In 72 patients with calcific aortic stenosis treated by "closed" transventricular valvotomy the mortality was 17% and good results were obtained in 44%.

In 20 patients with subvalvar stenosis the operative mortality was 20% and initially good results were obtained in 55%, but deterioration in the follow-up reduced these to 30%.

The present position and future prospects of surgical treatment are discussed.

We are particularly indebted to Sir Russell Brock, who initiated the surgical treatment of aortic stenosis, and to him and to Mr. Donald Ross for co-operation and encouragement in assessing their results. We are grateful to all the physicians who have referred patients and helped us in the follow-up, and especially to Dr. Lawson McDonald, who referred 19 patients from the National Heart Hospital. We thank Mr. Frank Muir and Miss Sylvia Treadgold, of Guy's Hospital, and Miss Nicolette Larbey, of the National Heart Hospital, for their help with the figures.

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Relationship Between Aortic Plaques and Age, Sex, and Blood Pressure*

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The intimal surfaces of aortas removed at necropsy show a wide variety of disease patterns, and many attempts have been made to correlate these variations with such factors as the age, sex, and blood-pressure level of the patients. Widely divergent results have been obtained, but much of this confusion has arisen because of imprecise definitions of the various lesions observed, and because of the inaccuracy of visual grading methods (Cranston *et al.*, 1963). We have determined the extent and type of disease in the aortas of a sample of hospital necropsies by a tracing and planimetry method, and report here the relationship between these findings and the age, sex, and arterial pressure of the patients from whom the aortas had been obtained.

Material

Unselected Necropsy Sample.—During the period of study the aorta was removed from every fifth patient aged 35 and over and from every patient aged 15–35 on whom a necropsy was carried out at the Radcliffe Infirmary, Oxford. This unselected sample of the hospital necropsies comprised 336 patients, 195 men and 141 women. For each of these patients the age, sex, and blood-pressure were recorded from the case-notes. If the pressures thus obtained were of doubtful validity, as in cases of haemorrhage, cardiac infarction, or stroke, the patient's general practitioner was asked if the pressure had been measured by him or recorded by any other examining doctor (for life assurance or at hospital visits) in the 12 months before death. Patients with invalid case-note pressures, and with no pressure recordings in the year before death, were omitted from the studies on the relationship between disease and blood-pressure. There were 75 such patients—42 men and 33 women.

Patients with Cardiac Infarction.—During the period of study a consecutive sample of patients with cardiac infarction was being collected for studies on the heart muscle and arteries (Mitchell and Schwartz, 1963), giving 116 patients (82 men, 34 women) whose aortas could be compared with those of the unselected series. Of these, 47 men and 12 women had blood-pressure recordings which were considered to be valid for analysis.

Methods

Preparation of Aortas.—Each aorta was removed, stripped of periadventitial debris, opened longitudinally along its anterior wall, and washed in 0.9% sodium chloride solution. It was then cut transversely at the level of the first paired intercostal arteries and at the bifurcation, the segment between these points being retained for assessment and fixed in 10% formalin.

Staining.—The segments were washed in tap-water, blotted dry, and immersed, intimal side upwards, for 15 minutes in a 0.5% solution of Sudan IV (Gurr), the solvent consisting of equal volumes of 70% ethanol and acetone. After staining, the segments were transferred to 80% ethanol for 25 minutes, then to fresh 80% ethanol until differentiation was complete, the normal areas of the aorta being unstained or only faintly pink, while the fatty lesions were deep red. The segments were then washed in running tap-water for an hour.

Tracing.—The aortas were placed on a wooden board and covered with a large sheet of waterproof tracing material which was completely transparent when wet (Kodatrace). This was pinned firmly to the board, thereby flattening the aortic segment, and the board with its attached paper and aorta was placed in a tray and covered with water. If the thoracic aorta was ballooned and would not readily flatten, a longitudinal midline incision was made in the expanded segment to enable it to be pinned out. The outline of the whole segment, and the boundaries of all the lesions were then traced with a pencil. Four types of plaque were recognized: (1) flat sudanophilic—fatty streaks; (2) raised sudanophilic; (3) raised non-sudanophilic—fibrous plaques; (4) complicated—plaques showing ulceration, thrombosis, haemorrhage, or calcification. Different symbols were used on the tracing to denote the four types of plaque.

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Planimetric Assessment.—The trace was examined, and all the lesions of each macroscopic type were numbered in sequence. The area of the complete aortic segment and the area of each of the individual lesions were then measured with a rolling-wheel planimeter (Allbrit) set to read in square centimetres, the tracing-point being taken round each area twice and the reading being then halved. For each of the aortas we recorded the total area, the areas affected by the four types of lesion, and the total diseased area. The percentage of the aortic area affected by disease could then be calculated.

The reproducibility and observer error of this method has been studied (Cranston *et al.*, 1963) and it has been found to be more satisfactory than simple visual assessment.

Results in Unselected Sample

(A) Aortic Area

When the areas of the standard aortic segments removed at necropsy were plotted against the patient's age a linear relationship was observed (Figs. 1 and 2). Enlargement or "unfolding" of the aorta is a common radiological finding in older subjects (Dotter and Steinberg, 1949), and it has been said to represent a "senile ectasia" (Aschoff, 1925, cited by Hill *et al.*, 1961). Our results show that the change in aortic area is, however, related to age in a linear fashion throughout the age-range studied (from 15 years onwards). Aortic enlargement does not therefore begin *de novo* in middle-life. It is thus not a "senile ectasia" but a steady ageing phenomenon similar in behaviour to changes which occur in the eye and in the skin with age.

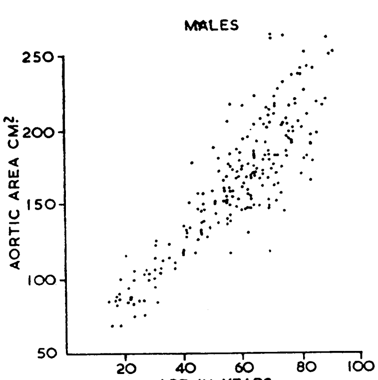

FIG. 1

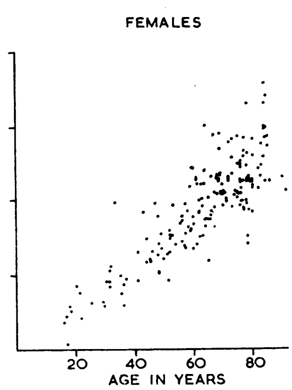

FIG. 2

FIG. 1.—Area of standard aortic segment, as measured by tracing and planimetry, in men from the unselected necropsy sample. FIG. 2.—Area of standard aortic segment in women from the unselected necropsy sample.

This increase in aortic area with age must affect the visual assessment and general interpretation of aortic disease. If at the age of 20, with an aortic area of 100 sq. cm., a man has 10 sq. cm. of fatty streaking, visual assessment would record 10% involvement. If this man had lived to the age of 80, his aortic area might then be 200 sq. cm. Assuming that the same fatty lesions are present, would they have increased in area *pari passu* with the aorta, so that they now occupy 20 sq. cm. with an unchanged visual grading of 10% ? Or, as they are perhaps different in structure and behaviour from the intervening normal areas, would they retain the same absolute area of 10 sq. cm., the visual grading thus "regressing" to 5% ? It is also possible that over the years each individual lesion may truly regress and disappear, be transformed into other lesions, or be covered over by new deposits and thereby obliterated ; and it is clear, therefore, that to try to determine the evolution of aortic disease by comparing the extent of disease on a visual basis in aortas of different sizes from patients of different ages is unlikely to give conclusive results. Furthermore, by expressing disease severity as a percentage of aortic area the possible importance of aortic size as a significant variable is eliminated. In all subsequent comparisons and calculations we have therefore used the actual area involved by each type of lesion.

(B) Area of Lesions

Relationship to Age

Schwartz and Mitchell (1962a, 1962b) showed that the structure and distribution of flat sudanophilic lesions, or fatty streaks, differed markedly from that of the three raised types of plaque (sudanophilic, fibrous, and complicated). We therefore subdivided the area occupied by lesions in each of the aortas into two categories—fatty streaks, and other lesions. Figs. 3 and 4 show the area of fatty streaking plotted against age ; there is no readily apparent correlation between these two variables, and this was confirmed by regression analysis, which showed that there was no significant relationship between the area of fatty streaking and age in either men or women.

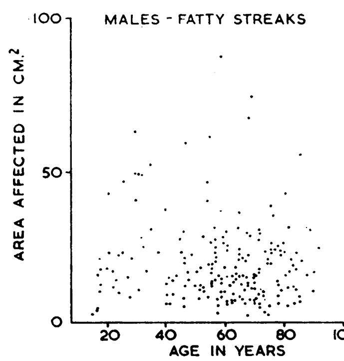

FIG. 3

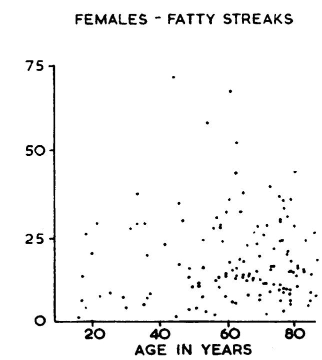

FIG. 4

FIG. 3.—Area affected by flat sudanophilic plaques in men from the unselected necropsy sample. FIG. 4.—Area affected by flat sudanophilic plaques in women from the unselected necropsy sample.

For the other types of lesion combined there was, however, a highly significant age correlation ($P<0.001$). Figs. 5 and 6 show the scatter-plots for these lesions, and it is apparent that they are present to an insignificant degree in the younger age-groups, and that the regression line therefore has two components—one running along the abscissa and another with a steep slope. The age at which this second relationship emerges is seen to be different for the sexes, being 10–15 years earlier in men. Analysing the same data in a different way, Mitchell and Schwartz (1962) found that women of a given age showed arterial disease of the same severity as men who were 10 years younger.

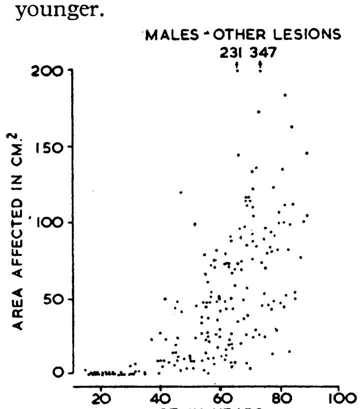

FIG. 5

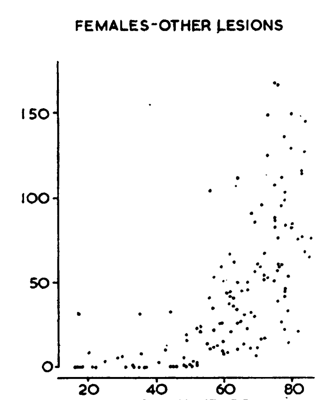

FIG. 6

FIG. 5.—Area affected by complicated, raised fibrous, and sudanophilic plaques combined, in men from the unselected necropsy series. FIG. 6.—Area affected by complicated, raised fibrous, and sudanophilic plaques combined in women from the unselected necropsy series.

Relationship to Blood-pressure and Aortic Area

As the area affected by the three raised types of plaque is strongly age-correlated it would show an apparent correlation with any other age-dependent variable, whether or not there was a true relationship between them. We have already shown that aortic area is age-dependent, and Figs. 7–10 show that for those patients in whom valid readings were available blood-pressure, and especially the systolic level, is correlated with age. Determination of the simple relationship between area of disease and blood-pressure would therefore be of no value, so multiple correlation analysis of the effect of each of the variables separately was carried out, using the Oxford University computer.

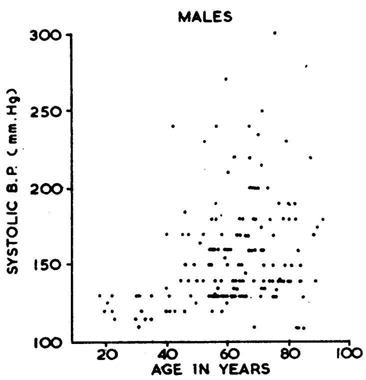

FIG. 7

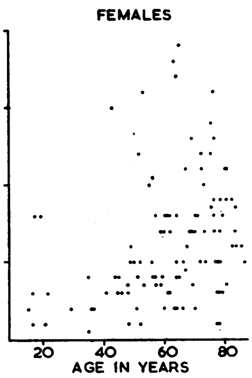

FIG. 8

FIG. 7.—Relationship between systolic blood-pressure and age in men from the unselected necropsy series for whom valid readings were available. FIG. 8.—Relationship between systolic blood-pressure and age in women from the unselected necropsy series for whom valid readings were available.

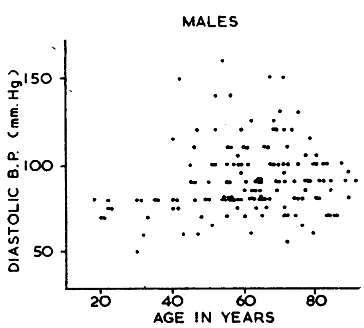

FIG. 9

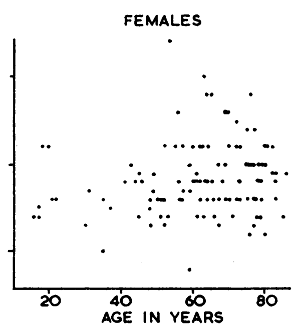

FIG. 10

FIG. 9.—Relationship between diastolic blood-pressure and age in men from the unselected necropsy series for whom valid readings were available. FIG. 10.—Relationship between diastolic blood-pressure and age in women from the unselected necropsy series for whom valid readings were available.

The area of fatty streaking was found to show no significant correlation with age, with aortic size, or with systolic or diastolic blood-pressure, alone or in combination. The findings with respect to the three raised types of plaque in men and women are shown in Tables I and II, the two most informative characteristics being the level of significance of any observed correlation, and the value r^2, the square of the correlation coefficient. This characteristic, the measure of certainty, indicates how much of the observed variability is accounted for by the correlation. The remainder ($1-r^2$) is due to random variation or to the effect of variables not considered in the analysis. Thus $r^2=0.20$ implies that 20% of the variability is explicable in terms of the linear model, leaving 80% unaccounted for.

In men the raised fatty plaques correlate with age and with aortic area, but not with systolic or diastolic blood-pressure. Combining pressure with the other variables does not add to the correlation, and only some 20% of the variability is accounted for by considering these factors. Raised fibrous plaques correlate with age, aortic area, and diastolic pressure, but not with systolic pressure ; combining diastolic pressure with the other variables improves the correlation, 30% of the variability thereby being accounted for. The complicated lesions show a very strong correlation with aortic area, 42% of the variability being accounted for, whereas the age correlation accounts for only 16%. This may merely reflect the influence of the complicated lesions on aortic size, or may arise because the complicated lesion is a late stage in the evolution of aortic plaques, dependent therefore on ageing ; everyday observation shows that ageing is not a simple function of the number of years lived, so one must assess it on a biological rather than a chronological scale. Aortic area may be a good measure of this true or biological ageing, whereas the patient's age merely records the number of years lived.

TABLE I.—*Results of Multiple Correlation Analysis for Men from Unselected Necropsy Sample*

Type of Plaque	Variable Tested	F Value	Level of Significance %	r^2
Raised sudanophilic	Age	43·8	0·1	0·22
	Aortic area	36·9	0·1	0·20
	Diastolic B.P. alone and with others ..		N.S.	
Raised fibrous	Age	33·4	0·1	0·18
	Aortic area	36·1	0·1	0·19
	Diastolic + age ..	26·0 29·7	0·1 0·1	0·30
	Diastolic + area ..	21·8 27·9	0·1 0·1	0·30
Complicated	Age	30·3	0·1	0·16
	Aortic area	108·1	0·1	0·42
	Diastolic alone and with others ..		N.S.	

TABLE II.—*Results of Multiple Correlation Analysis for Women from Unselected Necropsy Sample*

Type of Plaque	Variable Tested	F Value	Level of Significance %	r^2
Raised sudanophilic	Age	36·2	0·1	0·25
	Aortic area	60·7	0·1	0·36
	Diastolic B.P. + age	10·7 31·6	1·0 0·1	0·32
	Diastolic B.P. + area	6·6 49·4	10·0 0·1	0·40
Raised fibrous	Age	29·4	0·1	0 22
	Aortic area	33·4	0·1	0·24
	Diastolic B.P. alone and with others ..		N.S.	
Complicated	Age	33·1	0·1	0·24
	Aortic area	43·9	0·1	0·29
	Diastolic alone and with others ..		N.S.	

In women it is the raised fatty plaques which relate to area rather than age and which are related to diastolic but not systolic blood-pressure. The raised fibrous and complicated plaques are age- and area-dependent, but with a low r^2 value ; adding information about the pressure does not contribute to the correlation observed with age and area, and pressure alone does not correlate with the area of the plaques. This differential behaviour between the sexes may relate to the 10-year lag in the onset of raised lesions in women, for if there is a maturation from one type of lesion to another the variables considered, and in particular the patient's own time scale as reflected in aortic size, would show a different pattern of interrelationships.

Relationship to Malignant Disease

In all the analyses, the low value of r^2 is of interest, knowledge of the patient's age, sex, and diastolic pressure allowing only some 20–30% of the variability to be accounted for. The remaining 70–80% is either random variation or due to the effect of variables not considered so far. One factor which has been thought to modify arterial lesions is the development of malignant disease (Wilens, 1947). When we subdivided our 336 patients into those with malignant disease (79) and those without and compared them on an age and sex basis no significant difference in the pattern of disease was found, nor did patients with localized tumours differ from those with carcinomatosis. Indeed, only one group of patients showed any apparent trend, and that was women under 65 with malignant disease, in whom the area of raised plaques was less than in the women under 65 without carcinoma. This difference did not reach the 5% level of significance, but it is of interest to note that 72% of the tumours in this age-group were ones in which an endocrine influence may be of importance (breast, ovary, and uterus), whereas in the female patients over 65 in whom no trend in aortic disease severity was noted 65% of the tumours were in other sites (oesophagus, stomach, colon, and bronchus). If disease severity is in any way related to hormonal factors, women marked out by their endocrine pattern to have certain types of neoplasm may have an increased protection from the processes leading to the formation of raised plaques. This possibility has already been suggested by Rivin and Dimitroff (1954).

Results in Patients with Cardiac Infarction

Mitchell and Schwartz (1962) have shown that patients with cardiac infarction have a bigger area involved by raised aortic lesions than patients from an unselected necropsy sample, this difference not being accounted for by differences in the age structure and blood-pressure levels of the groups studied. Table III shows the findings in men with cardiac infarction (the number of women in the sample was thought to be insufficient for adequate analysis) with respect to the relationship between the area of aorta involved by the three types of raised plaque and the various factors studied.

TABLE III.—*Results of Multiple Correlation Analysis for Men with Myocardial Infarction*

Type of Plaque	Variable Tested	F Value	Level of Significance %	r^2
Raised sudanophilic	Age		N.S.	
	Aortic area		,,	
	Diastolic B.P. alone and with others ..		,,	
Raised fibrous	Age	5·3	10·0	0·10
	Diastolic B.P. + age	9·8	1·0	0 27
		7·0	10·0	
Complicated	Age	5·5	10·0	0·11
	Aortic area	62·0	0·1	0·58
	Diastolic B.P. alone and with others ..		N.S.	

Unlike the unselected group, in whom raised fatty plaques were correlated with age and aortic area, these patients showed no such correlation. The other two types of lesion show a pattern of relationships similar to that seen in the unselected group except that less of the variability is accounted for by age and diastolic pressure, and more of the complicated plaque variability is related to aortic area.

Thus the difference in raised aortic lesions observed by Mitchell and Schwartz (1962) in a group of patients with cardiac infarction as compared with an unselected necropsy group is not explicable in terms of differing age and blood-pressure composition of the groups, nor is it due to a differential effect of age and pressure in the two groups. The increased amount of disease and its variability remain unexplained.

Discussion

It has been tacitly assumed that fatty streaks represent the earliest stage in the development of arterial plaques. However, many creatures other than man show fatty streaks (Finlayson *et al.*, 1962), whereas raised stenosing lesions seldom appear in other species. Even in man there are ethnic groups with a high prevalence of fatty streaking but a very low prevalence of raised lesions (Holman *et al.*, 1958 ; Strong *et al.*, 1959), so that even if the lesions are related the factors responsible for maturation of the fatty streak into the raised lesion must differ from those which lead to its formation. The plaques are, moreover, different in structure (Schwartz and Mitchell, 1962a) and occur in different parts of the aorta (Schwartz and Mitchell, 1962b). The present study shows that the area of fatty streaking is unrelated to the age, sex, aortic area, or blood-pressure of the patient, differing thereby from the raised lesions, which are related to those factors. We would suggest that in future studies on arterial disease a clear distinction should be made between flat and raised lesions, and that these two types of plaque should not be assumed to be causally related for they do not necessarily represent stages in the evolution of one disease process. The current, and in our view erroneous, " unitary " concept is fostered by the tendency to call all intimal lesions " atherosclerotic," whatever their type, and whether occurring naturally in man or produced experimentally in animals. A descriptive classification of the lesions would avoid this confusion, and we suggest that a simple division into flat sudanophilic and raised lesions would be of value.

The relationship between age and aortic area and the possible effect of size changes on visual assessment of disease has not been considered previously. To try to determine the natural history of the disease from necropsy observations cannot be easy, for each specimen reveals only the extent of the disease process in that person at death, and assessment of the evolution of the lesions depends on comparisons between patients dying at different ages. Add to this our lack of knowledge of the behaviour and interrelationship of the individual lesions and the unknown effect of changing aortic size on our estimations, and the magnitude of the problem is apparent. We have tried to construct theoretical models of the ways in which aortic disease might evolve, with a view to analysing these on the computer and determining which model gives results which most closely approximate to the findings in our necropsy survey. This has proved impossible because of the extent to which the variability of aortic disease is unaccounted for by our analyses.

Our studies clearly show that the age at which raised aortic plaques appear differs in men and women. This is in keeping with necropsy studies on other arteries (Schwartz and Mitchell, 1962a, 1962b, 1962c) and with clinical observations on the rarity of myocardial infarction in women before the menopause (Spitzer *et al.*, 1957 ; Oliver and Boyd, 1959). As this relative immunity is apparently lost in women who have undergone bilateral oophorectomy (Oliver and Boyd, 1959) it would be of interest to study the aortas of such patients by our technique and compare them with normal women.

Previous studies have failed to clarify the relationship between blood-pressure and arterial disease, confusion having been introduced by the grouping of all types of lesion together as " atherosclerotic," and by the use of heart weight as an index of high blood-pressure (Wilkins *et al.*, 1959 ; Sacks, 1960). The finding of plaques in the pulmonary arteries of patients with mitral stenosis, such lesions being uncommon in normal patients, led Turnbull (1915) to suggest that pulmonary hypertension might play a part in their development. Davis and Klainer (1940) found a relationship betweeen coronary disease severity and arterial pressure, and Paterson *et al.* (1960) showed that the total extractable lipid in the coronary, cerebral, and femoral arteries was related to blood-pressure level. Our studies show that raised lesions and diastolic blood-pressure are indeed related, the type of lesion showing this relationship differing in men and women. Systolic pressure, however, showed no correlation with any of the lesions studied.

In our view the most significant finding in our study is the low values obtained for r^2, the measure of certainty. This means that in our necropsy sample some 60–80% of the variability of aortic disease was not explicable in terms of age, sex, aortic size, blood-pressure, or the presence of malignant disease. Most of the wide variations in aortic disease seen at necropsy and the systematic differences between groups of patients with and without cardiac infarction are thus due either to random variation, which seems unlikely, or to the effect of variables not studied in this survey. Further studies, using other variables, such as serum-lipid levels, smoking habit, amount of physical activity, and, when such tests become available, assessment of thrombotic activity, would clearly be of interest.

Summary

The area of aortic surface occupied by different types of plaque was determined by a tracing and planimetry technique on 336 unselected necropsy specimens, and on 116 specimens from patients with cardiac infarction.

The area of the standard aortic segment studied was found to increase with age in a linear fashion, and the implications of this for the assessment and interpretation of aortic disease are discussed.

The area of fatty streaking was found to be unrelated to age, sex, aortic area, and diastolic blood-pressure, whereas the area occupied by raised plaques was related to these factors. These findings emphasize the differential behaviour of the two types of plaque. Although raised plaques showed a relationship to these factors, some 60–80% of the variability of aortic disease observed in our sample was not accounted for by the factors considered, nor was any explanation found for the increased amount of disease seen in patients with myocardial infarction. Random variations, or the effect of factors other than those studied, must account for this residual variability and for the differences between a group of patients with cardiac infarction and an unselected necropsy group.

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Antigenic Properties of Human Tumours: Delayed Cutaneous Hypersensitivity Reactions

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The possibility of controlling human cancer by immunological means continues to excite the interest of many workers. The successful therapeutic application of such methods must depend primarily on the presence of specific cancer antigens, and it must be admitted that such antigens have not yet been demonstrated to the satisfaction of many immunologists. Efforts have been made to demonstrate tumour antigenicity in relation to the host by a variety of methods. In 1930 Witebsky produced an antiserum to human stomach cancer in guinea-pigs. He then absorbed these antisera with alcoholic extracts of normal stomach and found that the antiserum was still capable of producing a precipitation reaction against the cancer extract. This suggests that there is a different antigen present in gastric cancer which is not present in the corresponding normal tissue. Zilber *et al.* (1959) claim to have demonstrated specific tumour antigens by immunizing guinea-pigs with tumour extract. The animals were subsequently desensitized to normal tissue extracts, and, following this, were still found to develop anaphylaxis when challenged with tumour extracts. Graham and Graham (1955) found positive complement-fixation reactions in the sera of 12 out of 48 patients tested against extracts of their own tumours. Finney, Byers, and Wilson (1960) were able to demonstrate precipitating antibody in the serum of patients against a saline extract of their own tumour. Furthermore, they were able to demonstrate a rise in antibody titre after intramuscular injection of tumour extract and adjuvant, and in some cases after radiotherapy. Most recently, Nairn, Philip, Ghose, Porteous, and Fothergill (1963) have shown by means of gel-diffusion reactions the presence of apparently specific serum antibody to kidney carcinoma in a patient who was immunized by homologous human renal carcinoma.

In addition to this *in vitro* evidence of tumour antigenicity, there is much to suggest the presence of an immune response to the tumour on the part of the host, but this evidence is largely of an indirect nature. Black and Speer (1959) have shown that there is a correlation between the degree of

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