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Arteriosclerosis

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ARTERIOSCLEROSIS

A REVIEW OF THE HISTORY OF ARTERIOSCLEROSIS AND A STUDY OF THE RELATION OF LIPOIDS, WITH SPECIAL REFERENCE TO CHOLESTEROL AND ITS DEPOSITION, TO THE PATHOGENESIS OF ARTERIOSCLEROSIS WITH EXPERIMENTAL AND CLINICAL EVIDENCE.

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--INTRODUCTION--

ARTERIOSCLEROSIS IS A DISEASE ABOUT WHICH CONSIDERABLE THEORIZATION HAS OCCURRED. IT HAS PROVED TO BE ONE OF THE MOST INTERESTING SUBJECTS OF DISCUSSION, AND ALSO, AT TIMES, ONE OF THE MOST DISCOURAGING IN THE STUDY OF ITS SEVERAL PHASES. THE EVIDENCE OF THE SIGNIFICANCE OF ITS DIFFERENT PHASES HAS BEEN RATHER CONFLICTING. PERHAPS THE MOST UNDECIDED TRUTHS OF THE DISEASE LIES IN THE ETIOLOGY. ITS TRUE ETIOLOGY IS NOT KNOWN, NEITHER HAS IT BEEN UNIVERSALLY ACCEPTED AS TO ITS POSSIBLE CAUSES. PERHAPS IT HAS BEEN PROVEN BUT NOT BEEN RECOGNIZED.

THE PRESENT RECOGNIZED ETIOLOGICAL FACTORS THAT SEEM TO CAUSE THE DISEASE ARE BELIEVED TO BE TOO GENERAL. A MORE CAREFUL EXAMINATION SEEMS TO SHOW THAT THEY ALL HAVE SOME RATHER COMMON CHARACTERISTICS, AND SO IT WOULD SEEM THAT TO WORK ALONG THE LINES OF THESE SIMILAR FEATURES, A MORE DEFINITE FACT WOULD ARISE AS TO THE ETIOLOGICAL FACTOR OR FACTORS.

A REVIEW OF THE MANY ARTICLES SHOWED THAT CHOLESTEROL MAY HAVE A DEFINITE RELATION TO THE PATHOGENESIS OF THE DISEASE. AN ABNORMAL METABOLISM OF CHOLESTEROL, AN INCREASE IN THE BLOOD STREAM, OR SOME PHYSICO-CHEMICAL PROCESS RELATIVE TO ITS DEPOSITION IN THE ARTERIOSCLEROTIC PLAQUES MAY BE THE BEGINNING OF THE WHOLE PROCESS.

IT HAS BEEN ATTEMPTED TO SHOW A POSSIBLE RELATIO-SHIP BETWEEN CHOLESTEROL AND ARTERIOSCLEROSIS. THE EX-AMINATION OF THE WRITINGS OF THIS DISEASE HAVE BEEN VERY INTERESTING. THE TEACHINGS HAVE PROVEN OF GREAT VALUE.

--HISTORICAL DEVELOPMENT--

1. Among the Ancients-

Arteriosclerosis is one of the diseases having been long endured by the human race. This fact has definitely been shown by the examiners of the Egyptian mummies (1), (2).

Egypt itself being a very dry-climate country and the use of still envied methods of embalming, have preserved many bodies which could easily be examined for the condition of arteriosclerosis. Examiners noted that arteriosclerosis was a very common finding. The first notice of this condition was on opening the body of one of the most widely known of all the ancient royal Egyptians, Menepthah, the reputed Pharaoh of the Hebrew exodus. A part of his aorta was examined which revealed typical advanced sclerotic lesions with extensive deposition of calcium phosphate. The findings were that of senility otherwise(1).

Of the mummies examined, the time of their existence ranged from 1580 B.C. to 525 A.D. In general the findings of arteriosclerosis were very similar to the condition as described in the present day (2).

Marc Armand Ruffer(2), who was connected with the Cairo Medical School, did very extensive work along

THESE LINES. FROM HIS EXAMINATION OF MUMMIES FOR ARTERIOSCLEROTIC LESIONS, HE CONCLUDED THAT THE CONDITION WAS AS PREVALENT AMONG THE ANCIENT EGYPTIANS AS IT IS AS NOW PRESENTED, BUT ALSO SUGGESTES THAT IT MAY HAVE BEEN MUCH GREATER THAN THE MODERN INCIDENCE. IT MIGHT BE SAID IN REGARD TO THE PATHOGENESIS OF THE DISEASE THAT HE RULED OUT STRENUOUS EXERCISE, HARD LABOR, ALCOHOL, AND A HIGH PROTEIN DIET AS ETIOLOGICAL FACTORS. FROM THE KNOWLEDGE OF THE LIFE HABITS OF THE EGYPTIANS THIS DEDUCTION COULD EASILY BE MADE.

BECAUSE OF THE FACT THAT IN NO OTHER PLACE IS THERE ANY OPPORTUNITY TO STUDY ANCIENT PATHOLOGY, DUE TO THE LACK OF BETTER METHODS OF PRESERVING THE BODIES, IT CANNOT BE DEFINITELY DETERMINED AS TO THE CONDITION IN OTHER RACES. ITS PREVALENCE AMONG THE ANCIENTS CANNOT BE DOUBTED HOWEVER.

II. Early Written Suggestions of Arteriosclerosis-

IT WAS NOT UNTIL AFTER THE TIME OF VESALIUS(4) THAT ANATOMISTS FIRST WROTE DESCRIPTIONS OF PATHOLOGICAL CONDITIONS OBSERVED SIMULATING THE PRESENT DAY ARTERIOSCLEROTIC FINDINGS. THE DESCRIPTIONS AS RECORDED WERE NOT LENGTHY. THE WRITERS CONSIDERED THE FINDINGS A NATURAL CONCOMITANT OF SENILITY. THEIR WRITINGS CENTERED AROUND THE PRESENCE OR ABSENCE OF "BONE IN THE HEART". IN THE WRITINGS OF ARISTOTLE(3) AND THOSE OF

HIS PREDECESSORS, THIS PATHOLOGIC CONDITION IS DESCRIBED IN ANIMALS.

IN THE SEARCH FOR THIS BONY STRUCTURE IN MAN, THE EARLY ANATOMISTS SEEMED TO HAVE ENCOUNTERED CALCIFIED AREAS OF THE AORTIC VALVES AND AT THE ROOT OF THE AORTA(3).

THIS "BONE" AS WAS DESCRIBED, SEEMS TO HAVE BEEN ONE OF THE MANY SUBSTANCES USED AS INGREDIENTS IN THE COMPLEX AND UNPLEASAND MIXTURE OF THE POLYPHARMACISTS OF THE MIDDLE AGES(2).

FROM THE WRITINGS OF ABOUT THIS PERIOD, IT WAS SUGGESTED THAT A RELATIONSHIP BETWEEN ARTERIOSCLEROSIS AND SENILITY MIGHT EXIST, AND ALSO BETWEEN THE FORMER AND PROLONGED LABOR.

ARISTOTLE(3) HAD WRITTEN ABOUT CHANGES IN THE SINEWS OF OLD ANIMALS AND CORRELATED THIS FINDING WITH FAILING STRENGTH.

HEROPHILUS AND ERISTRATUS(4) WROTE RATHER EXTENSIVELY ON THE SUBJECT OF VASCULAR DISEASES DESCRIBING PATHOLOGICAL CONDITIONS RESEMBLING ARTERIOSCLEROSIS.

CELSUS AND GALEN, IT SEEMS, HAVE NO VOLUMES MENTIONING ANYTHING SIMILAR TO HUMAN ARTERIOSCLEROSIS(4).

III. <u>FIRST PERIOD-SIXTEENTH AND SEVENTEENTH CENTURIES</u>-

THROUGH THIS TWO CENTURY PERIOD, RECORDS RELATIVE TO THE SUBJECT OF ARTERIOSCLEROSIS ARE RATHER SCARCE.

THE MATERIAL ENCOUNTERED IS USUALLY REPORTS OF ARTERIOSCLEROTIC FINDINGS WITH THE DESCRIPTION OF THE CASES. ANY EXTENSIVE SCIENTIFIC WORK IS LACKING, NO DOUBT, BECAUSE OF THE GENERALLY ACCEPTED BELIEF THAT ARTERIOSCLEROSIS WAS A NATURAL PHENOMENON; THE ARTERIES BECOMING INDURATED WITH AGE. DURING THE SEVENTEENTH CENTURY THE BELIEF WAS THAT INDURATION AND CALCIFICATION OCCURED FOR THE PURPOSE OF KEEPING THE ARTERIES OPEN IN ORDER TO FACILITATE THE COURSE OF THE BLOOD AT AN AGE WHEN THE CONTRACTILE POWER OF THE HEART BECAME LESS ENERGETIC.

MOST OF THE INVESTIGATIONS WERE MADE ON THE LARGE AND MEDIUM SIZED ARTERIES AND IT WAS ONLY A LONG TIME LATER THAT ATTENTION WAS ATTRACTED TO THE LESIONS OF THE ARTERIOLES.

THE AUTHORS OF THIS PERIOD MADE SOME VERY GOOD ANATOMIC AND PATHOLOGICAL ATUDIES, BUT, ON THE CONTRARY, THE CLINICAL DESCRIPTIONS WERE FRAGMENTARY AND INCOMPLETE.

ANTONIO BENINIENI, IN 1507, REPORTED RATHER EXTENSIVE NECROPSY FINDINGS AND MENTIONED PATHOLOGICAL CONDITIONS TERMED "TUBERCLE IN THE HEART". IT IS VERY POSSIBLE THAT THESE MAY HAVE BEEN ARTERIOSCLEROTIC CHANGES. HOWEVER, THERE IS NO VERY COMPLETE DESCRIPTION OR MENTION OF ARTERIOSCLEROSIS(4).

In the great compendium on medicine of the time called, the Medicina, written in 1554 by Jean Fernel(5), there is, interestingly so, no mention of a condition that may have been arteriosclerosis.

During the succeeding years of the Sixteenth Century there appeared casual descriptions of "ossified arteries". Various writers recording bits of information on the subject. By 1600 practically all educated physicians were probably aware of this pathological condition of the arteries, but considered it a natural process in advancing years(4).

During the Seventeenth Century no particular outstanding advances were made along these lines. Writers such as William Harvey, Bartholin, Willis, and Malpighi (4), wrote briefly about arteriosclerosis. Lorenzo Bellini described a condition where he had seen petrifaction in the internal coat of the arteries which led to inflammation. This petrifaction remaining fixed to the inflamed place like a crust (4).

William Cowper(6), during the latter part of the Seventeenth Century, called attention to the fact that in the thickened calcareous arteries the passage of blood was impeded. This observation was recalled years later by writers who were well acquainted with gangrene of the feet as a sequel to hardening of the arteries.

JOHANN CONRAD BRUNNER, AFTER WITNESSING THE NECROPSY OF HIS FATHER-IN-LAW, JOHN JACOB WEPFER, DESCRIBED THE CONDITION OF HIS AORTA, WHICH CONTAINED BONE-LIKE PLAQUES THROUGHOUT(7). IT WAS VERY DIFFICULT TO CUT THROUGH IN THE UPPER PART OF THE ABDOMINAL AORTA. HE NOTED THAT THE INNER COAT WAS RUPTURED, LACERATED, AND RATHER LIKE FRUIT, AND HURT THE HAND WHEN THRUST IN IT FROM THE ROUGHNESS OF THE BONES.

IV. Second Period-Eighteenth Century-

THE AUTHORS AT THE BEGINNING OF THE EIGHTEENTH CENTURY STILL CONSIDERED INDURATION OF THE ARTERIES AS A PHYSIOLOGICAL PHENOMENON DUE TO PROLONGED LABOR AND ACTIVITY OF THE ORGANS, BUT THEY CONSIDERED THE CONSEQUENCES OF MODIFICATION OF THE ARTERIAL WALLS AND WERE FAR FROM CONSIDERING THESE MODIFICATIONS AS A FAVORABLE INFLUENCE AS DID THEIR PREDECESSORS OF THE SEVENTEENTH CENTURY.

THIS PERIOD IS NOTABLE FOR THE APPEARANCE OF SEVERAL IMPORTANT TREATISES ON THE PHYSIOLOGY AND PATHOLOGY OF THE VASCULAR SYSTEM. DISEASES OF THE HEART VALVES AND ANEURYSMS HELD PREFERENCE OVER DEGENERATIVE DISEASES.

WITH THE STEADY ACCUMULATION OF OBSERVATIONS, SPECULATIONS ON THE NATURE OF ARTERIOSCLEROSIS WAS A RATHER NATURAL CONSEQUENCE. THIS WITH THE IMPROVED ANATOMICAL KNOWLEDGE OF ARTERIES ENCOURAGED AN EFFORT TO LOCALIZE THE LESIONS MORE EXACTLY.

BOERHAAVE(8), IN 1708, NOTED THAT THE BLOOD CIRCULATED WITH DIFFICULTY IN THE RIGID ARTERIES AS ALSO DID WILLIAM COWPER(6). HE EXPLAINED THE RIGIDITY OF THE ARTERIES BY THE THICKENING OF THE WALLS OF THE VASA VASORUM UNDER THE INFLUENCE OF THE CONTINUAL FRICTION OF THE CIRCULATING BLOOD IN THESE SMALL VESSELS. HE WAS ALSO THE FIRST TO CONSIDER THE PRIMORDIAL ROLE OF THE ALTERATIONS OF THE VASA VASORUM IN THE PRODUCTION OF ATHEROMATOUS LESIONS.

SALZMANN, KUHN, AND VATER(9), ABOUT 1730 TO 1733, STUDIED THE PROCESSES OF CALCIFICATION AND OSSIFICATION WHICH TOOK PLACE IN THE ARTERIES AND IN OTHER TISSUES. THEY STATED THAT OSTEOGENESIS, SO ACTIVE IN THE FOETUS AND IN INFANTS, BECAME SUSPENDED IN THE ADULTS AND RECOMMENDED IN OLD AGE FINDING A FAVORABLE CONDITION IN THE VISCOSITY OF THE BLOOD. IT IS RATHER CURIOUS THAT THE VISCOSITY OF THE BLOOD SHOULD HAVE BEEN CONSIDERED AT THIS TIME IN VIEW OF THE FACT THAT SO MUCH INVESTIGATION HAD NOT BEEN DONE UNTIL AT A MUCH LATER DATE.

UP TO THIS TIME THE INDURATIONS AND CALCAREOUS PLAQUES WERE CONSIDERED AS MODIFICATION OF THE ARTERIAL WALLS OCCURRING WITH AGE BUT NOT PRESENTING ANY PATHOLOGICAL CHARACTERISTICS. LATER AUTHORS, HOWEVER, SHOWED THAT THE ALTERATIONS IN QUESTION WERE THE RESULT OF A MORBID DISORDER.

JOHANN FREDRICK CRELL, REPORTING IN 1740, WAS PERHAPS THE FIRST TO REPORT THE PATHOLOGICAL NATURE OF THESE PRODUCTIONS OF WHICH HE GAVE THE NAME "TROPHACEOUS DEPOSITS" (10). A MORE COMPLETE DESCRIPTION OF THESE PRODUCTIONS WAS GIVEN BY HIM. HE WROTE A TREATISE ON THE HARDENING OF THE CORONARY ARTERIES IN WHICH HE BELIEVED THAT THE INCRUSTATIONS, UNIVERSALLY SPOKEN OF AS "OSSIFICATIONS", WERE NOT BONY, BUT OF A TROPHACEOUS NATURE AND WERE DERIVED FROM PUS.

CRELL STATED THAT THE CONDITION WAS NOT CONFINED TO SENILITY, BUT COULD BE FOUND AT ANY AGE; A FACT WHICH WAS NOT VERY MUCH NOTED BEFORE BY OTHER INVESTIGATORS. HIS IDEAS AS TO THE PATHOGENESIS WERE THAT THE SLUGGISH, VISCID JUICES, PRESENT IN THE OLD OR INTEMPERATE YOUNG, TENDED TO OBSTRUCT THE ARTERIES' OWN INTRINSIC VESSELS, WHICH RESULTED IN INFLAMMATION AND SUPPURATION. THE OUTPOURED PUS TENDED TO SEPARATE THE FLESHY COAT FROM THE INTERNAL COAT; ITS AMOUNT DEPENDING UPON THE STATE OF HEALTH OF THE BODY. IN TIME, PETRIFACTION OF THE PUS TOOK PLACE WITH THE FORMATION OF SCALES BETWEEN THE COATS(10).

GIOVANNI BATTISTA MORGAGNI(11), IN 1761, CONSIDERED THAT THE ALTERATIONS OF THE ARTERIES FOLLOWED VARIOUS CONDITIONS.

THE LESIONS OF THE DISEASE WERE AT THIS TIME RATHER WELL DESCRIBED BY ANATOMISTS. ONE RECORD GAVE IT

THAT THE INTERNAL SURFACE OF THE AORTA WAS ENTIRELY COVERED BY ELEVATIONS AND PUSTULES WHICH CONTINUED INTO ALL OF THE BRANCHES WHICH WERE OPENED. ONE OF THE LARGER OF THESE BRANCHES SHOWED LARGER ELEVATIONS, AND HAVING BEEN INCISED, PRESENTED A CAVITY AND THIS CAVITY CONTAINED A SOMEWHAT SOFTENED MATERIAL(11).

ALBRECHT VON HALLER OF BERN(12), IN 1755, CONCLUDED FROM HIS NECROPSY WORK THAT A GRADUAL UNINTERRUPTED PROGRESSION TOOK PLACE FROM A SOFT STATE OF ATHEROMA TO A FINAL BONE-LIKE PLATE. HE, WITH CRELL AND A FEW OTHERS PERHAPS, HAVE THE HONOR OF DIRECTING ATTENTION TO THE SOFTENING PROCESS IN THIS COMPLEX ARTERIAL DEGENERATION. HALLER ALSO CONSIDERED INDURATIONS OF THE ARTERIES AS BEING MORBID ALTERATIONS(12).

V. THIRD PERIOD-NINETEENTH CENTURY-

AT THE BEGINNING OF THE NINETEENTH CENTURY IT HAD BEEN SHOWN THAT THE ARTERIAL INDURATIONS WERE NOT THE RESULT OF EITHER OF A FAVORABLE PROCESS OR A SIMPLE PHYSIOLOGICAL EVOLUTION, BUT THAT THEY CONSTITUTED TRUE LESIONS. THIS PERIOD INAUGURATED A NEW ERE IN GENERAL PATHOLOGY, BEING CHARACTERIZED BY INTENSITY OF EFFORT AND CODIFICATION OF FACTES LEARNED INTO A DISTINCT SCIENCE.

DURING THIS PERIOD THE AUTHORS DISCUSSED THE QUESTION AS TO WHETHER ATHEROMATOUS ARTERIES WERE OR WERE NOT OF INFLAMMATORY NATURE.

XAVIER BICHAT(13), CONSIDERED TO BE THE FIRST GENERAL HISTOLOGIST, STATED THAT THE POINT OF ATTACK ON THE MORBID LESIONS OF ANY ORGAN WAS THROUGH CONSTITUENT PARTS. IN 1801 HE LOCATED THE INITIAL LESIONS OF ARTERIAL "OSSIFICATION" IN THE INTIMA, WHILE CRELL(10) AND HALLER(12) LOCATED IT BETWEEN THE INTIMAL AND MEDIAL COATS. HE REACHED HIS DECISION BY CAREFUL DISSECTION AND DID NOT USE THE MICROSCOPE. IT WAS CONSIDERED AS BEING TRUE OSSIFICATION WITHOUT CARTILAGE FORMATION.

LAENNEC, IN 1819, CONTESTED THE OPINION THAT THE ATHEROMATOUS ALTERATIONS WERE DUE TO INFLAMMATION(14). IN REGARD TO THE LOCATION OF THE PLAQUES OF OSSIFICATION, HE RELOCATED THEM BETWEEN THE INNER AND MIDDLE COATS.

JOSEPH HODGSON(15), IN 1815, WROTE A LENGTHY DESCRIPTION OF THE DISEASES OF THE BLOOD VESSELS. IN HIS TREATISE HE STATED THAT THE ATHEROMATOUS CHANGES WERE THE RESULT OF ARTERIAL INFLAMMATION AND THE CONTENT OF THE SOFT LESIONS TRUE PUS. HE ALSO CONSIDERED THAT THE PRIMARY LESIONS TO BE WITHIN THE SUBSTANCE OF THE INNER COAT OF THE ARTERIAL WALL. IN REGARD TO THE QUESTION OF TRUE BONE BEING PRESENT IN THESE CALCAREOUS PLAQUES OF THE ARTERIES, HE ASKED HIS FRIEND, MR. BRANDE, TO DETERMINE THE CHEMICAL CONTENT. IT WAS FOUND THAT

THESE PLAQUES WERE COMPOSED OF 65.5 PERCENT PHOSPHATE OF LIME, 34.5 PERCENT ANIMAL MATTER. THE LATTER BEING OF ALBUMINOUS NATURE. THIS CONVINCED HIM THAT IT WAS MERELY AN EARTHY DEPOSIT AND NOT TRUE BONE.

A FEW YEARS LATER LOBSTEIN, DOING SOME WORK ON THIS CONDITION, GAVE THIS THE TERM "ARTERIOSCLEROSIS"(16). HE OPPOSED THE IDEA ALREADY ACCEPTED THAT ANGINA PECTORIS WAS THE RESULT OF CORONARY ARTERY DISEASE; NOTING AN ABSENCE OF THE DISEASE IN THE PRESENCE OF THE DISEASE, AND VICE VERSA. HIS IDEA WAS THAT THESE PATHOLOGICAL ALTERATIONS WERE THE RESULT OF DISORDERS OF NUTRITION WHICH USUALLY DEVELOPED UNDER THE INFLUENCE OF GOUT AND RHEUMATISM.

LATER THE TERM WAS SOMEWHAT CHANGED FROM ITS ORIGINAL MEANING. SOME AUTHORS USED THE TERM TO DESIGNATE A GENERALIZED AFFECTION OF THE ENTIRE ARTERIAL SYSTEM OF WHICH ATHEROMA WAS A SINGLE LOCATION OF THE CONDITION. OTHER AUTHORS CONSIDERED THAT ATHEROMA AND ARTERIOSCLEROSIS WERE TWO DIFFERENT AFFECTIONS AND RESERVED THE LATTER TERM FOR ALTERATIONS OF THE ARTERIOLES OF WHICH LOBSTEIN WAS IGNORANT(17),(18).

CARL ROKITANSKY (17) PUBLISHED HIS INVESTIGATIONS IN 1844. THE FINDINGS INDICATED THAT THE THICKENINGS OF THE AORTA WERE DUE TO THE DEPOSIT OF A BLASTEMA. THIS BLASTEMA CAME FROM THE BLOOD AND WAS DEPOSITED IN

OR ON THE INTERNAL SURFACE OF THE VESSEL. THE BLASTEMA WAS NOT DUE TO MODIFICATION IN THE STRUCTURE OF THE AORTA BUT WAS THE RESULT OF A SPECIAL BLOOD CONDITION. THE STRUCTURE COULD UNDERGO VARIOUS METAMORPHOSES; IT COULD BE TRANSFORMED INTO A CONNECTIVE TISSUE AND INTO AN ELASTIC AND FENESTRATED MEMBRANE. FINALLY, THE LATER METAMORPHOSES OF THIS SAME BLASTEMA CAUSED THE PRODUCTION OF ATHEROMA AND CALCAREOUS PRODUCTIONS.

DURING THE SECOND HALF OF THE NINETEENTH CENTURY THE INTRODUCTION OF SUCH INSTRUMENTS AS THE MICROTOME, MICROSCOPE, KYMOGRAPH AND THE SPHYGMOMANOMETER AIDED EXTENSIVELY IN THE INVESTIGATION OF THE CONDITION.

RUDOLF VIRCHOW(18), IN 1856, CONTESTED THE OPINION OF ROKITANSKY(17) IN THAT HE BELIEVED THAT THE LESION LAY UNDER THE ENDOTHELIUM. THE HYPERPLASIA OF THE INTERNAL TUNIC WAS NOT THE RESULT OF THE DEPOSIT OF A SUBSTANCE COMING FROM THE BLOOD; IT WAS THE INFLAMMATION COMPARABLE IN ALL RESPECTS TO THAT OBSERVED IN ENDOCARDITIS. THE INFLAMMATORY PRODUCTS THEN SHOWED SECONDARY TRANSFORMATIONS OF WHICH ATHEROMA WAS THE MOST FREQUENT. VIRCHOW(18) CLEARLY SEPARATED ATHEROMA FROM SINGLE FATTY DEGENERATION, THE LATTER BEING PURELY PASSIVE WHILE THE FIRST WAS ASSOCIATED WITH AN IRRITATION. THE SCLEROUS LESIONS WERE EQUALLY DUE TO TO INFLAM-

MATION. ACCORDING TO HIS PUPIL, EDWARD RINDFLEISCH, IN HIS MANUAL OF PATHOLOGICAL HISTOLOGY, VIRCHOW DESCRIBED THE INITIAL LESION AS BEING A REPRESENTATION OF A CHRONIC INFLAMMATION WITH AN OVERGROWTH OF CONNECTIVE TISSUE, DUE TO THE MECHANICAL IRRITATION OF THE BLOOD PRESSURE ON THE INTIMA AT THE AFFCTED POINT. ADVANCED AGE, FREE LIVING, AND EXCESSIVE USE OF ALCOHOL WERE TO BE CONSIDERED PREDISPOSING FACTORS. THIS SCLEROSIS RESULTED IN A DIFFICULT NUTRITIONAL PROBLEM BECAUSE OF THE LACK OF VESSELS. FATTY DEGENERATION OF THE CONNECTIVE TISSUE OCCURRED WITH SOLUTION OF INTERCELLULAR GROUND SUBSTANCE FOLLOWED BY IMPREGNATION OF THE INTERCELLULAR SUBSTANCE WITH CALCIUM SALTS.

THE DOCTRINE OF VIRCHOW(18) UNDERWENT MODIFICATIONS IN PROPORTION AS THE IDEAS ON INFLAMMATION CHANGED. HOWEVER, THE QUESTION AS TO WHETHER THE ARTERIAL LESIONS WERE OR WERE NOT OF INFLAMMATORY NATURE, WHETHER INFLAMMATION WAS OR WAS NOT POSSIBLE IN A TISSUE DEPRIVED OF VESSELS SUCH AS THE ENDARTERIUM, HAD LOST A PART OF THEIR INTEREST. NEW PROBLEMS HAD ARISEN AND PATHOGENIC PROCESSES WERE VIEWED FROM A DIFFERENT ANGLE. THE FIRST DESCRIPTIONS OF THE ALTERATIONS OF THE VISCERAL ARTERIOLES MARKED AN IMPORTANT DATE AND THE BEGINNING OF A NEW PERIOD IN HISTORY OF OUR KNOWLEDGE REGARDING DISEASES OF THE ARTERIES AND ESPECIALLY ARTERIO-

SCLEROSIS. THE INVESTIGATIONS OF PREVIOUS AUTHORS MUST BE CONSIDERED VALUABLE BECAUSE OF THE EXACTNESS OF THE DESCRIPTIONS OF THE LESIONS (18), (11).

ONE OF THE FIRST TO DESCRIBE THE ARTERIAL LESIONS WAS GEORGE JOHNSON, IN 1852(19). HE CALLED ATTENTION TO THE THICKENING OF ARTERIAL WALLS OF THE KIDNEY IN CHRONIC BRIGHT'S DISEASE FROM HIS MICROSCOPIC STUDIES. SOON AFTER, THIS FACT CONCERNING THE ARTERIOLES WAS WELL ESTABLISHED.

AT THIS TIME IT WAS RATHER WELL ESTEBLISHED AS TO THE NATURE OF THE CLINICAL AND PATHOLOGICAL FEATURESOF THE DISEASE. THE VIEWS TAKEN WERE WELL ACCEPTED BY THE INVESTIGATORS. AS TO THE PATHOGENESIS, SOME VERY INTERESTING THEORIES WERE EXPOUNDED; SOME UNIQUE AND OTHERS POORLY HANDLED. BUT IT WASN'T UNTIL ABOUT THIS TIME THAT THE PATHOGENESIS WAS VERY MUCH CONSIDERED. IT SOON GAINED CONSIDERABLE MOMENTUM AND HAS BEEN GAINING EVER SINCE. THE PATHOGENIC INVESTIGATIONS CONTINUED TO BE MOST ACTIVE AMONG THE GERMAN ANATOMISTS.

RICHARD THOMA, IN 1883, DEVELOPED ONE OF THE MOST INFLUENTIAL PATHOGENIC THEORIES OF THE TIME(4). HIS ARTICLES ON THE SUBJECT ARE NUMEROUS. THOMA BELIEVED THAT THE INTIMAL PROLIFERATION WAS A COMPENSATORY MECHANISM FOR A PRIMARY LESION ELSEWHERE IN THE ARTERIAL WALL.

JORES(9), IN 1890, DEVELOPED A THEORY CONCERNING THE ELASTIC TISSUE WHICH WAS PREVIOUSLY IGNORED. HE

STATED THAT AN OVERGROWTH OCCURRED FOLLOWING RETROGRESSIVE CHANGES IN THE ARTERIAL WALL.

VI. Fourth Period-Twentieth Century-

During this period there have been many important investigations upon the etiological conditions which determine the appearance of arteriosclerotic lesions. This is a rather natural happening however. The only other phase of the disease of which was little known was the therapeutic phase. So naturally it would follow logically to turn to the cause to endeavor to outline the treatment of the disease. As to the etiology of the disease very numerous works have appeared on very numerous possible causes of the disease. Also many works have appeared on the clinical aspect of arteriosclerosis.

It was at the beginning of this period that a new subject arose in regard to the etiology of arteriosclerosis. This was the relation of cholesterol to arteriosclerosis(20).

Ignatowski(20), in 1908, performed experiments to determine the effects produced by feeding protein. This was done to determine the metabolism and renal functions of herbivorous animals by the ingestion of food which is not natural to them, such as, meat, milk and eggs. In the course of his experiments he made the observa-

TION THAT SOME OF HIS EXPERIMENTAL ANIMALS EXHIBITED PRONOUNCED AORTIC CHANGES, CONSISTING OF THICKENING OF THE INTIMA, WHICH RESEMBLED THOSE OBSERVED IN HUMAN ARTERIOSCLEROSIS. FROM HIS RESULTS HE STATED THAT IT MUST HAVE BEEN DUE TO THE PROTEIN IN THE FOOD. THIS ASSUMPTION WAS SUBSEQUENTLY QUESTIONED AND DISPROVEN BY LATER AUTHORS WORKING ALONG THE SAME LINES.

CONSIDERABLE LIGHT WAS THROWN ON THE SUBJECT WHEN ANITSCHKOW(20), IN 1912, WORKING ON RABBITS, SUCCEEDED IN PRODUCING THE TYPICAL PICTURE OF RABBIT ATHEROSCLEROSIS BY FEEDING PURE CHOLESTERIN DISSOLVED IN VEGETABLE OIL. HE WENT FURTHER STATING THAT THE EXPERIMENTS BY IGNATOWSKI REPRESENTED THE SAME CONDITION BECAUSE HE FED HIS ANIMALS FOODS THAT CONTAINED VERY HIGH AMOUNTS OF CHOLESTERIN.

SINCE THIS WORK BY ANITSCHKOW(20), CONSIDERABLE AMOUNT OF WORK HAS BEEN DONE ALONG SIMILAR LINES TO DETERMINE MORE ACCURATELY THE PATHOGENESIS OF THE DISEASE IN REGARD TO THE RELATION OF CHOLESTEROL OR THE METABOLISM OF CHOLESTEROL TO ARTERIOSCLEROSIS.

ALONG OTHER LINES HAS THERE ALSO BEEN MUCH INVESTIGATION. HOWEVER, THE EVIDENCE ALONG THE LINES OF ANITSCHKOW(20) HAVE PROVEN MORE ENCOURAGING THAN HAVE THOSE IN REGARD TO OTHER POSSIBLE EIOLOGICAL FACTORS.

--PATHOLOGY--

ANATOMY-

In beginning the study of the pathology of this condition it would be well to review the anatomy of the blood vessels briefly(21).

In the walls of the arteries there can be distinguished three layers; 1. an inner coat, tunica intima or interna, the constituent elements appearing longitudinally. 2. the intermediate coat, tunica media, structures arranged circularly, and 3. the external coat, tunica adventitia or externa, merging with the loose adjacent connective tissue. Its elements mostly run parallel to the long axis of the vessel.

There is placed between the tunica intima and the tunica media a structure, termed the internal elastic membrane, which is most prominent in the arteries of medium caliber. Also between the tunica media and the tunica adventitia is a similar structure called the external elastic membrane. It however is not always observable but being present in most cases. The tunica media is the thickest layer of the wall and its character determines the type of artery.

The chief difference of the arteries of different caliber is in the thickness of the different layers. There is also some difference in that some have not all the layers as is the case in the smaller arteries, which

LACK A DEFINITE EXTERNAL ELASTIC MEMBRANE. IN THE LARGER CALIBER ARTERIES, BENEATH THE ENDOTHELIUM, IS A LAYER OF MANY BRANCHING ELASTIC FIBERS WHICH FUSE IN PLACES INTO A MORE OR LESS WELL PRONOUNCED, STRIATED MEMBRANE, WHICH BY THE LOCATION IS THE INTERNAL ELASTIC MEMBRANE.

THE ENDOTHELIUM IS A LINING MEMBRANE OF THE ARTERIES COMPOSED OF A SINGLE LAYER OF FLATTENED ENDOTHELIAL CELLS WHICH OFFERS A SMOOTH SURFACE AND ACTS AS A PROTECTION FOR THE BLOOD AGAINST ANY CONTACT WITH OTHER TISSUES. THE MEDIA IS COMPOSED OF ELASTIC TISSUE, SMOOTH MUSCLE, AND CONNECTIVE TISSUE. THE ADVENTITIA IS COMPOSED OF A LOOSE CONNECTIVE TISSUE CARRYING BLOOD VESSELS, NERVES, AND CONTAINING A LOOSE NETWORK OF ELASTIC FIBRILS.

PATHOLOGY-

THE EARLIEST CHANGES THAT HAVE BEEN RECOGNIZED IN THE AORTAS AT THE BEGINNING OF ARTERIOSCLEROSIS ARE FOUND IN THE FORM OF VERY SLIGHTLY ELEVATED, FLATTENED YELLOW STREAKS, WHICH USUALLY RUN ON THE POSTERIOR SURFACE OF THE VESSEL(22). THESE RUN LONGITUDINALLY IN THE REGION OF THE OPENINGS OF THE INTERCOSTAL ARTERIES. THESE FINDINGS ARE NOT CONFINED TO THESE REGIONS HOWEVER. WITH A FURTHER ADVANCE OF THE DISEASE THESE YELLOW PATCHES ARE TO BE FOUND DIFFUSELY DISTRIBUTED AMONG THE OLDER LESIONS. FROM SECTIONS PASSING THROUGH THEM,

IT IS SHOWN, THAT WHILE THE ARTERY IS NORMAL ELSEWHERE THE ELEVATION IS DUE TO A DISTINCT THICKENING OF THE INTIMA, PRODUCED BY A NEW FORMATION OF CONNECTIVE TISSUE WITH SMALL AND LARGE WANDERING CELLS. BOTH THE ORIGINAL BRANCHED CONNECTIVE TISSUE CELLS AND THE WANDERING CELLS ARE FOUND TO BE LOADED WITH FAT. THIS FAT EXTENDS TO THE SURFACE WHERE THE FAT-LADEN WANDERING CELLS LIE FREE IN THE CREVICES.

IN A LATER STAGE THE RAISED THICKENED INTIMA BECOMES MORE EXTENSIVE AND THICKER, AND THE TISSUE BECOMES HYALINE OR NECROTIC ABOUT THE MOST ABUNDANT ACCUMULATION OF FAT.. THE SUPERFICIAL OR INNERMOST LAYERS BECOME VERY MUCH THICKENED AND ARE NOW COMPOSED OF A DENSE, HOMOHENEOUS CONNECTIVE TISSUE. IT IS VERY RARE THAT THE VASA VASORUM PENETRATE FROM THE MEDIA TO TAKE PART IN THIS NEW FORMATION OF TISSUE, AND GENERALLY THEY CAN BE FOUND ONLY IN THE LATER STAGES. THERE IS ALSO NO INVASION OF WANDERING CELLS AT ALL COMMENSURATE WITH THE NEW FORMATION OF TISSUE.. THE DENSE CONNECTIVE TISSUE FORMED OVER THE MASS OF FAT-CONTAINING TISSUE IS BLUISH-WHITE AND TRANSLUCENT. IT COVERS THE YELLOW, OPAQUE, FATTY MATERIAL SO THAT IT NOW APPEARS TO LIE IN THE DEPTHS OF THE INTIMA, ENCROACHING ON THE MUSCULO-ELASTIC LAYER AND THE INTERNAL ELASTIC LAMELLA.

UPON OPENING THE AORTA, ELEVATED, ROUNDED OR IRREGULAR PLAQUES OR PATCHES STAND UP FROM THE INTIMAL SURFACE LIKE SOLIDIFIED DROPS OF PARAFFIN. ON CUTTING THROUGH THEM THERE IS ALWAYS TO BE FOUND THE MASS OF OPAQUE, YELLOW, FATTY MATERIAL HIDDEN IN THEIR DEPTHS. FROM THE CUT EDGE, THIS YELLOW MASS CAN BE EXPRESSED OR DUG OUT, AND ITS SOFT MUSHY CHARACTER IS THE ORIGIN OF THE NAME "ATHEROMA", WHICH MEANS "MUSH" IN GREEK(23). OFTEN THE FAT EXTENDS SO AS TO FORM A HALO ABOUT SUCH A PLAQUE, THE OPAQUE MATERIAL SHINING THROUGH THE RELATIVELY THIN SURROUNDING INTIMA.

AT THIS STAGE THE INTERNAL ELASTIC LAMELLA UNDERLYING THE PLAQUE GENERALLY SHOWS FRAGMENTATION OR INTERRUPTIONS, OR IT IS FRAYED OUT INTO SEVERAL THIN LAMINAE WHICH AGAIN UNITE AT THE OTHER EDGE OF THE PLAQUE. USUALLY THE LONGITUDINAL MUSCLE FIBERS OF THE MUSCULO-ELASTIC LAYER ARE INVOLVED IN THE NECROSIS IN THE DEPTHS OF THE PLAQUE AND IN A GREAT PART, DESTROYED. DELICATE ELASTIC FIBRILS APPEAR IN THE NEW TISSUE WHICH FORMS INSIDE THE MUSCULO-ELASTIC LAYER.

THE MEDIA UNDER THE PLAQUES GENERALLY SHOWS VERY SLIGHT ALTERATIONS. VERY DEFINITE THICK PLAQUES MAY FORM IN THE INTIMA, WHILE THE UNDERLYING MEDIA SEEMS PRACTICALLY INTACT. THERE ARE FOTEN SLIGHT ACCUMULATIONS OF FAT IN THAT LAYER, AND IT IS GENERALLY THINNER

UNDER THE PLAQUES THAN IN THE NEIGHBORING REGIONS. SUCH THINNING OUT MAY PROCEED ALMOST TO THE COMPLETE DISAPPEARANCE OF THE COAT. THE CENTRAL MASS OF THE PLAQUE BECOMES VERY SOFT SO THAT IF THE INNER WALL OR ROOF OF THIS SAC GIVES WAY AND THE CONTENTS ARE WASHED OUT INTO THE BLOOD STREAM AND THE RAGGED EDGES AND BASE ARE EXPOSED TO THE CIRCULATING BLOOD WHERE OFTEN THROMBI FORM.

THE SOFT MATERIAL IS FOUND TO BE RICH IN CRYSTALS OF CHOLESTERIN AS WELL AS GLOBULES OF FAT, SOME OF WHICH ARE EVIDENTLY CHOLESTERIN ESTERS, SINCE THEY ARE DOUBLY REFRACTIVE, WHILE OTHERS ARE NEUTRAL FATS(24). GRANULES OR LITTLE SPHERULES OR LARGER, IRREGULAR MASSES OF CALCIUM AND MAGNESIUM PHOSPHATE ALSO APPEAR, AND INDEED, THE DEPOSIT OF CALCIUM MAY BE SO GREAT THAT THE WHOLE PLAQUE BECOMES CONVERTED INTO A SOLID PLATE OF STONY MATERIAL WHICH WILL CRACK WITH A DRY SNAP(25). SUCH PLATES CORRESPOND FAIRLY WELL WITH THE CONTOUR OF THE ARTERY, ALTHOUGH THEY PROJECT AWKWARDLY WHEN THE VESSEL IS LAID OPEN. USUALLY THEY ARE SMOOTHLY COVERED WITH A DELICATE LAYER OF INTIMAL TISSUE AND ENDOTHELIUM, OTHERWISE THEY FORM A BASE FOR THE DEPOSIT OF THROMBI. ACTUAL BONE FORMATION MAY OCCUR WITH MARROW CAVITY AND MARROW RICH IN CELLS, EITHER IN CALCIFIED PLAQUES IN

THE VESSEL WALL OR IN OLD CALCIFIED THROMBI WHICH ADHERE TO IT (22). EXACTLY THE SAME PROCESSES IN THE SAME SEQUENCE ARE FOUND IN THE OTHER ARTERIES OF THE BODY. CALCIFICATION OF THE NECROTIC AND FATTY PLAQUE OCCURS IN ALL ARTERIES AS IT DOES IN THE AORTA. ALL THE STAGES OF THE PROCESS OF SCLEROSIS MAY BE PRESENT AT THE SAME TIME IN A REGION OF THE ARTERY PRESENTING VARIED APPEARANCES. ALL CASES SHOW A VERY GREAT DIMINUTION OF THE ELASTICITY OF THE ARTERY WALL, ALTHOUGH THE RIGIDITY MAY BE INCREASED(22).

OPHULS(26) DESCRIBES LESIONS WHICH OCCUR IN THE LARGE AND SMALL BRANCHES AND THE ARTERIOLES. IN THE LARGE BRANCHES THE FORMATION OF NEW ELASTIC MEMBRANES SEEMS TO BE THE MOST IMPORTANT FEATURE. IN THE ADVANCED CASES OF ARTERIOSCLEROSIS THE GROWTH OF FIBROUS TISSUE BETWEEN THE ELASTIC LAYERS OR ON TOP OF THEM IS RATHER COMMONLY SEEN. HOWEVER, THE DEGENERATIVE CHANGES ARE USUALLY NOT VERY MARKED. THE EARLY LESIONS CONSIST IN A FAIRLY DIFFUSE AND RATHER CELLULAR FIBROUS THICKENING OF THE INTIMA. LATER A CONSIDERABLE AMOUNT OF ELASTIC TISSUE MAY DEVELOP IN THE THICKENED INTIMA. THE MAIN CHANGES IN THE ARTERIOLES ARE THOSE OF HYALINE DEGENERATION.

ACCORDING TO CEELEN(27) THE DIFFERENT PROCESSES DISTINGUISH THEMSELVES FROM EACH OTHER BY THEIR LOCAL-

IZATION IN THE VASCULAR SYSTEM; BY THEIR SEAT IN THE LAYERS OF THE WALLS OF THE VESSELS; BY THEIR PATHOGENESIS AND ETIOLOGY; AND FINALLY, BY THEIR SIGNIFICANCE FOR THE ENTIRE BODY. THEIR INCLUSION IN ONE PATHOLOGICAL CONCEPTION IS NOT JUSTIFIED FROM A SCIENTIFIC POINT OF VIEW. THE THREE TRANSFORMATIONS ARE; 1. THE TRUE ARTERIOSCLEROSIS, WHICH IS ALSO TERMED ATHEROSCLEROSIS AND SCLERATHEROMATOSIS; 2. THE SO-CALLED CALCIFICATION OF THE MEDIA; AND 3. A PECULIAR HYALINE-SCLEROTIC TRANSFORMATION, WHICH AS A RULE IS DESIGNATED BY THE NAME OF ARTERIOLOSCLEROSIS. TRUE ARTERIOSCLEROSIS IS CHIEFLY A DISEASE OF THE INTIMA WHICH IS DUE TO NUTRITIONAL DISTURBANCES OF A PROGRESSIVE AND REGRESSIVE NATURE.

IN THIS WRITING IT WILL BE CONSIDERED THAT ARTERIOSCLEROSIS IS SOMEWHAT OF A GENERAL TERM INCLUDING THE CONDITIONS DESCRIBED AS ATHEROSCLEROSIS AND ARTERIOLOSCLEROSIS.

--PATHOGENESIS--

CONSIDERING THE PATHOGENESIS OF ARTERIOSCLEROSIS, THE SIGNIFICANCE OF THE FATTY STREAKS FOUND IN THE WALLS OF THE ARTERIES MUST BE CONSIDERED.

A GOOD DESCRIPTION OF THE FATTY STREAKS IS GIVEN BY LANGE (28). THEY WERE OBSERVED AS BEING ROUND OR OVAL, SLIGHTLY PROJECTING YELLOW SPOTS, WHICH ARE SOMETIMES QUITE ELONGATED OR ARRANGED IN ROWS. MICROSCOPIC EXAMINATION REVEALS THAT THE INTIMA IS SLIGHTLY SWOLLEN AS IF IT WERE EDEMATOUS. THE CELLS IN THE INTIMA ARE SWOLLEN AND LOADED WITH FINE ANISOTROPIC LIPOID DROPLETS CONSISTING LARGELY OF CHOLESTEROL AND FAT.

ACCORDING TO KLOTZ AND MANNING (29), THESE LIPOID DROPLETS MAY BE DEPOSITED IN THE SUB-ENDOTHELIAL LAYER OR IN THE MUSCULO-ELASTIC LAYER OR BOTH. PATHOGENICALLY THEY BELIEVED THAT THESE FATTY DEPOSITS HAVE A DEFINITE CAUSAL RELATIONSHIP TO ATHEROMATOUS CHANGES IN THE ARTERIES. IT MAY BE THAT SOME OF THESE MAY BE REABSORBED IN THE EARLY STAGES, BUT IN OTHERS, LATER THE SUPERFICIAL PARTS OF THE INTIMA BECOME THICKENED BY THE DEVELOPMENT OF HYALINE FIBROUS TISSUE. THIS IS MORE PARTICULARLY TRUE WHEN THE FAT HAS BEEN LIBERATED BY A DISINTEGRATION OF THE FAT-CARRYING CELLS. FURTHER WORK ALONG THIS LINE CONVINCED KLOTZ THAT THE ABOVE CONDITIONS WERE TRUE (30).

SANDERS (31) DOING CONSIDERABLE WORK ON THE PHYSIOLOGY AND PATHOLOGY OF CHANGES OF THE INTIMA COULD NOT CONCEIVE OF ANY CAUSAL RELATIONSHIP BETWEEN THE FATTY STREAKS AND ARTERIOSCLEROSIS. HOWEVER, THIS DID NOT DETER THE WORK DONE BY KLOTZ AND MANNING (29) WHO, AFTER STUDYING THE OCCURRENCES OF FATTY STREAKS, BROUGHT OUT STATISTICS SHOWING THAT THE GREATEST INCIDENCE IS BETWEEN THE AGES OF TWENTY (20) AND THIRTY (30) AND THAT IT WAS UNUSUAL BEFORE TEN (10) AND AFTER FIFTY (50) YEARS.

THE DEPOSITS IN THE AORTS OF THE YOUNG, AS SHOWN BY KLOTZ (30), SEEMED TO CONTAIN THE LIPOID MATERIAL AT FIRST IN LARGE LUTEIN-LIKE CELLS LOCATED IN THE INTIMA. IT SEEMED THAT THESE CELLS WERE HIGHLY PHAGOCYTIC FOR THE LIPOIDS OF THE CIRCULATING BLOOD. THE PROBABILITY WAS PRESENTED THAT THE ACCUMULATION OF FAT IN EXCESS, IN THE TISSUES OF THE ARTERIES, OWES ITS PRESENCE TO PROCESSES OF A HYPER-PHYSIOLOGICAL NATURE.

ANITSCHKOW (32), FROM HIS STUDIES OF THE HISTOPATHOLOGY OF THE ARTERIES PRESENTED THE THEORY THAT THE ENDOTHELIAL LINING OF THE ARTERIES IS PERMEABLE FOR LIPOIDS AND VARIOUS COLLOIDAL SUBSTANCES DISSOLVED IN THE PLASMA. THESE SUBSTANCES ARE ABSORBED BY THE INTERSTITIAL CHROMOTROPHIC SUBSTANCE OF THE WALLS, ESPECIALLY OF THE INTIMA, AND ON THE SURFACE OF THE ELASTIC FIBERS. BECAUSE OF THE SEVERITY OF ARTERIOSCLEROSIS IN DIABETES, WITH THEIR HIGH LIPEMIA AND

CHOLESTEREMIA, HE BELIEVED THAT THERE WAS A DEFINITE RELATION BETWEEN LIPOID INFILTRATION AND THE GENESIS OF ARTERIOSCLEROSIS.

BALDAUF (33) HAS SHOWN FROM A CHEMICAL ANALYSIS OF ATHEROMATA OF THE AORTA THAT THERE IS AN INCREASE IN THE FATTY EXTRACTIVE SUBSTANCES. THERE WAS ALSO A HIGHER PERCENTAGE OF FATTY ACID IN THOSE AORTAS THAT WERE NOT CALCIFIED.

IT MAY BE PROBABLE THAT THE DEPOSITION OF CHOLESTEROL TAKES PLACE FOR REASON SOMEWHAT SIMILAR TO THE DEPOSITION OF CALCIUM. CALDWELL (34) SHOWED AN INCREASE IN THE CHOLESTEROL CONTENT IN CASEOUS TUBERCLES AND WITH TIME THERE IS A GRADUAL ACCUMULATION OF THIS SUBSTANCE THERE. BY FEEDING CHOLESTEROL TO TUBERCULOUS ANIMALS THERE IS A TENDENCY FOR AN INCREASE IN THE AMOUNT PRESENT IN THE TUBERCLES (35). FROM THIS IT MAY SEEM THAT CHOLESTEROL MAY BE DEPOSITED AS IS CALCIUM TO ACCUMULATE IN NECROTIC TISSUES GENERALLY.

MORE SPECIFIC REFERENCE TO THE PATHOGENICITY OF ARTERIOSCLEROSIS, BLEITZKE (36) PRESENTS TWO CARDINAL LINES OF THOUGHT WHICH CONFRONT EACH OTHER. THE ONE, RULING AT THE PRESENT TIME, SEES THE ESSENTIAL FACTOR IN A PENETRATION OF LIPOID PLASMA INTO THE INTIMA; MECHANICAL CONDITIONS NOT ONLY FACILITATE THE ENTRANCE OF THE PLASMA AT CERTAIN POINTS, BUT ALSO PROMOTE THE APPEARANCE OF DEGENERATIVE TRANSFORMATIONS AND REACTIVE PROLIFERATIONS IN THESE PLACES. THE OTHER LINE OF THOUGHT CONSIDERS THE CHIEF CAUSE TO BE MACULATED LESIONS OF THE MEDIA,

REGARDLESS OF WHETHER THEY MAY BE OF ANATOMICAL OR FUNCTIONAL ORIGIN; IT CONSIDERS THE INTIMAL PROLIFERATIONS TO BE COMPENSATORY AND THE FATTY AND OTHER DEGERATIVE TRANSFORMATIONS TO BE SECONDARY, OR AT MOST, OF EQUAL IMPORTANCE. IT IS NOT BELIEVED BY HIM THAT THE INFILTRATION OF LIPOID SUBSTANCE TO BE PRIMARY. LIPOID SUBSTANCES AND CALCIUM ARE ALREADY DEPOSITED IN THE NORMAL WALL OF THE ARTERY, THEY CAN ONLY ORIGINATE FROM THE BLOOD. THE STRENGTH OF THE DEPOSITS IS IN A CONDITION OF DEPENDENCE UPON THE PLETHORS OF THE BLOOD OF THESE SUBSTANCES. IN THIS, THE GENERAL DISORDERS OF METABOLISM PLAY A CERTAIN PART, ABOVE ALL, HYPERCHOLESTEREMIA, WHICH CAN EASILY BE PRODUCED EXPERIMENTALLY IN THE HERBIVOROUS RABBIT (19)

CONCERNING THE LIPOID MACULATIONS FOUND IN THE AORTA (36), WHICH DO NOT REVERT INTO THE SCLEROTIC PLATES, IT IS NOTED THAT THEY APPEAR AND CORRESPOND IN FORM ENTIRELY TO THE SO-CALLED "SPONTANEOUS" AORTIC RUPTURES, WHICH GENERALLY APPEAR IN SUDDEN INCREASES OF HIGH BLOOD PRESSURE. IT IS KNOWN THAT THE SITE AND FORM OF SUCH RUPTURES ARE DETERMINED BY THE FACT THAT IN SEVERE INCREASES OF BLOOD PRESSURE THE GREATEST TENSION MUST SET IN AT THE POINT WHERE A GENERAL EXPANSION OF THE WALL IS NOT POSSIBLE. THESE POINTS CORRESPOND TO THE SITES OF THE LIPOID MACULATIONS. THE INTIMA NOT BEING SO PERMEATED WITH ELASTIC COMPONENTS WILL SUFFER MECHANICAL LESIONS AT THE POINTS OF THE GREATEST TRACTION,

WHICH FACILITATES THE PENETRATION OF THE LIPOID PLASMA AND PROBABLY ALSO FAVORS THE FALLING OUT OF THE LIPOIDS.

ASCHOFF (37) PRESENTS A DIFFERENT VIEW AS TO THE FOLE OF THE LIPOIDS AND CHOLESTEROL IN THE PATHOGENESIS OF ARTERIOSCLEROSIS. THE DEPOSITION OF THE LIPOIDS PRIMARILY TAKES PLACE IN THE INTIMA OF THE BLOOD VESSELS EXCEPT IN THOSE PLACES WHERE THE DEEPER LAYERS OF THE INTIMA--NEXT TO THE MEDIA- ARE PARTICULARLY LOOSELY KNIT AS IN THE AORTA, CAROTIDS, AND CORONARY ARTERIES.

IT IS KNOWN THAT THE INTIMA AND THE INNER TWO-THIRDS OF THE MEDIA OF THE LARGE VESSLES DERIVE THEIR NOURISHMENT FROM THE BLOOD STREAM (21). THERE IS A CONTINUOUS FLOW OF LYMPH FROM THE CIRCULATING BLOOD INTO THE VESSEL WALL. WITH THESE FACTS ASCHOFF (37) SUGGESTED THAT THE LIPOIDS ARE BROUGHT INTO THE VESSEL WALLS FROM WITHIN THE LUMEN. IN THESE CIRCUMSTANCES THIS LIPOID DEPOSITION APPEARS FIRST WHERE PHYSICAL PROPERTIES ARE MOST FAVORABLE WHICH IS IN EVERY CASE AT THE BORDER OF THE MEDIA. VIA THE LYMPH THE LIPOID SUBSTANCE IS DEPOSITED IN THE FINE MESHWORDS OF THE JUNCTION OF THE INTIMA AND THE MEDIA. THIS CONDITION BECOMES MORE PROGRESSIVELY OBVIOUS AS THE ABSORPTION OF THE DEPOSITS INCREASES. THE FINE MESHWORK OF THE ELASTIC LAYER BECOMES CONGESTED BY THE ACCUMULATING LIPOIDS. THEREFORE, IT BECOMES A PROCESS OF INFILTRATION. FURTHERMORE, ATHEROMATOUS CHANGES OCCURRING IN THE VESSEL WALL CANNOT TAKE PLACE UNLESS THE SUBSTANCE THAT PRODUCES THEM ARE PRESENT IN SUFFICIENT AMOUNTS.

ASCHOFF CONCLUDES THAT ALL DISEASES WHICH ARE ASSOCIATED WITH A CONSIDERABLE INCREASE OF THE BLOOD CHOLESTEROL LEAD TO AN INCREASE IN THE DEPOSIT OF LIPOID. IT IS CONCEIVEABLE THAT THE ENDOGENOUS FORMATION OF CHOLESTEROL WHICH HAS BEEN SHOWN TO OCCUR IN THE CARNIVORA, MAY BECOME DISTURBED RESULTING IN AN OVERPRODUCTION, AND SO IT CAN BE CONSIDERED A METABOLIC DISEASE(43). THERE IS A PRECIPITATION OF AND DEPOSITION OF LIPOIDS WHICH ARE CLOSELY RELATED TO CHOLESTEROL METABOLISM(37).

THE MECHANISM OF CHOLESTEROL DEPOSITION IS ALSO DISCUSSED BY HURXTHAL(38). THE BLOOD CHOLESTEROL IS THOUGHT TO BE PRESENT IN COLLOIDAL SUSPENSION OR LINKED WITH BLOOD PROTEINS. ALMOST ALL ABNORMAL CHOLESTEROL DEPOSITS ARE ASSOCIATED WITH GROUPS OF FAT OR FOAM CELLS WHICH ARE SUPPOSEDLY OF RETICULO-ENDOTHELIAL ORIGIN. HIS THEORIES AS TOTHE MECHANISM OF ABNORMAL CHOLESTEROL DEPOSITS ARE; 1. THERE IS A PRECIPITATION OF CHOLESTEROL IN THE BLOOD FOLLOWED BY A PHAGOCYTIC ACTION THERE BY THE RETICULO-ENDOTHELIAL CELLS WHICH THUS BECOME FAT CELLS. THERE IS A MIGRATION OF THESE CELLS INTO THE TISSUES WHERE THEY MAY DEGENERATE, THUS LIBERATING CHOLESTEROL. 2. AN INFILTRATION OF TISSUES BY CHOLESTEROL BECAUSE OF THEIR ALTERED PERMEABILITY, DUE TO DISEASE, AND INGESTION IN THE TISSUES BY THE RETICULO-ENDOTHELIAL SYSTEM CELLS OF THE DEPOSITED CHOLESTEROL. THE FAT CELLS ARE THUS FORMED AT THE SITE WHERETHEY ARE

FOUND.

REASONS AGAINST THESE LIPOIDS IN THE MACULAE BEARING A CAUSAL RELATIONSHIP TO ARTERIOSCLEROSIS HAVE BEEN GIVEN BY BLEITZKE(36). 1. DIVERSITY OF FORM; LIPOID MACULATION APPEARS IN THE FORM OF ELONGATED SPOTS AND STREAKS WHICH DO NOT, OR VERY RARELY SO, PROJECT BEYOND THE SURFACE OF THE INTIMA. ATHEROSCLEROSIS PRODUCES CIRCULAR, ELONGATED, OR SACCULAR DEFINED PLAYES, WHICH, IN THE CADAVER, USUALLY PROJECT BEYOND THE SURFACE OF THE INTIMA. 2. DIVERSITY OF OCCURRENCE; LIPOID MACULATIONS ARE FOUND IN CHILDREN AND EARLY MANHOOD AND IS CAPABLE OF A PROCESS OF INVOLUTION, IT THEREFORE OCCURS VERY RARELY AT AN ADVANCED AGE. ATHEROSCLEROSIS GENERALLY BEGINS IN THE FIFTH OR SIXTH DECADE AND IS NOT CAPABLE OF A PROCESS OF INVOLUTION. 3. DIVERSITY OF LOCATION; THE LIPOID MACULATION IS LOCATED AT THE VENTRICULAR SIDE OF THE MITRAL VALVE, AT THE INTIMA OF THE AORTA AND THE LARGER ELASTIC ARTERIES; ATHEROSCLEROSIS OCCURS IN THE ARTERIES OF ANY CALIBER. AT THE CARDIAC VALVES THERE IS FOUND AN AFFECTION AT THE MARGIN OF CLOSURE WHICH COULD BE COMPARED TO ATHEROSCLEROSIS OF THE VESSELS. 4. DIVERSITY OF STRUCTURE HISTOLOGICALLY.

IN CONTRAST, HURXTHAL(38) PRESENTS EVIDENCE OR ARGUMENTS THAT LIPOIDS, ESPECIALLY CHOLESTEROL, BEAR A DEFINITE CAUSAL RELATIONSHIP TO ARTERIOSCLEROSIS. ATHEROSCLEROTIC PLAQUES CONTAIN CHOLESTEROL; THE AMOUNT

OF WHICH INCREASES WITH THE EXTENT OF THE ATHEROSCLEROSIS. 2. THE CHOLESTEROL CONTENT OF THE BLOOD INCREASES WITH AGE AND WITH THE EXTENT OF ATHEROSCLEROSIS. 3. ATHEROSCLEROSIS, ANALOGOUS TO HUMAN ATHEROSCLEROSIS, MAY BE PRODUCED IN RABBITS BY FEEDING CHOLESTEROL IN LARGE AMOUNTS, OR SMALL AMOUNTS OVER A LONGER PERIOD OF TIME. 4. ATHEROSCLEROSIS IS MORE FREQUENT IN CONDITIONS SUCH AS, DIABETES MELLITUS AND MYXEDEMA IN WHICH THERE ARE ABNORMALLY HIGH FIGURES OF BLOOD CHOLESTEROL.

ARESU(39) QUESTIONS HYPERCHOLESTERINEMIA AS AN ETIOLOGICAL FACTOR. THE SMALL AREAS OF FATTY DEGENERATION, HE BELIEVES, ARE LITTLE FOCI IN REPARATION WHERE THE LYNPHATIC CIRCULATION HAS BEEN REESTABLISHED; THE MUCOID DEGENERATION HAS DISAPPEARED AND THERE STILL REMAINS A LITTLE QUANTITY OF CHOLESTERIN WAITING TO BE ELIMINATED. AS TO THE PATHOGENESIS OF ARTERIOSCLEROSIS HIS IDEAS ARE THAT THERE IS A PARESIS FIRST IN THE ARTERIES OF ALL CALIBER, FOLLOWED BY A DYSTROPHIC CONDITION DUE TO SLOUGHING OFF OF THE LYMPHATIC CIRCULATION.

FROM THE WRITINGS OF THE INVESTIGATORS AND THEIR WORKS, IT SEEMS THAT THERE IS SOME DEFINITE ETIOLOGICAL RELATIONSHIP BETWEEN CHOLESTEROL AND ARTERIOSCLEROSIS. THE PATHOGENIC PROCESS HAS AS YET NOT BEEN DEFINITELY PROVEN BUT THE ARGUMENTS AND THEORIES ARE VERY CONVINCING OF THIS FACT. PERHAPS IT MAY REQUIRE A DIFFERENT

APPROACH, DIFFERENT METHODS OF ANALYSIS OR MORE INTENSIVE INVESTIGATION OF THE THEORIES.

--EXPERIMENTAL AND CLINICAL EVIDENCE--

EXPERIMENTAL PRODUCTION OF ATHEROSCLEROSIS RELATIVE TO ITS ETIOLOGY HAS BEEN EXTENSIVELY ATTEMPTED SINCE THE EARLY PART OF THE PRESENT CENTURY. NUMEROUS CONCEPTS OF THE CAUSAL RELATIONSHIP OF VARIOUS FACTORS HAVE BEEN ATTEMPTED. EXPERIMENTAL EVIDENCE WAS MEAGER DISCOURAGING UNTIL ANITSCHKOW(19), IN 1912, PRODUCED ATHEROSCLEROSIS IN RABBITS BY FEEDING PURE CHOLESTEROL DISSOLVED IN VEGETABLE OIL. IN THIS WAY WAS ACHIEVED THE EXPERIMENTAL DEMONSTRATION OF THE IMPORTANT PART WHICH THIS SUBSTANCE PLAYS IN THE PATHOGENESIS OF ARTERIOSCLEROSIS.

SINCE THAT TIME IT HAS BEEN SHOWN BY MANY INVESTIGATORS THAT CHOLESTERIN IS A VERY IMPORTANT FACTOR IN THE PATHOGENESIS OF ARTERIOSCLEROSIS. NOT ALL EXPERIMENTERS HAVE OBTAINED SIMILAR RESULTS, BUT THE EVIDENCE PRESENTED IS VERY MUCH IN FAVOR OF A DEFINITE CAUSAL RELATIONSHIP BETWEEN THIS SUBSTANCE AND ARTERIOSCLEROSIS.

A SUMMARY OF THE KNOWLEDGE OF THE CHOLESTEROL METABOLISM MAY WELL BE GIVEN AT THIS POINT(38).

FUNCTIONS-

1. A CONSTITUENT OF THE FRAMEWORK OF CELLS BECAUSE OF ITS STABILITY TO ORDINARY CHEMICAL CHANGE.
2. A PROTECTIVE SUBSTANCE IN CELLS.
   - A. AN ANTI-TOXIC, ANTI-HEMOLYTIC, AND ANTI-INFECTIOUS AGENT.
   - B. AN INSULATOR OF THE CENTRAL NERVOUS SYSTEM.

c. A conditioning constituent of the skin.

3. A conveyor of fatty acids to and from fatty deposits.

4. A facilitator of fat absorption.

Abnormal variations may arise by;

1. Abnormal synthesis beyond normal tolerance or destruction.

2. Abnormal affinity of tissues for cholesterol.

3. Abnormal precipitation or liberation.

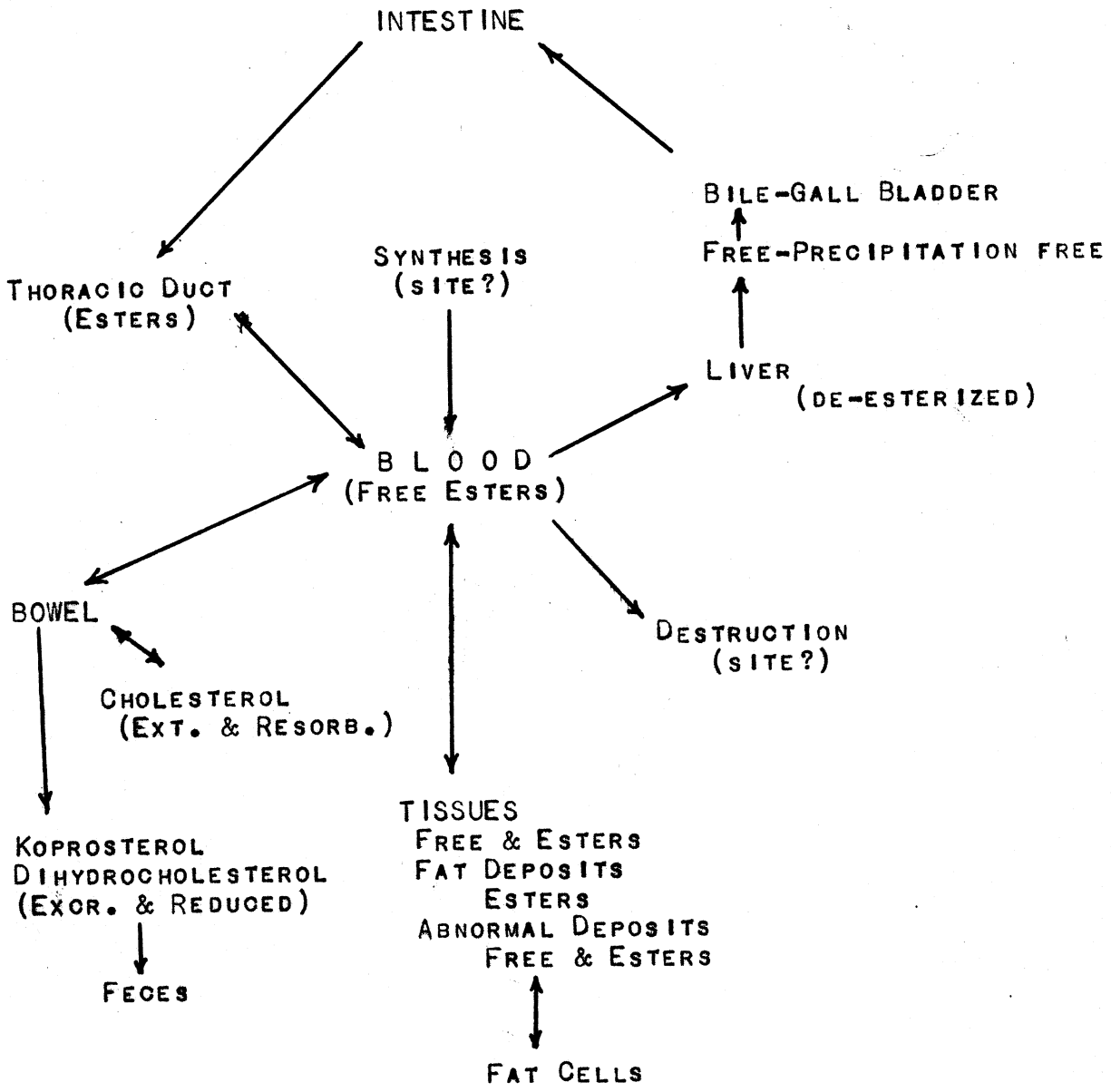
4. Hemoconcentration or dilution.

5. Failure of elimination (See diagram).

Bailey(40), (41), Scarff(42), Faber(43), and Klotz (44) have shown that experimentally atherosclerosis can be produced by feeding cholesterin or foods rich in cholesterin to animals. Their experiments were not all carried out in all the same details but their prime object was to produce atherosclerosis by feeding cholesterin and they received results that proved clearly to them that there is a definite causal relationship.

It having been proven by these investigators that cholesterin is an important factor, other experimenters worked along somewhat different lines to note any further or associated relationship.

Moehlig and Osius(45), in attempting to produce arteriosclerosis in rabbits by the administration of



DIAGRAMMATIC REPRESENTATION OF THE METABOLISM OF CHOLESTEROL (38).

PITUITRIN ALONE AND ALSO WITH CHOLESTERIN WORKED ALONG THESE LINES. THEY HAD THREE GROUPS OF RABBITS. TO GROUP A, WHICH WAS COMPOSED OF FIVE(5) RABBITS, THEY FED A NORMAL DIET PLUS 12 CC. COTTON SEED OIL AND 4 GRAMS OF ANHYDROUS LANOLIN FOR EACH RABBIT. THIS CONTAINS A HIGH DEGREE OF CHOLESTEROL. TO GROUP B(10)RABBITS) THEY FED THE SAME AS A PLUS L CC. OF OBSTETRICAL PITUITRIN. TO GROUP C THEY FED (10) RABBITS A NORMAL DIET PLUS THE PITUITRIN. THIS WAS CARRIED ON FOR ONE HUNDRED (100) DAYS. AFTER THIS TIME THEY OBSERVED THAT THE GROUP A RABBITS ALL HAD A MARKED DEGREE OF ARTERIOSCLEROSIS, BUT IN GROUP B THERE WAS A MORE EXTENSIVE ARTERIOSCLEROSIS CHANGE THAN IN GROUP A. GROUP C CONTAINED NO SIGNIFICANT CHANGES IN THE AORTA AFTER A HUNDRED (100) DAYS OF FEEDING. THE RESULTS SHOW THAT THERE IS A CAUSAL RELATIONSHIP BETWEEN CHOLESTERIN AND ARTERIOSCLEROSIS IN RABBITS. ALSO THERE IS AN INDICATION THAT POSSIBLY THERE ARE OTHER FACTORS ASSOCIATED WITH THE INCREASED CHOLESTERIN INGESTION BY THE RESULTS OBTAINED IN GROUP B. (45)

SHAPIRO (46) UNDERTOOK EXPERIMENTS TO DETERMINE THE INFLUENCE OF THE REMOVAL OF THE THYROID, SPLEEN, GONADS, AND SUPRARENALS UPON THE DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS. HE FED HIS RABBITS A DIET OF ALFALFA HAY, OATS AND VEGETABLES PLUS 4 GRAMS

OF LANOLIN IN 12 CC. OF COTTONSEED OIL DAILY. (SEE TABLE 1). HE DETERMINED BY THIS THAT THE DEPOSITION OF CHOLESTERIN OR CHOLESTEROL ESTERS WITHIN THE INTIMA OF THE AORTA INDICATES CELLULAR ALTERATIONS WHICH RESULT IN ATHEROMATA. ALSO FROM THE RESULTS OBTAINED IT SHOWS THAT CONDITIONS WHICH ARE ACCOMPANIED BY LONG STANDING HYPERCHOLESTERINEMIA CAUSE OR FACILITATE THE DEPOSITION OF CHOLESTEROL WITHIN THE AORTA. THESE OPERATIVE PROCEDURES AUGUMENTED THE HYPERCHOLESTERINEMIA AND THEREBY FACILITATE AND ACCELERATE THIS DEVELOPMENT OF THIS CONDITION.

GORDONOFF (47) PERFORMING SOME PHARMACOLOGICAL EXPERIMENTS ON THE THERAPY OF ARTERIOSCLEROSIS, REPORTED FINDINGS SIMILAR TO THE HUMAN FORMS OF THE DISEASE. HIS METHOD OF PRODUCING ATHEROSCLEROSIS WAS TO FEED RABBITS CHOLESTERIN DISSOLVED IN SUNFLOWER OIL FOR A CERTAIN LENGTH OF TIME.

ALONG A DIFFERENT LINE OF INVESTIGATION, PAGE AND BERNHARD (48) ALSO PRODUCED ATHEROSCLEROSIS BY HIGH CHOLESTEROLDIETS. THEY INVESTIGATED TO DETERMINE THE ACTION OF AN ORGANIC IODINE COMPOUND IN THE PREVENTION OF ATHEROSCLEROSIS. THEY USED TWENTY-FOUR (24) RABBITS WHICH WERE FED A GENERAL DIET WITH AN ADDITION OF CHOLESTERIN DISSOLVED IN WARM OLIVE OIL TO MAKE A 5 PERCENT

TABLE I

Number of Rabbits	Operative Procedure	Period of Lanolin Feeding	Degree of Atheromatosis
10	None	110-120 days	Early
6	Gonadectomy	50-60 "	Early
7	Splenectomy	50-60 "	Early and moderate
8	Thyroid-ectomy	40-50 "	Moderate
-	-	7 "	Severe
6	Bi-Suprarenalectomy	85-100 "	None
-	-	110 "	Early
1	Thyroid and Bi-Suprarenalectomy	50 "	None
1	Thyroid and Splenectomy	50 "	Severe
2	Gonad and Splenectomy	100 "	Severe

Results showing the relations between the experimental production of arteriosclerosis and the various operative procedures (46)

SOLUTION. THIS WAS FED ORALLY THROUGH A TUBE. 200 MG. OF CHOLESTERIN WERE FED DAILY ON SIX DAYS OF THE WEEK. THE FEEDINGS LASTED FROM 109 TO 180 DAYS. THE RABBITS WERE DIVIDED INTO TWO GROUPS; ONE RECEIVING THE ABOVE AND THE OTHER AN ADDITION OF DI-IODID OF RICINSTEROLIC ACID RANGING FROM 12 MG. TO 27.38 MG. OF THE ACID. THE LATTER GROUP SHOWED ONLY SLIGHT ATHERMATOUS CHANGES WHILE THE OTHER SHOWED THE EXPECTED MARKED ATHEROMATOUS CHANGES. THE ORGANIC IODINE APPEARED TO INCREASE THE LIPEMIA. THROUGHOUT THE EXPERIMENT THE ANIMALS HAVING RECEIVED THE IODINE COMPOUND SHOWED HIGHER VALUES FOR ALL THE LIPID FRACTIONS THAN DID THOSE RECEIVING CHOLESTERIN IN OIL ALONE. HOWEVER, THE CHOLESTERIN DEPOSITS IN THE ARTERIES WERE VERY SMALL. THEY INTERPRETED THIS PHENOMENON TO MEAN THAT WHEN THE METABOLISM OF THE TISSUES OF THE RABBITS IS CHANGED BY THIS ORGANIC IODINE COMPOUND, DEPOSITION EVEN FROM THE LIPEMIC PLASMA MAY BE PREVENTED. MOREOVER, IF THE STATE OF METABOLISM OF THE TISSUES IS SUCH AN IMPORTANT FACTOR IN DETERMINING WHETHER LIPOIDS WILL BE DEPOSITED, IT IS EASY TO UNDERSTAND THE REASONS WHY ATHEROSCLEROSIS IS A FOCAL AND NOT A GENERAL CONDITION. FROM THE ABOVE IT SEEMS PROBABLE THAT THERE IS A CLOSE RELATION BETWEEN THE CHOLESTEROL METABOLISM AND THYROID METABOLISM.

ANALOGOUS ATHEROSCLEROTIC CHANGES HAVE BEEN PRODUCED IN OTHER ANIMALS. BAILEY (41) PRODUCED CHANGES

IN THE AORTAS OF GUINEA-PIGS FED FOR MONTHS ON FOODS RICH IN CHOLESTER. IT HAS BEEN PRODUCED IN MICE, GOATS, HENS, AND PIGEONS (19). HOWEVER, IT IS VERY IMPORTANT TO NOTE THAT IT HAS NEVER BEEN PRODUCED IN CARNIVOROUS ANIMALS AFTER ATTEMPTING TO PRODUCE THIS CONDITION EXPERIMENTALLY. THIS IS NO DOUBT DUE TO THE FACT THAT UNDER NORMAL CONDITIONS THESE ANIMALS CAN EXCRETE THE CHOLESTERIN WHICH IS NOT THE CASE IN HERBIVOROUS ANIMALS (19)

THERE IS MUCH CLINICAL EVIDENCE IN FAVOR OF AN ETIOLOGICAL RELATIONSHIP BETWEEN CHOLESTEROL AND ARTERIOSCLEROSIS. ROBINOWITCH (49) IS VERY MUCH CONVINCED THAT FROM THE STUDY OF DIABETIC PATIENTS THERE IS DEFINITE EVIDENCE TO SHOW THAT AN EXCESS BLOOD CHOLESTEROL IS AN IMPORTANT ETIOLOGICAL FACTOR IN THE PRODUCTION OF ARTERIOSCLEROSIS IN YOUNG DIABETICS. SINCE THE INTRODUCTION OF INSULIN ARTERIOSCLEROSIS HAS BECOME THE CHIEF CAUSE OF DEATH IN DIABETICS, REPLACING COMA. HE HAS FOUND THAT ARTERIOSCLEROSIS IS NOT CONFINED TO ELDEREY PEOPLE AND THAT ONLY FIVE (5) YEARS IS THE USUAL TIME NECESSARY FOR ITS DEVELOPMENT AND DOES SO REGARDLESS OF AGE.

IN A RECENT STUDY OF FIVE HUNDRED (500) CASES A DIABETIC CLINIC, THE INCIDENCE OF CARDIO-VASCULAR DISEASE WAS FOUND TO BE 62.6 PERCENT (SEE TABLE II)

FROM AUTOPSY STUDIES OF 108 DIABETIC PATIENTS THERE WAS AN INCIDENCE OF 65.7 PERCENT. PATIENTS HAVING

TABLE II

		Cardio-Vascular Dis.	
Age Period	Number	Number	Percent
-10	4		
11-20	14	4	28.6
21-30	34	5	14.7
31-40	67	33	49.2
41-50	124	91	73.3
51-60	158	106	67.1
61-70	80	59	73.7
71-80	18	14	77.8
81-90	1	1	--
	500	313	62.6

Incidence of Cardio-vascular Disease among 500 Diabetics according to Age(49).

HAD DISEASED FIVE YEARS OR MORE, REGARDLESS OF AGE OR SEVERITY, SHOWED AN INCIDENCE OF OVER 80 PERCENT HAVING CARDIO-VASCULAR DISEASE. (SEE TABLE III)

THERE IS EVIDENCE TO SHOW THAT THERE IS A DEFINITE RELATION BETWEEN THE FEEDING OF HIGH FAT DIETS, WHICH INCREASES THE CHOLESTEROL, TO INCREASE THE INCIDENCE OF ARTERIOSCLEROSIS. ALSO FEEDING LOW FAT DIETS THERE IS A REDUCTION OF THE INCIDENCE OF ARTERIOSCLAROSIS (49).

GIBBS, BUCKNER AND BLOOR, WORKING ON THE BLOOD PLASMA OF DIABETICS, NOTED THE TOTAL AND ESTERIFIED CHOLESTEROL VALUES IN TWO SERIES OF DIABETIC PATIENTS WITH ARTERIOSCLEROSIS WERE FOUND TO BE ABNORMALLY HIGH AND HIGHEST WITH THE MOST ADVANCED ARTERIOSCLEROSIS (50). IN BOTH GROUPS THERE WAS A 10-15 PERCENT INCREASE OF THE RATIO ABOVE THE NORMAL. THEY SUGGESTED A POSSIBLE RELATIONSHIP BETWEEN THE HIGH CHOLESTEROL VALUES IN THE BLOOD PLASMA AND THE DEVELOPMENT OF ATHEROMATOUS CHANGES IN DIABETIC PATIENTS.

JOSLIN (51), HENDERSON (52), AND GRAY AND SWANSON (53) ALSO SHOWED THE HIGH INCIDENCE OF ARTERIOSCLEROSIS IN DIABETES. JOSLIN (51) NOTED AS THE ABOVE (50) THAT THERE WAS ALWAYS A NORMAL OR MUCH ABOVE NORMAL CHOLESTEROL VALUES IN THE BLOOD EXAMINATION OF HIS PATIENTS. IN REGARD TO THIS FACT IT WAS CONSIDERED IMPORTANT TO TREAT THE PATIENTS IN REGARD TO THE EARLY POSSIBLITY OF DEVELOPING ARTERIOSCLEROSIS AND SHOULD BE AIMED AT THE REDUCTION OF THE BLOOD CHOLESTEROL.

TABLE III

Period	Five years and under			Under five years		
	Total Number	C-V Disease		Total Number	C-V Disease	
		No.	%		No.	%
*10				4		
11-20	2	2	100.0	12	2	16.7
21-30	4	2	50.0	30	3	10.0
31-40	21	18	85.7	46	15	32.6
41-50	54	47	86.0	70	44	62.8
51-60	50	43	66.7	108	63	58.3
61-70	12	8	100.0	68	51	75.0
71-80	1	1		17	14	82.3
81-90				1	1	100.0

Relationship between the Cardio-vascular disease, Age, and Duration of diabetes among 500 Diabetics(49).

In the diabetic patients from autopsy reports, it has been shown that there is, from the deposition of lipids and their subsequent calcification, a greater deposit of lipid and a more marked change in the lipid allocation (54).

There was a careful study made by Davis, Stern and Lesnick (55) on the lipoids and cholesterol content of the blood of patients with angina pectoris and arteriosclerosis. A careful selection of patients was made; those with rheumatic and syphilitic hearts were excluded. From the results of the determinations of total blood cholesterol and free cholesterol, they found a considerable increase in the upper levels of cholesterol in patients having angina pectoris. The highest cholesterol level in the control group was 287 mg. and in the angina group thirteen (13) patients were above this figure. Thirty-five (35) angina pectoris patients had values above 250 mg. while only sixteen (16) were above that in the control group. Further studies on these patients of the phospholipids and fatty acid contents showed higher values in the angina group. It was further noted that the basal metabolic rate and hypertension had no possible effect on the finding. It was concluded that the lipid and cholesterol metabolism is disturbed, either primarily or secondarily, in at least a certain group of patients with angina pectoris.

Covering a large number of conditions relative to the vegetative nervous system, Glazer (56) studied the question whether the level of cholesterol rises after the stimulation of the sympathetic nervous system. Injections of adrenlin may cause a hypercholesterinemia. Adrenalin perhaps acts in some manner upon the liver which plays an important part in the metabolism of cholesterol (56).

Interestingly and significantly so, is there a large amount of clinical evidence to show a definite relation between diseases having a high blood cholesterol and the incidence of arteriosclerosis in these diseases. However, in not all diseases having a high blood cholesterol has the evidence been so conclusive, as was shown by Maxwell (57) in regard to nephrosis. In this condition there is a high blood cholesterol and it was shown that arteriosclerosis is not associated with this disease. This would certainly be a strong argument against any relation, but certainly it must be agreed that there is still much to be learned about nephrosis, and of course also considerable to be learned in regard to arteriosclerosis. There may be other factors entering into the picture.

What about the numerous cases of arteriosclerosis that show no hypercholesterinemia? This condition has been explained by the fact that the changes of the blood may be of a transient nature. Also, in some cases

HYPERCHOLESTERINEMIA MAY NOT BE NECESSARY FOR THE GENESIS OF ARTERIOSCLEROSIS BECAUSE CHOLESTEATOSIS MAY BE PRESENT WITHOUT AN INCREASE IN THE BLOOD CHOLESTEROL AND VICE VERSA (56)

GLAZER (56) CONSIDERS THAT ARTERIOSCLEROSIS RESULTS ONLY FROM A COMBINATION OF PROLONGED HYPERCHOLESTERINEMIA WITH LOCAL MECHANICAL OR TOXIC INJURIES OF THE WALL OF THE VESSEL. THE ABSORPTION OF THE CHOLESTEROL BY THE WALLS OF THE VESSELS FROM THE BLOOD DEPENDS UPON PHYSICO-CHEMICAL CONDITIONS, THE RATIO OF THE FREE CHOLESTEROL, AND CHOLESTEROL ESTERS AND THE ABILITY OF THE BLOOD TO FORM DEFENSIVE COLLOIDS.

CONSIDERING THE EVIDENCE AND ARGUMENTS, PRO AND CON, IN REGARD TO ANY CAUSAL RELATIONSHIP BETWEEN CHOLESTEROL AND ARTERIOSCLEROSIS, IT WOULD BE WELL TO PRESENT THEM AS WERE SUMMARIZED BY LEARY (58). THE EXPERIMENTAL EVIDENCE HAS BEEN CRITICIZED WITH REFERENCE TO THE TYPE OF ANIMAL USED. THE RABBIT NEVER SUFFERS NATURALLY FROM ARTERIOSCLEROSIS AND THE DIET USED TO PRODUCE ARTERIOSCLEROSIS IS A PERVERTED DIET FOR THE RABBIT. ALSO THERE ARE CRITICISMS THAT THE ATHEROSCLEROTIC LESIONS OF THE RABBIT ARE NOT SIMILAR TO THE HUMAN LESIONS. (36)

EVIDENCES THAT THERE IS A DEFINITE RELATIONSHIP BETWEEN CHOLESTEROL AND ARTERIOSCLEROSIS ARE: 1. CHOLESTEROL IS CONSTANTLY PRESENT IN THE LESIONS (19)

2. WHEN FED TO RABBITS IN PURE FORM IT WILL GIVE RISE TO THE LESIONS OF THE DISEASE (42). ACCORDING TO THIS, BACTERIOLOGICALLY, CHOLESTEROL WOULD BE THE ETIOLOGICAL AGENT. 3. EXPERIMENTS ON HUMANS, FED HIGH FAT DIETS RICH IN CHOLESTEROL, PRODUCED TYPICAL LESIONS OF ATHEROSCLEROSIS (58). 4. THE CHOLESTEROL CONTENT OF THE BLOOD INCREASES WITH AGE, AND 5. AHTEROSCLEROSIS IS MORE FREQUENT IN CONDITIONS SUCH AS DIABETES MELLITUS AND MYXEDEMA IN WHICH THERE IS AN ABNORMALLY HIGH CHOLESTEROL CONTENT IN THE BLOOD (38).

IT APPEARS THEN THAT THE MOST IMPORTANT FACTOR OF ALL IS A DISTURBANCE OF THE CHOLESTERIN METABOLISM, IN CONSEQUENCE OF WHICH AN ACCUMULATION OF THAT SUBSTANCE TAKES PLACE IN THE ORGANISM. OF COURSE THIS FACTOR ITSELF DEPENDS UPON A NUMBER OF OTHER FACTORS BY WHICH THE REGULATION OF THE CHOLESTERIN METABOLISM IS INFLUENCED. IF THE INSUFFICIENCY OF THE CHOLESTERIN METABOLISM IS OF A PRONOUNCED CHARACTER, IT MAY LEAD TO THE DEVELOPEMENT OF ATHEROSCLEROSIS WITHOUT ANY CONCOMITANT CAUSES. IF IT IS LESS SEVERE, IT MAY HAVE THE SAME CONSEQUENCES, PROVIDED THAT IT IS EITHER OF LONG DURATION OR ASSOCIATED WITH OTHER PREDISPOSING FACTORS. AMONG THE LATTER, THOSE OF A MECHANICAL NATURE ARE PROBABLY THE MOST IMPORTANT. OTHER FACTORS THAT MAY EXERT A NOXIOUS INFLUENCE ON THE ARTERIAL WALL ARE THOSE OF TOXIC, OF

INFECTIOUS-TOXIC AND OF NERVOUS NATURE. THIS IS THE SO-CALLED "COMBINATION THEORY" (19).

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