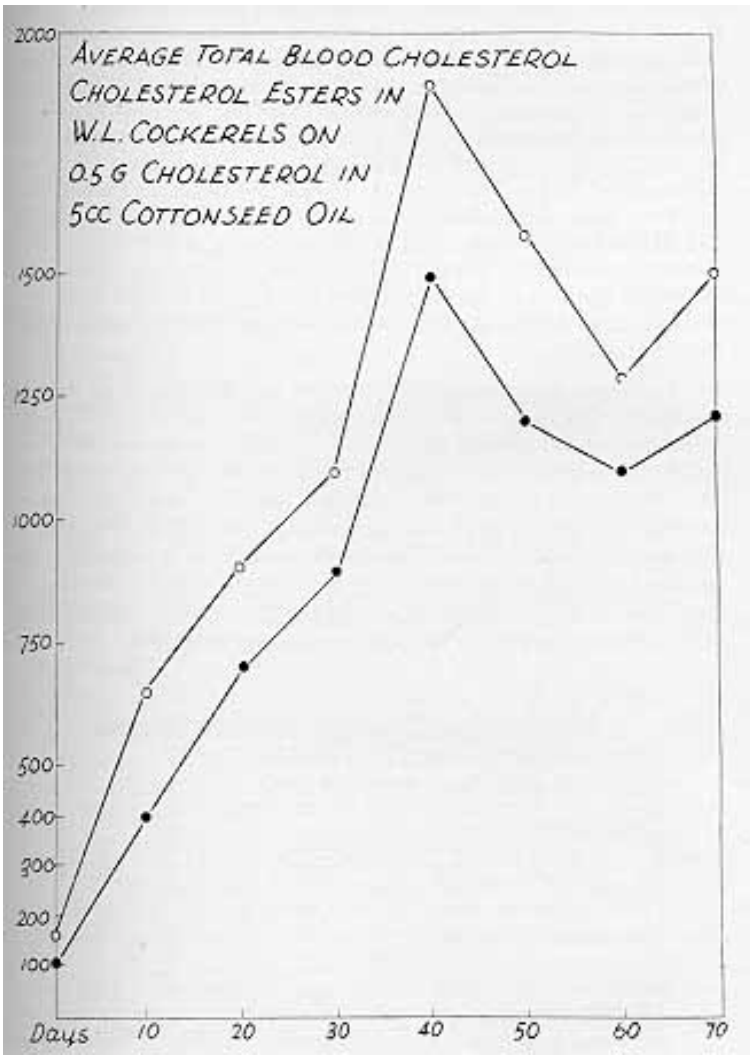

Table 5

HUMAN STUDIES

Pathologists and clinicians long ago learned that in certain types of patients atheromatosis was an unusually common occurrence and frequently the cause of death. Atheromatous pathological process was often found in strategic arteries in patients who had died suddenly with cardiac pains, angina pectoris, had hypertension, aortic sclerosis with hypotension and metabolic disease as diabetes mellitus, nephrosis, or nephritis. In certain intoxications in patients, the possibilities of atheromatous complications are recognized. Clinicians have tried to identify the factors which contributed to the development of atherosclerosis, and efforts were made to control the factors. There seemed to be no single common denominator, no single factor. The prevention of mechanical strain, and a lowering or a rasing of the blood pressure as indicated. Hueper [18] felt that the permeability of the intima to plasma lipids was the chief factor but hypercholesterolemia seems to the clinician to be very important, if not the most important, readily attackable, factor.

In the past few years, we have carried out extensive blood chemical studies, particularly for the total cholesterols, cholesterol esters, and sometimes for the plasma, phosphate lipid levels in normal individuals and from several groups of patients with chronic medical conditions. The results are tabulated in tables 6, 7 and 8. This study has impressed upon us the fact that hypercholesterolemia is an important predisposing factor. Since hypercholesterolemia is a factor we may attack or study it in patients while treating the primary disease process. We know that hypercholesterolemia of diabetes mellitus disappears on adequate insulin therapy and that of myxedema responds to

BLOOD TOTAL CHOLESTEROL E CHOLESTEROL ESTERS IN KNOWN ARTERIAL DISEASE CASES

Under 50 yrs	*Total Mg %*	*Over 50 yrs*	*Total Mg %*	*Esters Mg %*	*Total Cases*		
ATHER CAD CO-MI-AP	*78*	***295*** *SD ± 64*	***202*** *± 54*	*85*	***292*** *± 66*	***193*** *± 51*	***263***
ATHER AORTITIS	*55*	***296*** *± 81*	***199*** *± 64*	*142*	***291*** *± 75*	***190*** *± 54*	***197***
HIPERTENSION	*98*	***262*** *± 61*	***175*** *± 51*	*167*	***276*** *± 89*	***189*** *± 68*	***265***
NO VASC DISEASE	*168*	***225*** *± 58*	***152*** *± 45*	*72*	***252*** *± 70*	***161*** *± 50*	***240***

Table 6

BLOOD LIPIDS IN MISCELLANEOUS CONDITIONS

	Under 50 yrs	Cholesterol Total Mg %	Cholesterol Esters Mg %	Over 50 yrs	Cholesterol Total Mg %	Cholesterol Esters Mg %	Total Cases
CHOLECYSTITIS	48	**274** SD + 78	**169** ± 68	29	**304** ± 135	**178** ± 99	**77**
CIRRHOSIS	28	**220** ± 56	**142** ± 49	43	**225** ± 55	**150** ± 45	**71**
SYPHILIS LATENT	14	**218**	**141** ± 39	10	**257** ± 50	**163** ± 48	**24**
TUBERCULOSIS	16	**214** 214± 48	**152** ± 50	7	**250** ± 41	**169** ± 21	**23**
RHEUMATIC H.D.	31	**226** ± 47	**140** ± 39	9	**277** ± 57	**177** ± 34	**40**

Table 7

BLOOD LIPIDS IN METABOLIC THAT SHOW A.S.

	Under 50 yrs	Cholesterol Total Mg %	Cholesterol Esters Mg %	Over 50 yrs	Cholesterol Total Mg %	Cholesterol Esters Mg %	Total Cases
DIABETES	40	**277** ± 98	**188** ± 80	69	**277** ± 98	**173** ± 50	**109**
NEPHRITIS E NEPHROS'S	27	**436** ± 324	**296** ± 253	10	**337** ± 150	**222** ± 159	**37**
HYPOTHYROID	26	**304** ± 111	**200** ± 63	15	**311** ± 103	**200** ± 88	**41**
HYPERTHYROID	33	**208** ± 38	**128** ± 43	9	**239** ± 45	**176** ± 53	**42**
C.A.	26	**236** ± 59	**153** ± 42	45	**224** ± 61	**146** ± 43	**71**

Table 8

adequate thyroid extract administration. Beyond that, our therapy must be based upon our results in experimental animal studies and empiricism. The use of potassium iodide and potassium thiocyanate in hypertensive patients, and sex hormones in otherwise normal adults, are still in the experimental stage of the use of all decholesterolizing agents. The experimental results that we have observed with choline and inositol, are not as encouraging as those reported with lipocaic. We have had no results with soya lecithin, Kumbacha and other preparations on the hypocholesterolemia and atheromatosis.

There is no more practical, direct approach to the problem in humans than the therapeutic trial method. During the past two years, patients with high blood cholesterol level have been put on low cholesterol diet and given potassium iodide, thyroid extract, and various lipotropic substances that we had used in the experimental studies. The levels of the blood were determined at intervals from 3 to 6 months. Choline, cloride, bicarbonate, and dihydrogen citrate, and inositol were used and the results are given in Table 9.

EFFECT OF TREATMENT OF HYPERCHOLESTEROLEMIA

No of cases drug treatment		Cholesterol Total	Esters	% Change in Relation to deviation from Normal	
BI CHOLINE	Before[c]Chloride	306	222	53%	46%
	After	273	188		
	% Drop	14.3%	17.1%		
9 CHOLINE	Before[c]HCO_3	385	240	53%	54%
	After	309	173		
	% Drop	19.9%	23.9%		
17 CHOLINE	Before[c]DihCr	304	220	70%	57%
	After	256	165		
	% Drop	20.5%	19.1%		
39 CHOLINE	Before i-inox	325	198	40%	38%
	After	286	185		
	% Drop	10.7%	14.8%		
20 SOYALECITHIN	Before[acletin]	322	206	13%	24%
	After [Granulestia]	308	191		
	% Drop	2.3%	6.5%		

TABLE 9

The patients who were placed on a low cholesterol diet, potassium iodide alone, showed no significant reduction. After 6 to 12 months, the patients with thyroid extract were more definitely affected. No more cases have been studied than previously reported and these were too few to be significant. The same may be said for the cases receiving methionine. Choline and inositol have been used more extensively. Only such patients with initially very high levels were included. The percentage changes are not very great although the cholesterols and esters reductions amounted to 10-20%. The percentage changes calculated in relation to the deviation from normal and a return toward normal showed 50-70%. These latter figures are somewhat encouraging. A completely satisfactory decholesterolizing agent however has not yet been found. The specific hormone has not been discovered. Little is known of the intermediary metabolism of cholesterol, its syn-

thesis, transport or catabolism. The enzyme system responsible for the degradation of cholesterol has not yet been elucidated. There may be some significance to the level of blood serum albumin "fraction (Cohn)" which showed a high titre of antilipfanogens (Simms and Pashley [19]). The permeability of the intima, the internal receptivity of the subintimal tissues may play important roles.

Maintainance of:the colloid equilibrium and prevention of altered precipitability of the lipids must be the goal of treatment. Whether thyroid extract, potassium iodide, choline and inositol affect the formation of atheromatous lesions in humans as in animals is not known. Once the atheromatous plaque has developed, its recession, as apparently happens in animal experiments, is hoped for, but we should continue to seek methods of therapy that will alter or remove the contributory conditions.

The attack on the age-old problem of atherosclerosis must continue and new methods of attack must be evolved with the new isotope tools. In the meantime, we must continue to be patient and prosecute the studies with the means that we now have available. Much more difficult and extensive longterm experimental studies, including absolute and relative quantities of blood lipids and serum protein fractions, identification of sources of lipfanogens and antilipfanogens, cholestorolytic agents, status of intracellular and intercellular colloids, as to aggregation and water binding power, vibratory lability, colloid stability, of lipoid substance, detergents or substances increasing the permeability of the intima and the receptivity of the subintimal tissues, calcium, oxygen, CO_2 oxidases, phosphatases and lipases levels must be done. We must be content with small rewards until the problem in solved. The metabolic disorders must be corrected before the destructiveness of the atheromatosis processes and advances to the point of contributing to this final and fatal phase. We may stay the execution and post-pone the premature pathological aging and normal physiological aging of senescense and senility.

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