The demonstration here of multiple tubercles in the pleura of patients with tuberculous effusion would tend to indicate that direct pleural involvement in tuberculous pleural effusion is far more extensive than previously believed. Schuman [10] cites Jacobeus as noting multiple pleural tubercles in patients with effusion who were examined by thoracoscopy. Auerbach,[11] in a careful study of tuberculous serous effusions at autopsy, reported 103 cases with pleural effusion (55 with only serous manifestation of tuberculosis and 48 combined with other serous involvements). Cases of effusion secondary to artificial pneumothorax were excluded, but those with definite pulmonary tuberculosis were not. Thirty-five cases were felt to represent direct spread from the lung (25 from chronic pulmonary lesions and 10 from primary complexes). Two cases developed from diseased ribs and five from the peritoneum. Forty-six cases were found to be manifestations of hematogenous dissemination. Fifteen cases showed isolated pleural tuberculosis. In all of these the tracheobronchial lymph nodes were enlarged. The pathology was significantly extensive in these cases, with two types represented about equally; these were miliary tubercles and caseous pleuritis. In all these cases, the pleural pathology appeared sufficient to cause changes warranting the amount of effusion noted. The pleural biopsy cases presented here make this point even stronger, because, clinically, they were of comparatively minor severity. Therefore, it is our feeling that sensitivity phenomena play a far smaller role than previously considered. These facts would be in keeping with the current tendency toward prolonged treatment of tuberculous pleural effusion with both bed rest and chemotherapy.

SUMMARY AND CONCLUSIONS

Pleural biopsy was done in five cases in which the etiology of the pleural effusion could not be established by bacteriological methods. The findings of a surprisingly large amount of tuberculous pathology in these cases casts doubt on the validity of previously accepted concepts of etiology. Pleural biopsy is a minor procedure in the hands of experienced thoracic surgeons. Its routine use is recommended for the diagnosis of pleural effusions of undetermined etiology.

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PATHOGENESIS OF CORONARY DISEASE IN AMERICAN SOLDIERS KILLED IN KOREA

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Recently we [1] presented a paper describing the gross lesions found in the coronary arteries of American soldiers killed in Korea. This series consisted of 300 men with an average age of 22.1 years. In 77.3% of the cases some gross evidence of coronary disease was demonstrated that varied from minimal eccentric thickening to complete occlusion of one or more of the main coronary branches (fig. 1*A*). The locations of the lesions indicated that the hemodynamics of the coronary circulation, as modified by the variations of the coronary arterial tree, is one of the factors in coronary disease (fig. 1*C* and *D*). The purpose of this paper is to present all available clinical data concerning the cases studied and to discuss the histopathology of the lesions.

MATERIAL

All the clinical data were obtained from photostatic copies of the induction physical examinations or were taken from the emergency medical tags. At the present time, some 200 records have been received. The coronary arteries were sectioned in a horizontal or longitudinal plane through obviously diseased areas and other areas that were not involved in the disease process. These sections were embedded in paraffin, sectioned at about 7 μ and stained with hematoxylin and eosin, Masson's trichrome, Weigert's resorcinol-fuchsin elastica, and Rinehart's mucopolysaccharide. Frozen sections for lipids were stained with oil red O.

CLINICAL DATA

It was estimated that the average age of the 200 men on whom complete records have been received was 22.1 years, average height 5 ft. 7¾ in. (171 cm.) and average weight 145.8 lb. (66 kg.). No definite statements can be made concerning body build or weight in that somatotyping was not done at the time of the autopsies. Further, the majority of the induction physical examinations do not state whether the examinee wore shoes at the time his height and weight were recorded. The data do indicate, however, that severe coronary disease is not confined to the older men in our series. For example, in 20 cases with lesions causing over 50% luminal narrowing the average age was found to be 22.6 years (see table). Furthermore, there is no evidence that hypertension played a role in this disease process.

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The illustrations were supplied by the Armed Forces Institute of Pathology, Washington 25, D. C.

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PATHOLOGICAL OBSERVATIONS

As Moon and Rinehart [2] pointed out, the earliest lesions were composed of a subendothelial proliferation of fibroblasts and a deposition of mucoid ground substance. Slight increases in thickness of the intima were usually accompanied by fragmentation of the internal elastic membrane and not infrequently by herniation of the intimal elements into the media. Accompanying eccentric intimal thickening or plaque formation was the appearance of phagocytized sudanophilic lipid material in the intima. The lipid was found in globular macrophages and in spindle-shaped mesenchymal cells. The internal elastic membrane of the main branches of the coronary arteries in all cases was split and concentrated in two distinct layers with numerous connecting fibers. The inner one usually was mantled in sudanophilic lipid material (fig. 2*C* and *D*). Both layers exhibited fragmentation and reduplication in areas where there was eccentric intimal thickening. As the plaque increased in thickness due to fibroblastic proliferation, increased accumulation of mucoid ground substance, formation of collagen fibers, and accumulation of lipid, the phagocytes at the base of the plaque degenerated, spilling lipid into the parenchyma of the plaque. This resulted in the appearance of acellular areas with cholesterol slits and patches of intimal calcification. The media under such foci usually was atrophic and often was traversed by small vessels from the adventitia, which supplied the base of the plaque (fig. 2*B*). In some instances the lipid extended well into the media. The cellular elements in large plaques consisted of fibroblasts, phagocytes, and a scattering of mononuclear cells. In one case chronic inflammatory cells were encountered about the adventitial vessels at the base of a plaque.

Lesions Causing More Than Fifty Per Cent Luminal Narrowing in American Soldiers Killed in Action

	Age	Race	Height, In.	Weight, Lb.	Blood Pressure, Mm. Hg	Pulse Rate, Per Min.	Luminal Narrowing, %
	21	W	62¾	124	110/72	84	100
	21	W	60	114	120/80	76	100
	22	W	66½	155	140/85	76	98
	20	W	67¼	133	120/80	86	98
	40	W	64	156	130/80	80	98
	21	W	69	174	116/70	72	98
	44	W	70¼	171	146/86	86	98
	22	N	64	123	110/70	84	95
	22	W	67½	165	120/75	90	90
	19	W	63¾	120	128/84	84	90
	19	W	71	176	124/68	78	85
	21	W	67½	145	142/80	90	80
	21	W	66½	185	145/70	96	80
	20	W	71½	160	118/72	78	70
	22	W	65	136	126/70	84	70
	19	W	70	148	140/80	78	60
	21	W	73	162	138/78	84	60
	18	W	69	165	122/70	81	50
	19	W	67	120	120/76	72	50
	20	W	69	171	136/70	78	50
Average	22.6		67.2	152.6			

COMMENT

The factor of stress on the intima resulting from the hemodynamics of the coronary circulation as modified by anatomic variations in the coronary tree has been mentioned by many investigators [3] as one of the main factors of plaque formation. It is postulated that stress on the intima causes fibroblastic proliferation and the deposition of the mucoid ground substance. Another factor of importance in the production of the lesions appears to be the phagocytosis of certain plasma lipids within the traumatized intima. Geiringer [4] has pointed out that the normal intima is an avascular structure nourished by a transendothelial filtrate. Weinhouse and Hirsch [5] have shown that there is a close relationship between the lipid extracts of the plasma and those of the intima. Wilens,[6] using human autopsy material, has demonstrated experi-

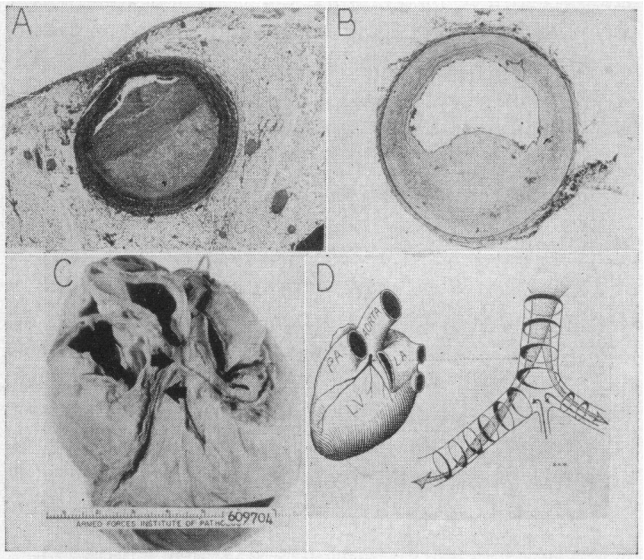

Fig. 1.—*A*, cross section through anterior descending artery of a 22-year-old white man killed by penetrating shell fragment wound of the head. A large plaque almost completely occludes the vessel (Masson stain). × 7.6. *B*, cross section through anterior descending artery of a 22-year-old Japanese man, revealing a large plaque. No evidence of lipid phagocytosis in the stroma of the plaque (oil red O stain). × 4.3. *C*, epicardial wall of the vessels has been dissected away, revealing spiral plaque formation in the left, anterior descending, and circumflex arteries. *D*, schematic drawing from specimen in *C*. Stippled arrows indicate spiral flow of blood; black arrows, regurgitation at points of bifurcation. Thickened portions of ellipses represent the sites of stress and plaque formation.

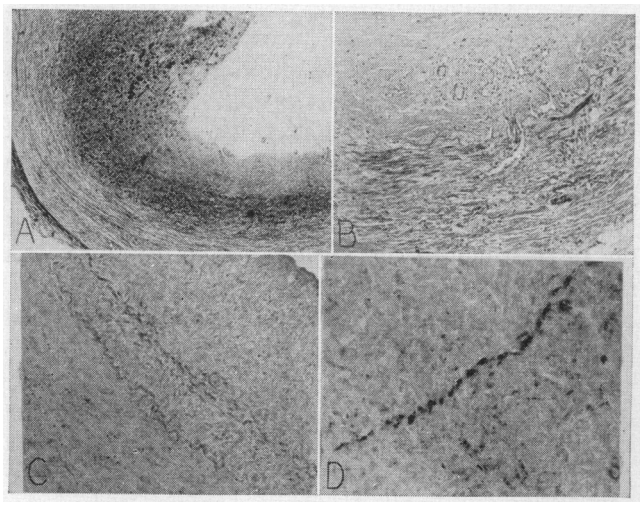

Fig. 2.—*A*, phagocytosis of lipids in plaque. Deposition of lipids on elastica outside of plaque. Note the absence of phagocytosis in this area (Gomori's aldehyde fuchsin stain and oil red O). × 40.3. *B*, adventitial vessels traversing the media to nourish the plaque. × 99. *C*, a double internal elastic membrane. The inner layer is mantled with sudanophilic lipid material (oil red O). × 99. *D*, lipids on inner layer of the internal elastic membrane (oil red O). × 99.

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mentally that the amount of lipid deposited in the intima depends to some extent on the thickness of the intima. The histological characteristics of the lesions in our series of cases were compatible with these experimental findings, for with plaque formation it appears that certain plasma lipids are trapped in the stroma of the plaque and are phagocytized, thus aggravating the disease process. The presence of lipids on the inner layer of the internal elastic membrane beneath the intima, where there is no eccentric intimal thickening or plaque formation, indicates that the lipids of the transendothelial filtrate have successfully traversed the intimal stroma. Some are deposited on or are filtered out by the elastica, but this does not incite phagocytosis (fig. 2*A*).

It is of interest to compare the lesions found in the American soldiers with the lesions found in a small series of Japanese natives now being studied. At the time of this presentation, material from 114 cases representing both sexes has been examined. Of this group 30 are males approximating the age group of the United States soldiers. The incidence of clinical coronary disease is low in Japan. For example, 2,550 native Japanese representing all ages were recently examined at a clinic in Japan, and in only 1.7% of the cases were the electrocardiographic findings suggestive of coronary disease. During a five year period, there were 1,480 medical examiners' cases in a Japanese city with a population of approximately 2 million and only 14 cases were coded as coronary deaths. In the studies now being conducted, lesions have been found in over 65%. The plaques are located at points of stress, just as in the American series. There are two main differences in the Japanese series as compared to the American series. 1. No plaques causing over 50% luminal narrowing have been found in young males (20 to 30 years). 2. The amount of phagocytized lipids in the stroma of the plaques was far less than that observed in the American series (fig. 1*B*). Sudanophilic material was present within the stroma of most cases, but it was extracellular. These findings indicate that plasma lipids of the type that are phagocytized in the plaques, aggravating the disease process in the Americans, probably are less abundant in the plasma of the Japanese. This suggests diet as the source of the lipids.

Thus far no mention has been made of the hormonal factor in atherosclerotic coronary disease. In this connection a case recently observed by one of us (W. F. E.) may be pertinent. The patient was a 40-year-old woman who was lactating at the time of her death. Histological studies revealed large amounts of fine sudanophilic material distributed throughout the intima and inner portion of the media of the coronary arteries, but the evidence of phagocytosis of lipids was minimal. Katz and Stamler [7] point out that spontaneous lipid infiltration of the elastic aorta of a chicken occurs during the egg-laying period, but there is little evidence of phagocytosis. Here, then, are two conditions marked by physiological hyperlipemia and lipid infiltration of the arterial wall without much evidence of phagocytosis. This phenomenon may be related to the size of the lipoprotein aggregates investigated by Hirsch and Weinhouse.[8] In their opinion the larger aggregates stimulate phagocytosis. We postulate that this phenomenon hastens and aggravates the coronary disease process. It is conceivable that the sex hormones influence the size of the lipoprotein aggregates, thus accounting for the sex difference in this disease.

SUMMARY

The gross and microscopic studies of the coronary arteries of Americans killed in action in Korea indicate that the coronary lesions are due in part to intravascular stress caused by the hemodynamics of the coronary circulation as modified by anatomic factors. The stress results in subendothelial fibroblastic proliferation, deposition of a mucoid ground substance, and fragmentation of the internal elastic membrane. The accumulation and phagocytosis of certain plasma lipids in the plaques aggravates and hastens the disease process. The amount and the distribution of the lipids on the elastica and within the parenchyma of the plaques found in the Americans as compared to the Japanese indicate that certain plasma lipids as modified by diet are another important agent in the development of coronary disease in young males.

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Coarctation of the Aorta.—Prior to the advent of definitive vascular surgery the improvement in the diagnosis of coarctation of the aorta was of academic interest only. The outlook for these patients was radically changed by the introduction of these surgical techniques, and coarctation of the aorta now may be listed among the few forms of hypertension and of congenital heart disease that are potentially curable. Following successful resection of a narrowed aortic segment, the majority of the usual causes of death in such patients—i. e., rupture of the aorta, cardiac failure, cerebral hemorrhage, or thrombosis—are made unlikely. Bacterial endarteritis and cardiac insufficiency secondary to associated congenital cardiac lesions are potential complications little altered by operation. The diagnosis still depends upon adequate physical examination. Refinements in diagnostic technique such as ballistocardiography, angiocardiography, oscillometry, et cetera, serve only to delineate the degree of aortic obstruction. Occasionally the alert roentgenologist will note rib notching and a small aortic knob, and direct attention to the correct diagnosis. Careful examination of the peripheral vascular system is the rule in elderly patients because of the stress placed on vascular changes in diabetes mellitus and arteriosclerosis. Similarly, the pediatrician has made such an examination a routine part of the postnatal evaluation of each newborn infant. . . . The clinical picture can be variable, but a common denominator was *decreased* arterial pressure in the lower extremities. Palpation of the peripheral arterial system in all patients must be the rule if the condition is to be recognized.—Capt. L. L. Bean and Lieut. D. B. Carmichael, (MC), U. S. N., Coarctation of the Aorta, *United States Armed Forces Medical Journal*, May, 1955.