The epidemiological approach to atherosclerosis

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Summary

ATHEROSCLEROSIS HAS NOT as yet been fully understood through particulate and highly specialised types of investigation. Epidemiology offers means of exploring heart disease and other afflictions on the organismic level, and provides the basis of relating ecological, geographical, social, ethnic and many other factors to the incidence of man's diseases.

Epidemiology seeks to demonstrate relationships and associations of factors rather than expecting to achieve cause-and-effect results on initial investigation, a logical failing of many scientific endeavors.

Correlational statistical analysis provides a useful way of studying relationships among diseases and other variables on the populational sub-level. A matrix of correlation coefficients demonstrated statistically significant relationships between arteriosclerosis and socio-economic variables such as number of telephones. Senility correlated negatively and significantly with arteriosclerosis. A significant negative association between suicide and natality indicates that population density rather than increase in natality per se may be an implicated stress in suicide rates.

A crucial need of epidemiology is definition of uncomplicated yet reliable traits or factors that can be linked with disease incidence. The number of telephones and the amount of deep facial wrinkling may seem an odd couple to form a troika with coronary heart disease but the study of arteriosclerosis and other human afflictions probably has even greater surprises in store for us.

Introduction

"*Act I, Scene II*

Celia: Peradventure this is not fortune's work neither, but nature's, who perceiveth our natural wits too dull to reason of such goddesses, and hath sent this natural for our whetstone: for always the dullness of the fool is the whetstone of the wits. — How now, wit? wither wander you?

Act V, Scene IV

Jaques: Is not this a rare fellow, my lord? he's as good as anything, and yet a fool.

Duke S.: He uses his folly like a stalking-horse, and under the presentation of that he shoots his wit.

As You Like It

In this classical excerpt from Shakespeare, we see two levels of awareness — the one by the play's characters who described their companion as a whetstone and the other directly by the author who named him Touchstone[1]. Clearly the Bard intended the audience to consider his "Clown" simultaneously from both perspectives.

It is interesting to note that a common property of both the touchstone and the whetstone is to remain relatively unchanged after evoking the reaction in other substances and in this sense the function of Shakespeare's Touchstone is similar to that of a catalyst in chemistry.

The early history of medical science is interwoven with the genesis of modern chemistry in the practice of the Medieval alchemists who attempted to turn "baser" metals into gold, prolong life, and perfect a *panacea* or cure-all for the diseases of man, in their search for the philosopher's stone (Reichen 1963). At the same time, the common man sought the key to the mysteries of life by indulging his impatience among the paraphernalia of the clairvoyant including the fortune-telling Tarot, T. S. Eliot's "wicked pack of cards" which has, as was pointed out in *"The Waste Land"* (1932), persisted to this day.

This Faustian urge for either a natural or mystical embodiment of the *elixir vitae* is based on the assumption, as stated in Celia's dialogue, that there is a purpose and not randomness in certain natural associations.

The association of sickle cell anaemia with malaria, of blood groups, dermatoglyphics, voice prints, PTC tasting, color blindness and anthropometric formulae with various abnormal conditions, of such objects as fava beans with favism and G6PD deficiency (Stern 1960, McKusick 1969), and of dietary changes with Familial Mediterranean Fever (FMF) (McKusick and Elliot, in preparation) are all examples of the use of apparently simple, naturally observable things to indicate the presence, experimentally increase the penetrance (as in the glucose tolerance test) and therapeutically affect the prognosis of certain medical afflictions.

Genetic linkage has proved a useful tool of not only the hospital-bound specialist but also of the epidemiologist. Epidemiology has been variously defined but can be briefly considered "—— as the study of health and disease of populations and of groups in relation to their environment and ways of living" (Morris 1957, p.16).

It is too expensive and often impossible in epidemiological application to carry methods of detailed clinical investigation into field situations and in terms of global comparisons, there would never be enough time to complete such investigations. Therefore in atherosclerosis research such variables as serum lipids (especially cholesterol), subcutaneous fat deposits (Damon, Bleibtreu, Elliot and Giles 1962, Keys et al. 1966), deep facial wrinkling (Elliot, in preparation), number of telephones in the population (Jolliffe and Archer 1959), and other apparently simplistic, basic, and in some cases supposedly farfetched topics, form the paraphernalia of the epidemiologist who seldom anticipates cause and effect results but looks for associations, whether they make logical sense or not, between serious medical conditions, such as atherosclerosis, and easily measured traits of supposedly reproducible nature.

Epidemiologists hope that consistent associations that are statistically significant may act as keys to our understanding of basic underlying disease processes that until now are hidden from our view.

The employment of large-scale survey methods of social and other local environmental factors is particularly pertinent to investigation of ischemic heart disease which is apparently subject to alteration by many environmental stresses.

Causal relationships are therefore out and associative relationships are in, as far as the epidemiologist is concerned. Multifactoral approaches combining constitutional, cultural and geographical studies will, predictably, provide us with not just one but several touchstones on which to test the statistical purity of the approaches used in the diagnosis and prognosis of coronary heart disease (CHD).

In the following discussion, it should be remembered that many of the factors concerned are guilty by association only in the investigation of CHD and that although they may be unwilling accomplices

1
According to Webster (1951, p.2677) Touchstone is 1) a mineral "used to test the purity of gold and silver by the streak left on the stone when rubbed by the metal" and 2) "—— any test or criterion by which to try a thing's qualities." 'Whetstone is defined (Webster 1951, p.2911) as: "A stone, natural or artificial, for whetting edge tools." and, 2) "To make sharp, keen or eager, excite, stimulate, as to whet the appetite" (Webster 1960, p.974).

we may, by persistent cross-examination, force them to reveal evidence that will help clinicians to track down the real offenders in the complex case of coronary illness.

Study at the Organismic Level

The epidemiological approach concerns itself with matters arising beyond genetics, such as environment, habitat, ecological niche and social groups. Large functional units are now as eagerly investigated as are molecular matters. Geneticists are as aware of this as anyone else, for, according to Dobzhansky (1963):

> "——— biology, must, however, deal not with one but with several levels of biological integration. Living matter is integrated on the molecular, chromosomal, cellular, individual, populational and biotic-community levels. It is convenient to divide these levels into two classes — the molecular and the organismic.
>
> The reductionistic faith, that if we knew a lot about the lower-most level than all the phenomena of the highest integration levels would somehow explain themselves, is still the religion of some scientists, but it is really contrary to the aim and method of science. The organismic phenomena have to be studied as such, not deduced from the molecular phenomena. Man is an organism, not a molecule, although some diseases which afflict his flesh are molecular diseases."

Populational Sublevel

Populations may be taken as units and valuable information can be gathered from averages derived from such data. Population may be defined as a group of interacting organisms or individuals of the same species in a common spatial arrangement and is unique in that it has important group characteristics shared neither by individuals in the population nor by the biome or community, the community being all the animal and plant populations in a given area (Hanson 1962)[2].

Epidemiology gives the appearance of covering limitless fields of inquiry and of being all things to all people. The basic purpose, however, of epidemiological investigation is to define and describe populations or social, ethnic and geographical groups that show a high incidence of certain diseases and to isolate the variables that effectively separate these disease-prone groups from other groups which are apparently free from the afflictions under study. Multivariate analysis using electronic computers has been particularly useful in such endeavours (Gertler et al. 1959, Damon et al. 1962).

According to Dawber and Kannel (1958):

> "The major endeavor of an epidemiological study is the identification and measurement of the various factors which are acting on the subject and which may be playing a role in the development of disease. For the successful outcome of such a study, it is necessary that there be sufficient variability in the factors studied and that the variability be measurable."

Alternate approaches to measurement of this variability include study of cardiovascular disease according to the dimension of time, as witnessed by the Framingham longitudinal heart study (ibid), or, conversely, to do cross-sectional clinical and vital statistical comparisons from country to country and among sub-regions of these countries.

International comparisons, based mainly on clinical diagnosis and vital statistics, have not only singled out atherosclerosis as first among causes of death in Europe and America but also as having a much lower incidence in some other regions of the world. Several environmental factors, such as diet, drinking water, stress, life style, climate and trace elements, differ geographically and have been shown to have statistically significant correlations with the incidence of heart disease (Yudkin 1957, Masironi 1969).

Caloric intake has been frequently related to cardiovascular complaints (Yudkin, op. cit.), one of the most dramatic relationships cited being the very significant positive correlation of saturated fats as contrasted to the negative correlation of unsaturated fats with the death rate due to arteriosclerotic and degenerative heart disease (Jolliffe and Archer 1959).

A wide variety of variables have been employed. Yudkin (op. cit.), for example, found high correlations between trends in coronary mortality and income, occupation and the number of radio and television licences as well as the abundance of registered motor vehicles. Jolliffe and Archer (op. cit.), in "illustrating the intercorrelations of the supposedly independent variables and their conco-

2
Some investigators are satisfied with the explanation that the population represents "—— the individuals of a given species which exists in a given area at any one time" (Benton and Werner 1966) although other scientists prefer Boulding's (as quoted in Bates 1960, p.106) characterisation of population as: "—— an aggregation of similar items enclosed by a picket fence of definition, with an entrance by way of birth and an exit by way of death."

Table I

Arteriosclerotic Heart Disease and Other Vital Statistics — International Comparisons

Variables (a)

Country		1	2	3	4	5	6	7	8	9	10	11	12
United States	A	704.7	319.7	35.8	21.6	9.6	25.2	18.2	1.2	23.1	30.3	11.0	4.9
Finland	B	621.7	255.6	11.3	18.1	9.2	18.2	13.7	1.2	20.5	36.3	19.2	2.4
Canada	C	588.3	241.5	27.6	24.6	7.8	26.3	18.1	0.8	23.6	30.7	7.6	1.3
Australia	D	577.4	273.0	18.5	21.6	8.7	19.5	14.3	0.7	24.5	24.6	15.7	1.5
New Zealand	E	525.7	255.8	25.6	25.4	8.8	19.6	12.8	0.5	16.5	28.1	9.6	0.6
United Kingdom (b)	F	427.5	333.7	14.0	18.5	12.2	21.7	14.6	1.1	13.5	26.7	11.7	0.7
German Federation	G	313.7	210.5	8.3	18.3	11.7	27.0	19.9	5.9	24.8	33.2	19.3	1.2
Denmark	H	294.8	263.2	20.5	17.6	9.8	19.1	14.8	1.3	17.9	31.1	19.1	0.8
Sweden	I	294.6	298.0	31.5	14.8	10.1	15.4	12.3	1.2	16.7	27.2	18.5	0.8
Austria	J	293.9	230.5	7.7	18.8	12.8	31.3	21.5	4.0	24.4	42.0	21.7	0.9
Switzerland	K	273.0	246.8	25.5	19.1	9.9	20.5	15.6	1.6	22.7	41.7	17.1	0.7
Chile	L	267.3	56.2	2.2	33.7	12.0	—	—	7.5	12.3	63.9	6.9	6.0
Belgium	M	250.1	133.5	10.6	17.1	12.6	27.2	17.6	7.3	18.5	36.1	14.0	0.7
Norway	N	248.8	263.5	17.8	17.3	10.1	16.9	11.9	6.3	11.0	40.0	8.0	0.7
Italy	O	226.8	205.4	5.4	19.0	10.2	40.1	23.3	4.3	22.2	27.3	5.3	1.1
Japan	P	122.5	51.6	3.8	17.3	7.0	23.2	13.8	9.2	15.7	25.5	16.1	1.6
France	Q	109.9	84.7	7.6	18.2	11.7	25.4	16.7	14.2	20.8	46.3	15.5	0.8
Portugal	R	107.7	116.0	3.2	23.4	10.8	73.1	26.4	14.5	11.4	29.5	9.5	1.0
Ceylon (c)	S	103.4	23.1	0.3	—	—	—	—	24.4	2.8	27.1	11.6	3.2
Yugoslavia	T	68.2	116.3	1.0	21.4	8.9	—	—	24.7	—	53.9	—	—
Mean		321.0	198.9	13.9	20.3	10.2	26.5	16.8	6.6	18.0	35.1	13.3	1.6
S. E. Mn. (d)		±54.7	±20.8	±2.4	±0.9	±0.4	±3.2	±1.0	±1.6	±1.3	±2.3	±1.2	±0.3
N		20	20	20	19	19	17	17	20	19	20	19	19

(a) Variables 2,4-12 are based on 1963 data from WHO Reports (1966).

(b) This represents the mean average for the United Kingdom as a whole since WHO made separate listings for England and Wales; Northern Ireland; and Scotland. In this case averages are derived after the separate figures have been adjusted for population size based on the World Almanac (Long 1968).

(c) 1962 only.

(d) S.E. Mn. = Standard Error of the Mean.

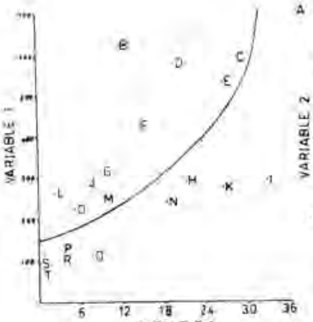

FIGURE 1(a)

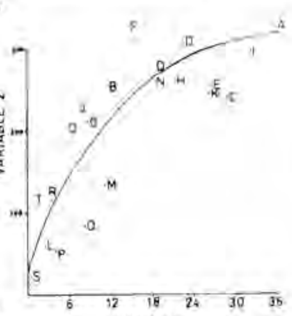

FIGURE 1(b)

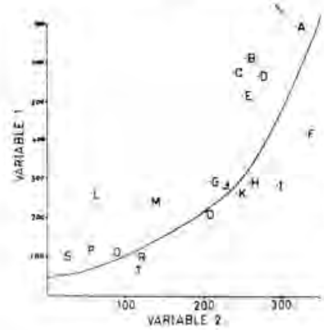

FIGURE 2

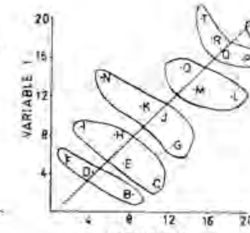

FIGURE 3

mitant indirect actions," cite the dramatic parallelisms between the number of telephones per 100 population and the cardiac death rate. We are reminded of an earlier occasion when polling of telephone owners before an American presidential election incorrectly predicted the outcome because of failure to sample voters who could not afford telephones. In the same way that we find more frequent diagnosis of coronary disease in cities with large medical centers and among the wealthier and better educated, it is also possible that this association between telephones and cardiac death is explained on the basis of medical accessibility. Other factors are undoubtedly involved and may illustrate more basic ethnic and geographical determinants of cardiac disease incidence.

It is doubtless true that we can prove nearly anything we wish to through the use of statistics. Vital statistics of death rates and other populational phenomena among countries have nevertheless provided useful clues to many disease problems and indicate that if we keep our minds open, we can only gain from the process.

Epidemiological reports from the World Health Organisation (1966) provide information on death rates and other vital statistics on a country-to-country basis and these may be compared to the cardiac death rate in the same way as Yudkin (1957) and Jolliffe and Archer (1959) studied dietary factors.

Variables

1. Arteriosclerotic and degenerative heart disease death rate per 100,000 for men aged 55 to 59 years. From Jolliffe and Archer (1959).
2. Arteriosclerotic and degenerative heart disease death rate (total population) per 100,000 (ISC category B-26).
3. Telephones per 100 population. From Jolliffe and Archer (*op. cit.*).
4. Natality per 1,000 population.
5. General mortality per 1,000 population.
6. Infant mortality per 1,000 live born.
7. Neonatal mortality per 1,000 live born.

Death Rates per 100,000 Population

8. Senility without mention of psychosis, ill-defined and unknown causes (ISC category B-45).
9. Motor vehicle accidents (ISC category BE-47).
10. All other accidents (ISC category BE-48).
11. Suicide and self-inflicted injury (ISC category BE-49).
12. Homicide and operations of war (ISC category BE-50).

Table 1 lists international figures for natality, general mortality and death rates due to atherosclerosis and various other causes along with two variables from Jolliffe and Archer's study. These figures are, of course, not completely comparable since they represent nations of differing size, sex and age composition and great variability in gene mixture. Some countries are relatively consistent as to ethnic groups. Others are political unions of very diverse genetic groups.

Scatter diagrams of the various relationships among the variables yielded non-linear regression lines in many instances as shown by Figure 1. In comparing the atherosclerosis death rates for men aged 55 to 59 years (Variable 1) to the general atherosclerosis death rates (Variable 2) a curvilinear relationship is likewise demonstrated (Figure 2). Various procedures may be employed to adjust such data to show more linear regression lines. Jolliffe and Archer (op. cit.) for example, used logarithmic transformations. In this instance, rank-order comparisons of the various countries have reduced the polynomial to greater rectilinearity and demonstrated some interesting clusters among nations on the atherosclerosis scale (Figure 3). Both atherosclerosis variables (1,2) varied likewise from linearity in their relationships with the other variables whose scatter plots are not shown here. Senility, for example, showed a J shaped curve of regression with the atherosclerosis variables (Figure 4). For these reasons, all the variables were transferred to rank orders and their relationships with the two athero-

Table II
Rank Order Intercorrelations of Vital Statistics Variables

1	2	3	4	5	6	7	8	9	10	11	12	Variables
—	.747	.779	.189	-.281	-.368	-.203	-.913	.532	-.194	.216	.123	1
	—	.839	-.081	-.146	-.529	-.461	-.814	.221	-.254	.149	-.293	2
		—	-.039	-.328	-.586	-.409	-.838	.372	-.134	.130	-.316	3
			—	-.177	.348	.409	-.203	.139	.090	-.501	.286	4
				—	.452	.426	.342	-.110	.377	.030	-.290	5
					—	.914	.444	.289	.115	-.235	.157	6
						—	.267	.456	.181	-.113	.292	7
							—	-.446	.354	-.093	.133	8
								—	.145	.404	.114	9
									—	.098	-.144	10
										—	-.032	11
											—	12

Levels of Statistical Significance of r_s

.01	.05
$r_{s1.2}$	$r_{s1.9}$
$r_{s1.3}$	$r_{s2.6}$
$r_{s1.8}$	$r_{s3.6}$
$r_{s2.3}$	$r_{s4.11}$
$r_{s2.8}$	
$r_{s3.8}$	
$r_{s6.7}$	

sclerosis variables were then demonstrated on scatter diagrams as in the examples presented in Figures 5-7.

Pearson — Product Moment Correlation Coefficients (Snedecor 1956) — calculated on the raw data yielded an r of .5944 (significant at $<$ .01 level) between the two atherosclerosis variable (1,2). Variable 1 showed an r of .5254 (significant at $<$ .05 level) with number of telephones (Variable 3) while the correlation of Variable 2 with telephones was .7637 (significant at $<$ .01 level). An increase in linearity led to more consistent covariation as shown in the calculation of rank order correlations for the semi matrix presented in Table 2, according to the procedure in Walker and Lev (1953).

Certain caveats are in order here in addition to questions regarding advisability of rank order correlations which do, however, have statistical justification (Walker and Lev, op. cit.). It is true that in one out of twenty times, we expect a significant r by chance alone. In addition, all countries were given equal weight in the calculations despite population differences in size and age composition.

It is well to keep these objections in mind while interpreting the figures in Table 2 while not overlooking the clues they may give us for plotting further research projects. One of the most interesting relationships was the negative one shown between the atherosclerosis variables and the number of telephones on the one hand and senility (Variable 8) on the other. Sociological influences, including varying techniques of health records, as well as ethnic factors, are probably indicated here and well worth further investigation.

The intercorrelations of Table 2 were examined further in a factor analysis carried out as described in Harman (1967). When the proper matrix calculations were completed, two factors were demonstrated (Table 3).

Factor I may be referred to as a "brevity of longevity" factor whereas Factor II is basically sociological which illustrates the point that many medical factors are basically social ones. General atherosclerosis (Variable 2) formed part of an additional factor, relatively minor for this analysis which, of course, depends on the number as well as type of variables plugged into the system. Another small factor singled out the country of Austria

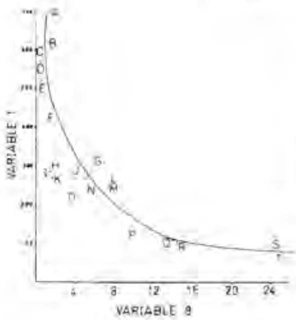

FIGURE 4(a)

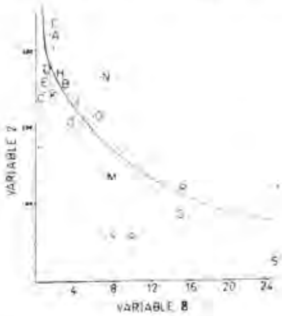

FIGURE 4(b)

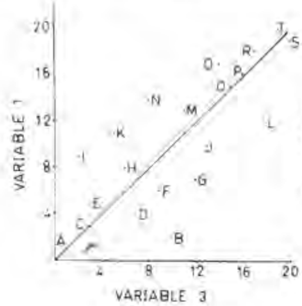

FIGURE 5(a)

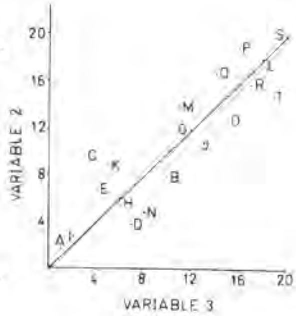

FIGURE 5(b)

Table III

Factor Loadings

(a) Factor I

Neonatal mortality	7	.775
Motor vehicle accidents	9	.768
Infant mortality	6	.555
Arteriosclerosis, men aged 55 to 59 years*	1	.447
All other accidents	10	.293
Natality	4	.279
General mortality	5	.217
Suicide	11	.161
Telephones*	3	.119
Homicide and war	12	.100
General arteriosclerosis	2	.064
Senility	8	-.248

(b) Factor II

Telephones*	3	.339
Motor vehicle accidents	9	.233
Neonatal mortality	7	.171
Infant mortality	6	.152
Other accidents	10	.107
Arteriosclerosis, men aged 55 to 59 years*	1	.105
General mortality	5	.083
Suicide	11	.069
Homicide and war	12	.067
General arteriosclerosis	2	.035
Natality	4	-.033
Senility	8	-.132

*From Jolliffe and Archer (1959). All other variable from WHO Reports (1966).

and appeared to be best decribed as a stress factor which is fraught with possible interpretations as Austria was, interestingly enough, the home of Freud and psychoanalysis.

The two atherosclerosis variables are not, of course, perfectly correlated with each other and may therefore be entered into together in analysis of this type. This factor analysis is presented here mainly for illustrative purposes and the resulting factors should be regarded likewise. There are many effects that can alter the outcome of any type of analysis on data of vital statistics, epidemiological surveys and even clinical investigation. As stated by Ciocco (1957):

"——we have yet to develope analytical procedures for long-term studies that will allow us to make adjustments for possible interactions between the incidence of the disease on the one hand and refusals, migration and morbidity and mortality from other disease conditions on the other; and thus allow us to estimate the true incidence of a disease condition.

The development of such procedures is the task which the statistician faces — until this development is accomplished, comparison of incidence rates from place to place or interpretations of relationships between incidence rate and possible etiological factors will have to be accepted with several grains of salt."

Perhaps in the case of heart disease, we can

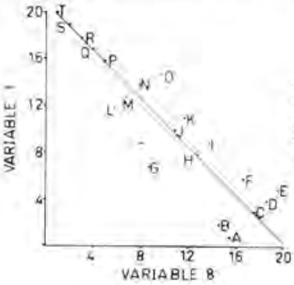

FIGURE 6(a)

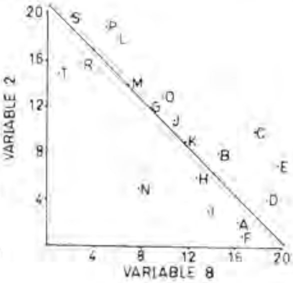

FIGURE 6(b)

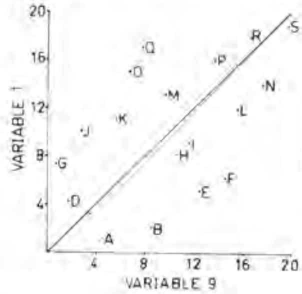

FIGURE 7(a)

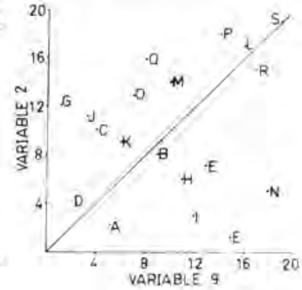

FIGURE 7(a)

literally very well do without the salt while digesting it figuratively. On the other hand, the various authors of epidemiological studies (Yudkin 1957, Jolliffe and Archer 1959, Groom 1961) have likewise noted these qualifications while pointing out the value of their comparisons as clues for further investigation rather than as end products in themselves.

Conclusion

The epidemiological approach to atherosclerosis research offers an excellent opportunity while at the same time presenting challenges in the way of statistical and logical nuances, some of which have been discussed above. Crossfertilisation between the organismic level and the particulate level may hopefully yield not only viable but fertile lines of investigation.

In this consideration of stones, several epidemiological avenues of study have been explored. Concretions come in many sizes and shapes and although analysis of atherosclerosis and certain calculi may invariably reveal cholesterol, another type of stone may serve as catalyst for our thoughts.

Rather than repeating in modern science the same lines of thinking of the alchemists and the readers of Tarot, we may resign ourselves to settling for touchstones and whetstones rather than the philosopher's stone. Our methods of analysis can be sharpened and refined by the whetstone of modern electronic computers whose output can encourage further efforts. This can enable adequate testing of concepts and techniques through use of the touchstone of multivariate statistical analyses of regression and genetic linkage.

The etiology of atherosclerosis and other afflictions indicates the final solution for a disease will rest on not one but several philosopher's stones derived from organismic as well as molecular strata.

Acknowledgement

I wish to thank Mr. Wong who drew the figures.

Final Note

"1941 The alchemists' dream is realised with the artificial production of gold from mercury by Sherr, Bainbridge and Anderson."

(Reichen 1963, p.110)

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