Genetic markers in atherosclerosis: A review*

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Summary. There is a growing number of lipoprotein markers recognized by immunological, electrophoretic, and other biochemical methods, and a beginning has been made on studying their modes of inheritance and linkage relations. Suggestive but inconclusive evidence of a relation between the cerumen polymorphism and arteriosclerosis has been published. Associations of the ABO blood groups with cardiovascular disease and serum lipid levels have been established, but the exact relation to lipoproteins and atherosclerosis remains to be determined.

The subject of genetic markers in atherosclerosis is at the intersection of genetics, medicine, epidemiology, immunology, and biochemistry. The observations are scattered, sometimes preliminary or conflicting, and any review must soon be obsolete. Recognizing these limitations, I shall discuss the present state of our knowledge on antigenic polymorphisms of lipoproteins (Ag, Lp, and Ld), the controversial evidence of a relation between Lp and the HL-A locus, the cerumen polymorphism (W), electrophoretic variants of lipoproteins, available evidence on linkage of lipoprotein markers, and associations of the ABO blood groups with cardiovascular diseases and lipoproteins. Citation in this review does not imply credence, and my comments in the last section are deliberately speculative.

Antigenic polymorphisms

Three genetic polymorphisms of β -lipoprotein have been reported on the basis of the Ouchterlony method of double diffusion in agar gel. Allison and Blumberg (1961) discovered in a multiply transfused patient (C. de B.) an antiserum which they attributed to a polymorphic factor Ag(+), later designated Ag(a). Subsequently, Hirschfeld (1963) showed that anti-Ag(a) is a mixture of three specificities, anti-Ag(a₁), anti-Ag(x), and anti-Ag(z), which behave as a factor-union system. A fourth determinant, Ag(y), is antithetical to Ag(x). Six

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TABLE I
AG CHROMOSOME FREQUENCIES IN SWEDEN
(after Hirschfeld and Rittner, 1969)

Chromosome Frequency	xa ₁ z 0.0048	xa ₁ 0.1935	x 0.0249	ya ₁ z 0.1549	ya ₁ 0.1010	y 0.5210
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TABLE II
GENE FREQUENCIES DEFINED BY x,y FACTORS OF
Ag SYSTEM
(after Giblett, 1969)

Alleles	Caucasoid (N = 248)	Negroid (N = 54)	Mongoloid (N = 1205)
Ag ^x	0.23	0.69	0.73
Ag ^y	0.77	0.31	0.27

alleles appear to account for the population frequencies and segregation in families (Table I). The Ag(z) factor is apparently a subtype of a₁, since chromosomes xz and yz have not been observed. All reported alleles have either the x or y factor, but not both. From limited gene frequency data, Ag^x is the common allele in Africa and Asia, while Ag^y predominates in Europe (Table II).

The symbol Ag has been suggested for all β -lipoprotein antigens detected by isoimmunization (Bütler, 1967). Patients with thalassaemia are especially good producers of antiserum, perhaps because of the associated splenomegaly (Blumberg *et al*, 1964). The relation of many of these antisera to the Ag system defined by a₁, x, y, and z is unclear (Hirschfeld, 1972). Dausset *et al* (1968) report

TABLE III
Lp^a GENE FREQUENCIES (after Berg, 1968)

Population	N	Gene frequency
Norwegians	1109	0.1948
Hadza, Tanzania	107	0.1912
Easter Islanders	106	0.0434
Indians, Labrador	234	0.0086

several apparent crossovers between the Ag(a) and Ag(t) factors (Berg, 1972).

European workers have obtained convincing evidence that Ag is a regular phenotype system. However, Okochi (1967) reported several exceptions to the dominant inheritance of Ag(y) and the postulated complementarity of Ag(y) and Ag(x). Antibodies to β -lipoprotein are exclusively located in the 7-S- γ globulin fraction and are quite stable, though often weak or poly-specific. The antigens, however, are notoriously labile, whether stored at 4° C or frozen. It is not clear at the present time whether exceptions to the theory of Hirschfeld with respect to Ag(a₁, x, y, z) are the result of technical problems or are real.

A little-studied LDL polymorphism was defined by anti-Ld(a), discovered in the serum of a frequently transfused haemophiliac (Berg, 1965). It is anomalous in reacting strongly at 4° C and 20° C, but not at 37° C. Nevertheless, the precipitin was found to reside in the γ_G fraction. The inheritance of Ld(a) is autosomal dominant, with a gene frequency of 0.24 in Norway. By the criterion of isoimmunization it would conventionally (if ambiguously) be called an Ag factor, but its relation to the Ag locus is unknown. There is no association or linkage between the Lp and Ld systems (Berg, 1966). An antiserum that may define Ld(b) was reported by Berg and Bearn (1970).

The Lp system is by far the best studied, and in recent years the most severely attacked. Berg (1963) immunized rabbits with human serum or β -lipoprotein; later horses, baboons, and sheep were shown also to produce Lp anti-sera. Isoimmunization has not been successful, though Lp(a-) baboons produce specific antisera against Lp(a). Conversely, anti-Ag is never heteroimmune. The only Lp antigen that has been much studied is Lp(a); there is an Lp(x) defined by a horse antiserum which precipitates in a different band from Lp(a) but is always concordant with it (Bundschuh, 1964). The Lp^a gene frequency is lower in Orientals than in Caucasians and Negroes (Table III). Chimpanzees, orangutans, baboons, and Rhesus monkeys are polymorphic for the Lp(a) antigen,

which is qualitatively different in the Rhesus monkey from man and the other primates tested.

The strongest evidence for dominant inheritance of Lp(a) comes from 574 families (Wendt, 1966). Only 1 of 547 children from Lp(a-) $\times$ Lp(a-) matings was Lp(a+); on the basis of several polymorphisms parentage was not excluded. Rider, Levy, and Frederickson (1970) identified the 'sinking' pre- β -lipoprotein (which in the ultracentrifuge does not float at the density 1.006) as Lp(a), and confirmed that this component segregated as a dominant trait in 51 kindreds. Both Wood (1969) and Rittner (1970) found a clearly bimodal distribution of the Lp(a) antigen in serum, and Wood found that Lp(a+) persons could be divided by radial immunodiffusion into two groups, which appeared to correspond to homozygotes and heterozygotes. Albers, Chen, and Aladjem (1972) were unable to demonstrate the Lp(a) antigen in the sera of Lp(a-) persons after 110-fold concentration. All these observations provide strong evidence for dominant inheritance of the Lp(a) antigen.

Against the prevailing view two criticisms have been raised. Schultz and Shreffler (1972) used preparative ultracentrifugation and absorption on sepharose gel to isolate what they considered to be purified Lp(a) substance, even for individuals classified by them as Lp(a-). Noting that an isoimmune anti-Lp(a) has never been found, they question the dominant inheritance of Lp(a). Interpretation of their results depends critically on identity of components recognized by immunological and biophysical techniques (Harvie and Schulz, 1973). With their antisera 13 per cent of children from Lp(a-) $\times$ Lp(a-) matings were classified as Lp(a+). They note that 'their original anti-Lp(a) antisera was prepared against the serum of an individual who was consistently classified Lp(a-) on Ouchterlony double diffusion.'

Berg (1972) stressed the negligible frequency of exceptional children (1/547) in European family data and the failure of Albers *et al* (1972) to demonstrate Lp(a) substance in concentrated sera from Lp(a-) individuals. Albers and Hazzard (1974) have subsequently reported a J-shaped distribution of purported Lp(a) substance in the general population, including individuals classified as Lp(a-). A recent report (Walton *et al*, 1974), which for the first time used sheep antisera and rocket electrophoresis, makes the situation seem even more confused. A J-shaped distribution is again found, with many but not all persons typed as Lp(a-) in Ouchterlony gels appearing to have Lp(a) substance after the serum is concentrated. Schultz *et al* (1974) now favour a dominant gene with nearly

complete penetrance, based partly on a bimodal distribution of antigen concentration and partly on family material (Sing, Schultz, and Shreffler, 1974).

The important genetic question here is not whether Lp(a-) individuals have trace amounts of Lp(a) substance, or whether this is an artefact of preparation or incompletely absorbed antisera. It is rather the bimodality of Lp(a) that is at issue. The only workshop on the Lp system was held in 1966, and the proceedings are not readily accessible (Wendt, 1966). Annual HL-A workshops have demonstrated their utility for resolving questions of techniques and serum quality (e.g. Dausset and Colombani, 1973). The answer to the Lp debate can only be found in the laboratory. The solution may have implications for the Ag and other lipid antigens and for the apparent homology of Lp(a) antigen, the sinking pre-beta lipoprotein detected in the ultra-centrifuge, the pre- β_1 band in agarose gel electrophoresis (Heiberg and Berg, 1974), and perhaps the double beta-lipoprotein of Seegers *et al* (1965).

Evidence of a relation between Lp and HL-A systems

Berg (1971) has reported two suggestions of a relation between the Lp and HL-A systems. First, skin grafts were observed to survive longer when donors and recipients were of the same Lp type (Berg *et al*, 1968). This study has not been repeated. Secondly, the amino acid compositions of HL-A and Lp(a) are remarkably similar by the difference index (DI) of Metzger *et al* (1968). Whereas the lowest DI observed by Metzger *et al* among 630 pairs of proteins was 9.1, with 13.9 for the α and β chains of human haemoglobin, Berg (1971) found 6.8 to 9.0 for the comparison of Lp(a) and HL-A and 6.7 to 8.4 for the DI between Lp(a) and murine H-2 antigen. This led Berg (1972) to raise the question whether Lp(a) lipoprotein is primarily synthesized as a component of cell membranes and whether it functions as a histocompatibility antigen.

This suggestion was severely attacked by Schultz and Shreffler (1972) on the grounds that there is no cross-reaction between anti-Lp(a) and anti-HL-A sera and there is frequent recombination between the two loci. Clearly the study on Lp incompatibility in skin grafts must be repeated. Structural homology of the same order as between myoglobin and haemoglobin or between the unlinked loci for α and β haemoglobin can only be established by amino acid sequencing. From immunological evidence Langdon (1974) has proposed that serum apopro-

TABLE IV
GENE FREQUENCY FOR DRY CERUMEN
(after Matsunaga, 1959)

Population	N	Gene frequency
Northern Chinese	216	0.9789
Koreans	381	0.9622
Mongols	1099	0.9375
Japanese	23 417	0.9150
Southern Chinese	708	0.8603
Micronesians	458	0.6092
Formosan aborigines	1420	0.5347
Ainus	30	0.3651
Germans	514	0.1764
American Negroes	63	0.0694

teins are the major lipophilic proteins of plasma membranes.

Cerumen polymorphism (W)

Beginning with Miyake (1932), Japanese workers showed that ear wax exists in two forms: grey, brittle, and dry, vs. brown, sticky, and wet, with intermediate or ambiguous types occurring with a frequency of only about 0.5% among Japanese (reviewed in Matsunaga, 1962). The two types may be distinguished soon after birth and are stable throughout life. From data on several hundred Japanese families they were found to be governed by a pair of alleles W,w, where the recessive *ww* determines dry cerumen. Among 634 children from dry $\times$ dry matings, there was none with wet cerumen. The frequency of dry cerumen is higher in northern Mongoloids than in other populations (Table IV).

The cerumen polymorphism appears to control the development of apocrine sweat glands and the nature of their secretory products. Most persons with wet cerumen develop axillary odour at puberty. Nagashima (1934) demonstrated multiple histological differences in the ceruminous glands of Japanese with wet and dry ear wax. On the basis of investigations in Caucasoid and Japanese populations dry cerumen contains 18% lipid and 43% protein, while wet cerumen has about 50% lipid and 20% protein. Since the cholesterol fraction of the lipid material is similar, the absolute amount of cholesterol excreted by persons with wet cerumen is inferred to be greater. Modern methods to characterize lipids and lipoproteins do not seem to have been applied to cerumen.

On the basis of these observations, Matsunaga (1962) suggested that the two cerumen types differ in lipid metabolism and that, 'an association between ear wax types and some internal diseases, such as arteriosclerosis' should be sought. Subsequently such an association between wet cerumen and arteriosclerosis without hypertension was briefly

TABLE V
TESTS FOR ASSOCIATION WITH CERUMEN TYPE

Miyahara <i>et al</i> (1969)	Wet	Dry	Total
Arteriosclerosis without hypertension	93	201	294
Control	1206	4798	6004
Total	1299	4999	6298
$\chi^2 = 22.82$ relative risk wet/dry = 1.84			
Miyahara and Matsunaga (1966)			
Hypertensive arteriosclerosis + heart disease	36	224	260
Control	311	1327	1638
Total	347	1551	1898
$\chi^2 = 3.97$ relative risk wet/dry = 0.69			

reported (Miyahara and Matsunaga, 1966). Since then only another abstract (in Japanese) has appeared (Miyahira *et al*, 1969). The relevant data are given in Table V. In their first and more detailed report the authors did not comment on the barely significant decrease of hypertensive arteriosclerosis and heart disease with wet cerumen. In an unstated number of observations, they found no relation between cerumen type and serum cholesterol.

It is conventional in studies of disease association to regard the first claim with due suspicion. At this point the relevance of cerumen types to lipid metabolism and arteriosclerosis can neither be asserted nor rejected. Since cerumen types can be classified by routine otoscopic examination (Petra-kis, Molokow, and Tepper, 1967), it should be easier to settle this question than to discuss it.

Electrophoretic variants

The Ag polymorphism has not been detected electrophoretically. Some genetic diseases of lipid

metabolism are enzymatic (e.g. LCAT deficiency) or have other metabolic errors besides hypolipae-mia and hypocholesterolaemia (e.g. hypochromic an-aemia, Hooft's disease). With these exceptions, genes for lipid variation determine the regulation or structure of lipoproteins which may be characterized electrophoretically in agarose gel, though originally cholesterol and triglyceride concentrations of whole serum, and subsequently ultracentrifugation, were used. Except for the pre- β_1 trait, the genetic forms appear to be idiomorphic (i.e. with gene frequencies less than 0.01). Berg (1972) cautions that the pre- β_1 band may be apparent on electrophoresis of Lp(a-) sera, since lipoproteins other than the Lp(a) antigen may occur in the region of the Lp(a) lipo-protein, both upon disc electrophoresis and ultra-centrifugation. Despite such problems, it seems reasonable to denote by Lp the major gene controll-ing the Lp(a) antigen, the pre- β_1 band, sinking pre- β , and perhaps the double β -lipoprotein (Seegers *et al*, 1965). The capitalized symbol Lp may be used for the corresponding phenotype, even when the mode of inheritance is in doubt.

Using this convention, the various electrophoretic variants presumed to be sometimes genetic are in-dicated in Table VI. Alpha lipoprotein is divisible on agarose gel electrophoresis into α_1 and α_2 bands, but no variant specific to one of these bands has been reported. Other variants are probably hetero-geneous. It would be hard to exaggerate the un-certainty of some of these entities. Even for the more common variants, where many cases have been studied, no careful genetic analysis has been per-formed. One can only conjecture the reasons for this: (1) variations in technique among investiga-tors and changes in time, so that a moderately large series of families has not been studied with the same

TABLE VI
ELECTROPHORETIC VARIANTS

Lipoprotein	Variant Allele	Name of Variant	Fredrickson Type	Presumed In-heri-tance of Clinical Form	Poly-morphic	Notes
Pre- β_1	Lp	Lp(a), pre- β_1 , sinking pre- β	—	Dom.	+	
Beta (LDL)	Hc	Hypercholesterolaemia	II	Dom.	0	Pre- β sometimes raised (same allele?)
Alpha (HDL)	Ha	(hyper- β -lipoproteinaemia)	—	Dom.	0	One case with reduced, slow pre- β
Chylomicrons (VLDL)	Hk	Hyperchylomicronaemia	I	Rec.	0	Heterozygote has reduced LPL
Floating β (VLDL)	Fb	Floating β -lipoproteinaemia	III	Dom.	0	'Broad beta', overlaps Ht
Pre- β (VLDL)	Ht	Hypertriglyceridaemia	IV	Dom.	0	
Beta	Db	Double β -lipoprotein	—	Dom.	0	Same as Lp(a) ?
Beta	b	A- β -lipoproteinaemia	—	Rec.	0	Absence of LDL
Alpha	a	An- α -lipoproteinaemia	—	Rec.	0	Tangier disease
Chylomicrons + pre- β	Hv	Hyper-VLD-lipoproteinae-mia	V	Rec., dom.	0	Hv, Hk, Ht overlap in heterozygotes
β + pre- β	Chl	Combined hyperlipopro-teinaemia	—	Dom.	0	Pre- β more raised than β

TABLE VII
LOD SCORES FOR LIPID MARKERS

System	Ag		Reference	Lp		Reference	Hc		
	$\theta = 0.1$	$\theta = 0.3$		$\theta = 0.1$	$\theta = 0.3$		$\theta = 0.1$	$\theta = 0.3$	Reference
Ag	X	X					ND	ND	
Lp	-2.16	-0.35	5	X	X		-2.61	-0.52	1
Hc	-3.55	-0.61	7				X	X	
ABO	ND	ND					ND	ND	
ADA	-8.56	-0.52	2	-0.21	-0.02	2	ND	ND	
AcP	0.24	0.17	2	ND	ND		ND	ND	
C'3	-0.79	0.37	2	-0.88	-0.15	2	ND	ND	
Fy	-3.09	-0.29	2	ND	ND		-1.44	0.82	3
Gc	-6.28	-0.89	2	-0.82	-0.13	2	ND	ND	
Gm	-6.08	-0.12	2	0.02	0.01	2	ND	ND	
Hp	-7.08	-0.24	2	-1.59	0.02	2	-10.92	-2.59	3
HL-A	-9.03	-0.47	2	-0.90	0.38	2	ND	ND	
Inv	-31.98	-3.40	2	-1.50	-0.31	8	ND	ND	
Jk	-2.79	0.14	2	-2.46	-0.45	2	ND	ND	
Lu				-3.55	-0.61	6			
Le	-6.90	-1.02	2	0.04	0.01	2	ND	ND	
MN	-0.25	-0.02	2	ND	ND		-4.06	-0.03	3
PGM ₁	-0.69	-0.02	2	ND	ND		ND	ND	
P	-21.29	-1.46	2	-1.95	-0.30	2	-6.69	-0.81	3
PTC	-10.90	-1.21	2	ND	ND		-7.06	-1.41	3
Rh	-10.93	-1.63	2	-0.38	-0.10	2	ND	ND	
	0.02	0.01	2	ND	ND		ND	ND	
	-13.60	0.10	2	-0.00	0.34	2	-10.46	-2.25	3

ND, not done; X, identical.

List of references: 1: Heiberger and Berg, 1974; 2: Edwards, 1974; 3: Ott *et al*, 1974; 4: Jackson *et al*, 1974; 5: Berg, 1967; 6: Gedde-Dahl and Berg, 1965; 7: Rittner, 1966; 8: Dausset *et al*, 1968.

protocol; (2) greater interest of lipid investigators in biochemical aspects; (3) unavailability of a geneticist competent to perform complex segregation analysis of a multivariate quantitative trait, under age and sex adjustment and incomplete ascertainment; and (4) deficiencies in the published techniques for family analysis, which have only recently become adequate for analyses of the required complexity (Elston and Stewart, 1971; Rao, Morton, and Yee, 1974; Morton and MacLean, 1974; MacLean, Morton, and Lew, 1975).

Whatever the reasons for neglect of genetic aspects of lipoprotein variation in the past, it is to be hoped that critical analyses will soon be done which will substantiate or refute the conjectures in Table VI. Until the major genes are delineated, debate about polygenic variation is sterile (Jensen and Blankenhorn, 1972).

Linkage

Once a gene has been identified by segregation analysis, its formal genetics can be elucidated through linkage studies (Morton, 1955). The method of choice is lod scores, the logarithm of the probability ratio for recombination fractions $\theta < 1/2$ (linkage) and $1/2$ (no linkage). Older studies often used sib pair and u-score methods, which are inefficient and unreliable for linkage data in man. We assume here that the markers are factor-union

systems (complete penetrance, dominant expression).

Of the lipoprotein markers, only Ag, Lp, and Hc have been studied for linkage. Table VII gives lod scores (z) for $\theta = 0.1$ and 0.3. A negative value argues against linkage at that value of θ , convincingly if $z < -1$. A lod score greater than 2 is suggestive of linkage, and $z > 3$ is conclusive evidence for linkage.

None of the lipoprotein markers has been securely assigned to a linkage group. However, Jackson *et al* (1974) reported one kindred with large satellites on a G chromosome identified as number 21. There was no recombination between the marker and the Ag system, giving a lod score of 2.1 for $\theta = 0$. As the authors note, this is sufficiently suggestive of linkage to warrant further study. However, there is no evidence of linkage between Ag and SOD-1 (superoxide dismutase dimer), which has been localized in somatic cell hybrids on chromosome 21 (Berg, Beckman, and Beckman, 1975). Either Ag is not on chromosome 21, or it is not close to SOD-1.

Ag is unlikely to be on chromosome 1 (large negative scores with Fy, PGM₁, and Rh), or on chromosome 16 with Hp or chromosome 6 with HL-A. The information about Lp is much less, while only a few systems are informative for Hc. Close linkage of the Ag, Lp, and HL-A systems is excluded, as is close linkage of Lp and Hc. There

are no data for many test loci (including PTC, Ak, Pi, Lu, etc. which are not tabulated).

Table VII indicates limitations both of theory and practice in human linkage studies. In practice the use of $\theta=0.1$ and 0.3 adequately summarizes evidence against linkage; however, if linkage is suspected, a good estimate can be obtained only if the interval from 0 to $1/2$ is mapped (say, at increments of 0.05). In theory, we would like to test for linkage not to particular loci but to their linkage group, given information about the location of one or more loci on it. For example, the information from Fy, Rh, and PGM₁ can be combined to test the hypothesis of linkage on chromosome 1 and if the evidence is significant, to assign the marker to its most likely location.

Some linkage data were not included in Table VII because insufficient information was available to derive lod scores. Matsunaga (1962) gave sib-pair data which argue against close linkage of the cerumen system to ABO, MN, P, and PTC. Mohr and Reinskou (1963) and Mohr and Berg (1963) published on linkage relations of Lp using what they called the Morton-Smith method. Unfortunately this gives a posterior probability which cannot be efficiently combined with any other body of data. I should not wish to be associated with that method, which I have never used nor advocated, and which represents Smith's Bayesian analysis of lod scores (Morton, 1962). Linkage was not suggested.

It would not be surprising if the structural loci for lipoproteins, presently recognized through antigenic markers, were unlinked to the predominantly regulatory loci detected as electrophoretic variants. By analogy with immunoglobulins and haemoglobins, linkage of some of the lipoproteins seems likely. More complex genetic architecture involving lipoprotein and regulator linkages is

possible, and could only be detected through linkage studies.

ABO associations

A bewildering number of diseases appears to be associated with ABO blood groups (Vogel, 1970; Allan, 1971, 1973; Mourant, Kopec, and Domaniewska-Sobczak, 1971; Vogel and Helmbold, 1972). The evidence ranges from stomach cancer (with more than 100 publications indicating a 22% higher risk for individuals of type A than for type O) to a single report of borderline significance on raised diastolic blood pressure in type O (Nance *et al*, 1965). Between these two extremes of uncertainty are several apparent associations between ABO groups and cardiovascular disease, mostly in the direction of a greater risk for types A+B+AB relative to type O. In support of this is a reported excess of type O in selected populations such as athletes and healthy aged (Jorgensen and Schwartz, 1968). The analytical unit in these studies has been the 2×2 contingency table of disease (+ or -) by blood group (e.g. O or non-O). If the numbers in the Table are $\begin{vmatrix} a & b \\ c & d \end{vmatrix}$, the relative risk is ad/bc (Woolf, 1955).

Tests for association between ABO blood groups and cardiovascular disease by this method are given in Table VIII. The highly significant association between rheumatic fever and non-O (also ABH non-secretor) is thought to be a result of repression of growth or virulence of haemolytic streptococci by water-soluble H blood group substance (Clarke, 1961). Though 14 of the 17 studies are concordant in direction the heterogeneity in magnitude is highly significant. The association remains highly

TABLE VIII
ABO ASSOCIATIONS WITH DIABETES AND CARDIOVASCULAR DISEASE (after Vogel and Helmbold, 1972)
A + B + AB vs. O

Disease	No. of Studies	No. of Patients	No. of Controls	Mean ad/bc	χ^2_1	χ^2 for Heterogeneity	F	Studies with ad/bc > 1	Observed Range
Rheumatic fever	17	6 589	179 385	1.234	57.40***	32.85**	27.96***	14	0.87-1.59
Ischaemic heart disease	12	2 763	218 727	1.174	15.03***	29.18**	5.67*	9	0.89-1.70
Diabetes mellitus	20	15 778	612 819	1.072	16.24	42.20**	7.31*	17	0.81-1.39
Arteriosclerosis obliterans (Weiss, 1972)	1	502	2583	1.468	14.86***	—	—	—	—
Venous thromboembolism	5	1 026	287 246	1.604	48.89***	22.54***	8.68*	5	1.26-2.91
Arteriosclerotic psychosis	1	271	49 979	0.771	4.56**	—	—	—	—
Hypertension	6	3 468	199 252	0.964	0.97	16.50**	0.29	2	0.48-1.15
Congenital heart disease	4	2 836	124 654	1.029	0.42	4.87	0.26	3	0.68-1.41

* $0.01 < P < 0.05$.
** $0.001 < P < 0.01$
*** $P < 0.001$.

TABLE IX
ABO BLOOD GROUPS AND SERUM CHOLESTEROL (after Vogel and Helmbold, 1972)

Population	Author	N	Mean cholesterol $\pm$ SE				Significance of A + AB vs. B + O
			A	B	O	AB	
British	Oliver, Cumming, and Geizerova, 1969	6000	212 $\pm$ 0.9	204 $\pm$ 1.7	206 $\pm$ 0.8*	213 $\pm$ 3.4	< 10 ⁻⁵
British	Langman <i>et al</i> , 1969	515♂ 344♀	248.0 258.4	238.0 240.5	238.7 250.7	236.2 252.7	~ 0.05 ~ .06
Indians in Singapore	Banerjee and Saha, 1969	325	173.9	161.9	163.7	158.3	NS
Swedes	Beckman and Olivecrona, 1970	285	3.85 $\pm$ 0.07	3.73 $\pm$ 0.13	3.70 $\pm$ 0.08	3.56 $\pm$ 0.19	Sig. only for esterified cholesterol
Thais	Flatz, 1970	715	2.183	2.156	2.141	2.174	< 10 ⁻³
Greeks	Polychronopoulou, Miras, and Trichopoulos, 1974	83	359.7	285.6	332.4	367.5	Sig.
Greeks	Mayo, Fraser, and Stamatoyannopoulos, 1969	532	2.71 $\pm$ 3.04	-1.75 $\pm$ 8.83	-6.15 $\pm$ 1.82	5.68 $\pm$ 3.66	Sig.

* Corrected according to Oliver *et al*, 1969.

significant when this heterogeneity is taken into account by an F test.

At a lower level of significance, non-O is associated with increased risk to myocardial infarction, venous thromboembolism, and perhaps arteriosclerosis obliterans and angina pectoris, but not arteriosclerotic psychosis, hypertension, or congenital heart disease. There is a suggestion that the A₂ gene behaves more like O than A₁ in these associations (Allan, 1971). A later report on ABO groups and hypertension claimed a barely significant association with type A, using the approximate method of Mantel and Haenszel (1959) instead of the more reliable method of Woolf or its small-sample modification (Morton and Chung, 1959). Preston and Barr (1964) and Kerr *et al* (1966) reported a significant excess of Factor VIII in persons of types A and B relative to group O, which with the evidence for thromboembolism led Weiss (1972) to suggest that ABO type affects risk for thrombosis, but not atherosclerosis and other components of cardiovascular disease.

Equivocal evidence for a relation between ABO type and atherosclerosis is supported by lipid and lipoprotein associations. Several studies show a significantly higher serum cholesterol in persons of type A and AB than in O and B persons (Table IX). Ledvina and Kellen (1962) found the serum concentration of β -lipoprotein to be in the order A₁ > O, AB > A₂, B, and Magis (1957, 1960) reported that ether extraction in the presence of heparin gives a higher concentration of lipids from types A and AB than from B and O. A recent publication finds group A and AB persons considerably more frequent in hyperlipoproteinemia type II than type IV (Table X). If this result is confirmed, it signifies that blood group A is more directly related to lipoprotein type than to serum cholesterol, and as the

TABLE X
ABO BLOOD GROUPS IN HYPERLIPOPROTEINEMIA
(Polychronopoulou *et al*, 1974)

ABO group	Type II	Type IV	Total
A + AB	30	12	42
B + O	18	23	41
Total	48	35	83

$\chi^2 = 6.45$.
Relative risk of II = 3.19.

authors note, 'credence would be added to the classification of hyperlipidemias according to the lipoprotein pattern.'

Associations between G6PD electrophoretic variants (Long, Wilson, and Frenkel, 1967) and the Kidd blood groups (Medalie *et al*, 1973) have been reported in ethnic mixtures. The possibility of confounding with environmental factors is not excluded, and these associations have not been found in other populations.

Discussion

Alpha-lipoprotein, which predominates in the newborn (Wille and Phillips, 1971), is usually thought to have no clinical significance. On the contrary, there is a substantial decrease in α -cholesterol in patients with heart disease, leading Brunner, Manelis, and Altman (1967) to assume, 'that the first step in the development of atherogenic lipid patterns is a redistribution of the serum cholesterol from the alpha- to the beta-lipoproteins.' The variant hyper- α -lipoproteinemia may be more frequent in diabetes (Wille and Aarseth, 1973).

With the possible exception of α -lipoprotein, there is no evidence that any of the lipoprotein.

variants is associated with decreased risk of atherosclerosis. There are even some claims of specific associations. Dahlen *et al* (1972) reported on pre- β_1 -lipoprotein, dominantly inherited, with increased risk for coronary heart disease. Berg *et al* (1973) identified this lipoprotein as Lp(a). In other material it appears to be a risk factor (Berg, Dahlén, and Frick, 1974) independent of hyper- β -lipoproteinemia (Heiberg and Berg, 1974).

Progress in understanding the role of genetic markers in atherosclerosis requires solution of several problems:

(1) It must be determined whether the antigenic polymorphisms are factor-union systems, and how Lp(a) relates to the electrophoretic band and ultracentrifugal class with which homology has been inferred. There appears to be urgent need for workshops of the kind which have elucidated the HL-A system.

(2) Complex segregation analysis (which in addition to a major locus specifically allows for common environment and polygenic variation, incomplete ascertainment, and covariance adjustment) should be applied to pedigree data on quantitative variants, both antigenic and electrophoretic, instead of making an arbitrary dichotomy into 'normal' and 'affected'. If the dichotomy is justified, it will be revealed by segregation analysis of the quantitative trait.

(3) The role of the cerumen polymorphism in lipid metabolism should be determined, and the reported association with arteriosclerosis should be confirmed or refuted. Such study is best done in Mongoloid populations with substantial frequencies of dry cerumen.

(4) Resolution of genetic entities should be sought not only by immunological and biochemical means, but also by linkage analysis.

(5) Serum cholesterol is apparently raised in groups A and AB, which have been reported to be susceptible to hyperlipoproteinemia type II. The relation of ABO groups (including A_1 , A_2 subtypes) and of ABH secretion to serum proteins should be elucidated.

(6) Homeostasis for serum lipoproteins would tend to reduce one component when another is specifically raised. Therefore, an increase in β or pre- β -lipoprotein could lower the concentration of α -lipoprotein, as various authors have observed (Barclay, 1972; Wille and Aarseth, 1973; Rhoads, Gulbrandsen, and Kagan, 1976). The associations between ABO blood groups and cardiovascular diseases could be explained if the A + B + AB types have faster blood coagulation (leading to thromboembolism), but A + AB increases the synthesis or

half-life of β -lipoprotein (leading to atherosclerosis) and to a lesser degree of pre- β -lipoprotein (giving a smaller increase for diabetes). This simple hypothesis (which probably does violence to the physiology of all three diseases) has only one merit: that by predicting an increased concentration of β -lipoprotein, a lesser increase for pre- β -lipoprotein, and a decreased concentration of α -lipoprotein in persons of types A + AB, it is not difficult to test.

(7) If this hypothesis is true, the ABH substances may act either at the cell surface (alcohol-soluble ABH) or in colloidal suspension (water-soluble ABH). In the latter event the lipoprotein concentration would depend also on the Se locus which controls ABH secretion.

(8) Evidence suggesting that atheromas develop because mucopolysaccharides in the arterial wall sequester plasma LDL (Adams and Bayliss, 1973) makes one wonder whether other mucopolysaccharides (such as ABH water-soluble substance of secretors) or glycolipids (such as ABH alcohol-soluble substances) can differentially affect this process. Subtyping of A may be important, because of the intermediacy of A_2 between A_1 and O. Complex interactions could occur if, for example, intimal fibrosis were promoted in group O by the mechanism which leads to increased risk for bleeding ulcers in persons of this type, while formation of atheromas after internal fibrosis was favoured in persons of types A and AB. Such an opposition would tend to give negative or conflicting evidence in arteriosclerosis, compared with myocardial infarction and thromboembolism in which type O is underrepresented.

(9) Rejnek *et al* (1963) reported that α_1 -lipoprotein from pregnant women either inhibits cell growth, or is associated with such an inhibitor. If persons of types A + AB have decreased levels of α -lipoprotein, as predicted, they might on this account be expected to have a high incidence of neoplasms, as observed. The ABO association is especially well shown for cancers of the gastrointestinal tract, where we should note that the ABO and Se loci (besides their effects on antigens and antibodies) interact in expression of intestinal alkaline phosphatase (Beckman, 1964).

(10) The existence of large registries of normal people, typed for ABO and under surveillance for atherosclerosis and other diseases, has not been exploited either in countries with national medical services or in those with large numbers of military conscripts, as the U.S. during the second world war. Control for stratification of the population is essential in such study. An excellent control is provided by dizygous twins discordant for the ABO groups. Adequate, though less elegant, controls

are available for much larger samples, though limitations are imposed by errors of typing or recording and lack of A₁, A₂ subtyping. Only epidemiological investigation provides the evidence which can confirm or refute predictions from biochemical and genetic studies.

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