as otherwise there would be a constant production of auto-antibodies. Until recently the idea that this could ever happen was contrary to all accepted immunological theory, and speculation now centres about the nature of the normally efficient mechanism for distinguishing between "self" and "not self."

It has been shown that the power of antibody-forming tissue to react is largely dependent on the presence of antigens at the time the tissues reach maturity, and that tolerance can be induced by presenting the tissues with antigen some time before the production of antibodies begins. This is somewhere round about the time of birth. It is possible that if the antigen cannot gain access to antibody-producing tissues at this time no tolerance is acquired, and later in life the antigen from the person's own tissues may lead to antibody production.

Macfarlane Burnet (1959), in his clonal selection theory of immunity, has suggested that body cells possess specific immunological properties or competence which are genetically determined. The antigen, according to this theory, does not, as in the classical theory of immunity, imprint its pattern by imparting information which results in the production of an antibody complementary to itself, a template, but it simply stimulates certain mesenchymal cell clones which are genetically determined to respond by antibody to it. A clone can be defined as a group of individuals of like genetic constitution obtained by asexual reproduction from a single original individual. When the clones multiply either their destruction may result, as normally happens, or proliferation may take place and a disease process follow. The clones of cells are called "forbidden clones" if the production of their union with antigen does not lead, as it normally does, to their destruction and elimination from the body, but rather to their proliferation and the further production of antigen, with the establishment of a vicious circle.

The antigen therefore, according to this theory, stimulates cells to produce the specific antibody which they have been genetically determined to produce, and does not itself determine the specificity of the antibody.

An alternative hypothesis is that antibody-producing cells may undergo somatic mutation themselves, with the result that they produce auto-antibodies and thus auto-immune disease.

Auto-immunity is an attractive theory by which to explain the association of neoplasms with dermatomyositis, and the presence of widespread vascular lesions with thromboses in patients with malignant growths. It could be postulated that the neoplasm produces breakdown products to which cells either lose their immunological tolerance or have genetically determined specific immunological properties.

That auto-immunity can occur is beyond doubt, but the nature of the breakdown of the normal mechanism existing to prevent the continual production of auto-antibodies is far from certain. It is also uncertain whether the auto-immunity is primary and a causative factor, or secondary and the result rather than the cause.

The position concerning the presence and significance of various and increasingly numerous auto-immune reactions in systemic lupus erythematosus has been reviewed most profitably in the *British Medical Journal* (1960). There can be some overlap between thyroid antibodies and antinuclear antibodies in Hashimoto's disease, and between the antinuclear factors and the

rheumatoid arthritis factor in both systemic lupus erythematosus and rheumatoid arthritis. It seems that the evidence at present suggests that in systemic lupus erythematosus, at any rate, auto-immune antibodies are the result rather than the cause of the disease.

The evidence that the connective-tissue disorders are in part due to auto-immunity, or even to hypersensitivity, is thus very far from complete, and it is sobering to reflect that if the role of hypersensitivity is disproved there is little at present to put in its place.

REFERENCES

- Bencze, G., Kovács, J., and Cserhádi, J. (1959). *Brit. med. J.*, **2**, 864.
Brit. med. J., 1960, **2**, 1141.
 Burnet, Macfarlane (1959). *Brit. med. J.*, **2**, 645, 720.
 Glynn, L. E. (1959). *Lectures on the Scientific Basis of Medicine*, 7, 359. Athlone Press, London.
 Klemperer, P. (1956). *Acta med. scand.*, **154**, Suppl. 312, p. 261.
 — Pollack, A. D., and Baehr, G. (1942). *J. Amer. med. Ass.*, **119**, 331.
 Meyer, K. (1954). *Connective Tissue in Health and Disease*, edited by G. Asboe-Hansen, p. 54. Munksgaard, Copenhagen.
 Neuberger, A. (1960). *Ann. rheum. Dis.*, **19**, 1.
 — and Slack, H. G. B. (1953). *Biochem. J.*, **53**, 47.
 Richardson, J. (1959). "Collagen Diseases," in Loosleaff Revision Service to *Cyclopedia of Medicine, Surgery and Specialties*. Davis, Philadelphia.
 Robb-Smith, A. H. T. (1960). *Brit. med. J.*, **2**, 1308.
 Scott, D. G. (1959). *Ann. rheum. Dis.*, **18**, 207.
 Slack, H. G. B. (1959). *Amer. J. Med.*, **26**, 113.

ATHEROSCLEROSIS: RESULTS OF A PILOT SURVEY IN A NORTH LONDON AREA

BY

KENNETH R. HILL, M.D., M.R.C.P.

*Professor of Pathology, Royal Free Hospital School of
Medicine, University of London*

FRANCIS E. CAMPS, M.D., D.T.M.&H.

*Reader in Forensic Medicine, London Hospital Medical
College, University of London*

KATHLEEN RIGG, M.B., B.S., D.C.P.

*Honorary Assistant Lecturer in Pathology, Royal Free
Hospital School of Medicine, University of London*

AND

BRIAN E. G. MCKINNEY,* M.B., B.Ch., B.A.O.

*Honorary Assistant Lecturer, Royal Free Hospital School of
Medicine, University of London*

The object of this survey, which was exploratory and limited in extent, was to examine the pattern of aortic atherosclerosis as it presented in a North London area, so as to study its natural history and to see if it differed in any way from that found in other parts of the world.

Currently, several surveys of atherosclerosis are being carried out on a geographical basis so as to ascertain the importance of the various factors of race, climate, terrain, social behaviour, and diet as aetiological agents in this disease (W.H.O., 1958), if, indeed, atherosclerosis is a disease as distinct from the physiological process of ageing.

As it is impossible to examine the progress of the disease in its various stages in the same human subject the only recourse is to examine trends in several hundreds of patients at necropsy. As is recounted below, there have been difficulties in assessing the extent and severity of the various lesions, both objectively and precisely, so as to be reproducible in the form of mathematical data.

*Now at Makerere College, the University of East Africa.

Notwithstanding these difficulties, the trends appearing from our survey suggest that the deposition of fat in the fourth and fifth decades is a factor of great importance, for at this period of life the lipid present (atheroma) has a tendency to fibrosis (atherosclerosis), and ultimately to the pathogenesis of more complicated lesions in later life.

Materials and Methods

A total of 382 aortas (206 male, 176 female) were examined. The majority were obtained from the public mortuaries, although a few came from several hospitals in the North London area. The cause of death was not taken into account for their selection. The aorta was opened and the whole of the intimal surface examined; the artery was then stained by Sudan IV for 15 minutes by the method recommended by Gore and Tejada (1957).

Histological examination was made of representative samples of specimens, prepared in the usual manner and stained by the following methods: H. and E., P.A.S., Mallory's phosphotungstic acid haematoxylin, toluidine blue, Hale's acid-mucopolysaccharide, Van Gieson and Verhoeff, and Von Kossa. Frozen sections were stained with Sudan IV for fat, and examined under the polarizing microscope for cholesterol crystals. The extent and severity of the lesions was assessed by a modification of the method suggested by Gore and Tejada. This assessment, briefly, was as follows:

Extent of Atherosclerosis		Type of Lesion	
Group	Proportion of Intima Diseased	Grade 1: Fatty deposits (streaking)	
O	Less than 5%	.. 2: Fibrous plaques with or without fat	
A	6 to 15%	.. 3: Plaques with ulceration, necrosis, haemorrhage, or thrombosis	} Complicated lesions
B	16 to 33%	.. 4: Calcified plaques	
C	34 to 50%		
D	More than 50%		

The "atherosclerotic profile" suggested by Gore and Tejada was also adopted. This consisted of a group letter followed by a number, each of whose four digits corresponded respectively and sequentially with one of the grades of lesions. Thus, D 1.4.3.2 refers to an aorta which had more than 50% of its surface area involved, of which one-tenth of the lesion was made up of fatty deposits (grade 1), four-tenths of fibrous plaques (grade 2), three-tenths with ulcerative or haemorrhagic lesions (grade 3), and two-tenths with calcification (grade 4).

Results and Comments

Type of Lesion

The relative incidence of the various types of lesion is given in Table I and Fig. 1. In these the numbers listed under fatty lesion are the numbers of cases in which fatty lesions were found alone; those under fatty-fibrous plaques were those in which discrete fatty lesions (grade 1) and discrete fatty-fibrous lesions (grade 2) together were found; and those under complicated lesions were those in which all types of lesion were found together—that is, grades 1, 2, 3, and 4.

Fatty deposits were found as early as the first year of life, and appear to be almost the only type of lesion in the first and second decades. One case with fibrous plaques containing fat was found in the 11–20-year age-group, but this patient was 20 years old. In the first decade only about half the cases were affected, but by the second decade nearly all cases were involved.

Fatty streaking was prominent during the third decade, at which time, however, the incidence of fibrous plaques

TABLE I.—Incidence of the Various Types of Aortic Atherosclerosis

Age-Group	Total No. of Cases	Normal	Fatty Lesions	Fatty-Fibrous Plaques	Complicated Lesions
S.B.	15	100% (15)	—	—	—
<1	28	75% (21)	25% (7)	—	—
1–10	11	45% (5)	55% (6)	—	—
11–20	15	—	93% (14)	7% (1)	—
21–30	31	—	77% (24)	23% (7)	—
31–40	31	—	42% (12)	52% (17)	6% (2)
41–50	54	—	8% (4)	46% (25)	46% (25)
51–60	64	—	3% (2)	34% (22)	63% (40)
61–70	46	—	—	7% (3)	93% (43)
71–80	62	—	—	—	100%
81–100	25	—	—	—	100%

Figures in parentheses indicate total number of cases in each category.

Fig. 1.—Incidence of various types of aortic atherosclerosis.

appeared to be increasing. An analysis of the ages of the patients in this group revealed that most of the cases with fibrous plaques were in the last five years of the decade.

By the fourth decade the incidence of cases with fatty deposits alone and fatty-fibrous plaques was about equal. In this decade two patients had complicated lesions, but they were aged 38 and 40.

During the fifth decade the relative incidence of fatty deposits as the only lesion present had fallen considerably, and the main lesions were both fatty-fibrous plaques and complicated lesions. However, an examination of the age-groups of the patients with the complicated lesions showed that the majority were in the last five years of the decade.

In the sixth decade, only two patients, aged 51 and 54, had discrete fatty lesions alone, and the incidence of cases with both fatty and fatty-fibrous plaques had begun to fall, with a corresponding rise in the incidence of complicated lesions, so that in the sixth decade onwards the majority of all cases showed lesions of the complicated type.

No particular significance in incidence was found in relation to sex or to the onset of puberty; a further investigation with greater numbers should be done before accepting this statement as valid.

From the foregoing it would seem that fatty deposition increases *de novo* as age progresses, but some authors (Aschoff, 1925) claim that the fatty deposits of infancy are reversible, especially the deposition of fat

FIG. 2.—Fatty streaking; showing foam cells subintimally with no cellular reaction. (H. and E. $\times 450$.)

FIG. 3.—Fatty deposit with early cellular reaction. (H. and E. $\times 450$.)

FIG. 4.—Fibrous plaque with central fat. It is believed that the fibrosis is secondary to the fat. (Frozen section; Sudan IV. $\times 66$.)

at the aortic ring. The following summarizes our findings in this area. Incidence of fatty deposition at aortic ring: under 1 year, 20%; 1–10 years, 40%; 11–20 years, 75%; and 21–30 years, 100%.

It can be seen that the incidence of fatty deposition at the aortic ring progresses with age, and it is unlikely that the original deposits of infancy disappear, to be redeposited at a later age—that is, it is probable that they are irreversible.

Extent of the Lesions

The extent of the lesions was estimated for each case by the method of Gore and Tejada (1957) as an "atherosclerotic profile." Table II gives the percentage

TABLE II.—Percentage of Cases Showing Areas of Intimal Surface Involvement, as Indicated by "Atherosclerotic Profiles"

Age-Group	Total No. of Cases	Group				
		O	A	B	C	D
<1	28	100				
1–10	11	80	20			
11–20	15	35	55	15		
21–30	31	25	35	25	15	
31–40	31	15	20	35	20	10
41–50	54	5	10	40	35	10
51–60	64	0	10	30	20	40
61–70	46	0	5	20	15	60
71–80	62	0	5	5	20	70
81–100	25	0	5	10	30	55

of cases in each decade, falling in the different categories of surface area involved—that is, groups O, A, B, C, and D.

It will be seen that there is an increased extent of involvement with increase of age. Thus by the fourth decade 10% of cases have more than half of their intimal surface involved, and by the sixth and seventh decades almost half the cases have such an extensive involvement.

When these figures are correlated with Table I it can be inferred that the increase in incidence of fatty deposition in the first and second decades is associated with either an increase in the number of deposits or an increase in the size of the deposits already present, or both.

Gross inspection, however, indicated that the increase in involvement was mainly due to an increase in the number of new lesions. Also, in the third and fourth decade there was observed an increase in the incidence of fibrous plaques (grade 2) (Table I, Fig. 1), as well as an increase in extent of area involvement (Table II). Was this due to fibrous plaques appearing *de novo* or to a fibrous reaction to the fatty deposits?

Histologically, examination of representative plaques in the first two or three decades showed the presence of fat with little or no cellular reaction (Fig. 2). In the fourth and fifth decades there seemed to be generally a fibrous-tissue reaction to the presence of fat (Figs. 3 and 4). By the fifth decade onwards the fibrous reaction had become more pronounced and was associated with degenerative changes and thrombosis, haemorrhage, necrosis, and calcification, with a reactive chronic inflammation.

Discussion

This study, within its limitations (and there are disappointingly many), has shown that the deposition of fat within the intima is the earliest lesion (atheroma), and that this lesion progresses, both in severity and in extent, with age.

It would seem from histological observation and analysis of our data (arrived at by subjective appraisal)

that there was a progression of events from fatty deposition to fibrosis to complicated lesions, in that order, and as distinct but overlapping phases. These observations are supported in the main by those of Strong *et al.* (1958) in their studies involving the aortas from patients in New Orleans, Guatemala, and Costa Rica.

In the younger age-groups there was no macroscopic or microscopical evidence of fatty deposition being secondary to organization of thrombi, haemorrhage, or fibrosis, but all evidence in our hands suggested that the deposition of fat occurred *de novo*. Thrombotic and haemorrhagic causes of atherosclerosis appear to be significant only in the older age-groups, from the fifth decade onwards.

We have concluded tentatively that fatty deposition is possibly not reversible, but further observations are necessary before we can be certain.

The presence of fatty deposits in the first, second, and even the third decades, generally without any reaction, appears to us to be physiological and harmless. Fibrosis (to any extent) appears only in the middle of the third to the middle of the fourth decade, and is well established by the fifth. Later, there is the development of the complicated lesions which become evident during the sixth decade, and are possible complications of the lesions arising in the previous phase.

An explanation of the above conclusions which is most favoured by us is that there are different reactions of the body at different ages. Aschoff (1925) has postulated three stages of ageing in the aorta. The first was an "ascending period" from birth to 33 years, during which there was, generally, a physiological increase in all tissue elements. The second was a "summit period" from 33 to 45 years, when the aorta retains its form. The third was a "descending period" after 45 years, in which the aorta becomes overstretched and dilated—"simple sclerosis" or "senile ectasia." The intimal reaction to this is an increase of connective and elastic tissue elements with degeneration and hyalinization. He found that deposition of intimal fat occurred at all ages.

The first part of the ascending period, which he called the "atheroma of infancy," he believed to be reversible. At a later period, from 16 to 33, and even to 40 years, which he named the "atheroma of puberty" or "youth," he found fatty deposition with very little reaction, which he considered might or might not prove to be reversible. However, in the descending period of life—that is, over 45 years—he found that the deposition of fat engrafted on the changes of physiological ageing resulted in "atherosclerosis" or "destructive sclerosis," which is irreversible.

It appears to us that Aschoff's conclusions help to explain our findings that the symptomless and harmless mild fatty deposits of the first part, or ascending period, of life tend to become pathological in the summit, or second period, due to fibrosis, and later become complicated in the third phase, the descending period.

If this is so, then it would seem that efforts should be directed to the study of the deposition of fat in the intima, particularly during the fourth and fifth decades. Before this age it does not seem to matter much, but after that it would appear that the complicated lesions of the descending period of life are all-important.

Added emphasis is given to this aspect of the disease when the results of Strong *et al.* (1958) are taken into

consideration. In their studies they compared the natural history of the disease between residents of the U.S.A. (New Orleans) and Central America (Costa Rica and Guatemala). They found that the deposition of intimal fat followed a similar pattern in both geographical areas. Their findings are, in general, similar to ours, except that they place importance on a greatly increased deposition of fat in the second decade which they believe may be due to the hormonal changes of puberty.

However, the cases from the U.S.A. had fibrous plaque formation much more advanced and extensive in the third and fourth decades than those in the cases from Central America. It would seem that fibrous-plaque formation in the cases we examined from North London are similar to those from New Orleans and different from those from Central America. Strong *et al.* suggest that fatty deposition may not be a function of the fat content of the diet or a function of race; they believe, however, that diet may be important in the genesis of fibrous plaques. They stress the importance of further studies in the factors influencing the conversion of fatty streaks to fibrous plaques, an opinion which we endorse.

Summary

A total of 382 aortas from a North London area were examined, both macroscopically and microscopically. Fatty deposits appeared to develop irreversibly as early as the first year of life, and increased in incidence as a lesion to involve *almost every* patient in the second decade.

In the third decade, particularly in the second half, fibrous plaques made their appearance, and by the fourth decade the incidence of cases with either fatty or fibrous lesions was about equal.

In the fifth decade, particularly in the second half, complicated lesions made their appearance, and did so increasingly, so that almost all patients had this lesion by the seventh decade.

It is suggested that the pathogenesis of the disease is the deposition of fat within an intima of different reacting capabilities, which latter is associated with age. In the early age-groups there is no reaction, but in the third, fourth, and fifth decades there is a fibrous-tissue reaction to the fat, leading to sclerosis. The reaction in the sixth decade and later is one producing complications.

It would seem that the disease, as found in North London, is similar to that found in other parts of the world from which studies have been reported, and, in particular, very much like that in New Orleans.

It is suggested that further studies should be directed on the factors influencing the conversion of fatty streaks to fibrous plaques.

Acknowledgment for the help given in this survey is made to Sir W. Bentley Purchase and Dr. R. I. Milne, H.M. Coroners, St. Pancras; to Drs. C. C. S. Pike and W. B. Obank, of Peace Memorial Hospital, Watford, and Dr. R. F. Welch, of Barnet General Hospital; to Mr. Phillips, for photographic work; to Miss Haestier and Miss Katherine Hill, for the secretarial work; and to the Board of Governors of the Royal Free Hospital for the award of funds for research.

REFERENCES

- Aschoff, L. (1925). *Lane Lecture VI—Atherosclerosis*, p. 887. (Delivered in the U.S.A., 1924.) Jena.
- Gore, I., and Tejada, C. (1957). *Amer. J. Path.*, **33**, 875.
- Strong, J. P., McGill, H. C., jun., Tejada, C., and Holman, R. L. (1958). *Ibid.*, **34**, 731.
- W.H.O. (1958). *Techn. Rep. Ser.*, No. 143.