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INTERNATIONAL CARDIOLOGY AND RESEARCH

by Ancel Keys

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Paul White has asked me to talk about international research in cardiology. This does not mean discussing the research of cardiologists in different countries. I know what he means--he wants me to talk about co-operation between different countries in research, about pursuing research regardless of national limits, about using the differences between nations as a research tool. Paul wants me to do this because he, as I do, believes profoundly in both the scientific and the human values of this kind of one-world research, where all the experiments of nature and of man, as they affect our most ubiquitous and persistent of diseases, are available to us for study.

Most of these natural experiments, because they involve differences in the mode of life, are geographically separated and are not conveniently at hand within a single country. But we cannot allow a line on a map to stop us from pursuing knowledge where it is to be found. If we wish to find out how to avoid coronary heart disease, for example, it should be useful to go to populations that have the trick.

With coronary and with hypertensive heart disease it seems idle to seek for single causes, ^{hope to} to trap the one agent in a test tube. With these diseases we have to do with a multivariable complex of causes and influential factors relating to what people do and how they live, all operating to produce

the resultant of more or less heart disease, more or less susceptibility, more or less resistance. Some of these variables can be isolated, qualitatively, in the experimental laboratory, but their quantitative expression must be sought for in human lives. ~~And~~ Some of the variables have no recognizable counterpart in the experimental laboratory, ^{And some important factors} ~~or~~ must remain unsuspected until clues are supplied by observations on the characteristics and disease experience of populations.

Elementary mathematical theory shows that the solution of a multivariable equation is least difficult, and most accurate, when the widest range of values is available for the several variables. But in any one environment and culture we are restricted by ^{homogeneity,} ~~homogeneity~~. Clearly we should seek out, wherever they may be, the extremes of our variables, and their combinations most favorable for analysis, populations where X is as big and again as small as it can be, where a big Y goes with a little X and vice versa, and where Z is a constant or is negligible, so the forces of each can be evaluated and given its place in the etiology of the disease.

In the genesis and development of these diseases we are mainly concerned with the factors of nurture, of the environment in its broadest sense, for only through these can we hope to achieve control and prevention. This is not to deny the boundaries set by the nature of man and the limiting factor of genetic endowment.

But I, for one, am not much impressed with the latter and hold, philosophically and scientifically, that most of us are much alike and that not often are we doomed to hypertensive heart disease or to early coronary occlusion by misfortune of our individual genes. A few families carry an hereditary

taint for these diseases, perhaps, and it is scholarly fun to track down the Jukes and the Kallikaks of the cardiac world. But it seems to me defeatist nonsense to say the Bantu doesn't have coronary heart disease simply because he has Bantu blood or that his brother, under the skin, the Minnesotan or the Bostonian, is hopeless in this regard because of the germ plasm of his father. I prefer to believe the Bantu rarely has a myocardial infarction for the same reason he rarely goes to Harvard; he doesn't live that way.

Besides being philosophically repugnant to me, the scientific evidence seems to be on our side. Paul White can tell you how much trouble we had in finding coronary cases among the general population in Naples but he, and many of you too, can testify that descendants of Neapolitans in this country are not rarely clients for the skill of the cardiologist. Indeed, it is not far to seek coronary cases even in Naples, provided you go with Dr. Mattioli and concentrate on the luxury-living upper crust, the few who have the means and the desire to indulge themselves alla Americano.

And I can tell you that the descendants of the Bantu and the Nigerian Negro, both singularly free of coronary disease at home in their native way of life, are by no means immune in America. Twenty years ago George Burch concluded that the local Negroes in New Orleans were only 70 per cent as likely as the whites to die of coronary occlusion, but even this small difference I doubt when I note that all of his Negro cases had their only diagnosis by the pathologist in the autopsy room but that half of his white cases were clinically or electrocardiographically diagnosed. From which my conclusion is that in New Orleans in 1935 nobody bothered to take an ECG on a Negro and to work up the case clinically. ^{in 1955,} Anyway, now Dr. J. Stamler tells us that the age specific death rate of Negroes from coronary heart disease in Chicago is higher than that of the whites.

I am reminded of an official of the World Health Organization who had a curious experience last year in the Gold Coast, perhaps the most up and coming Negro country today. He asked the local doctors and health officials what were their most pressing current problems. He was told that the major need of the Gold Coast was for political and administrative leadership among their own Negro people. And ^{that} one of their worst medical headaches was the fact that some of their best leaders, adopting personal modes of life as well as political and economic concepts like our own, were falling victim to coronary heart disease.

Negroes, even in Africa, can have coronary if they live right - or wrong - anyway if they live as we do.

(1) The story of the Japanese promises to be a good one. Our friend Noboru Kimura recently checked 10,000 autopsy protocols and personally examined over 1000 hearts in Kyushu. When, as in the first slide, we compare his findings with those of 1200 autopsies on adults in Minnesota, we find that severe coronary atherosclerosis is nearly ten times as frequent in Minnesota as in Japan at the same age. This corresponds with the vital statistics on mortality from ischemic heart disease in the two regions, incidentally, and reminds us that vital statistics may not be as bad as we have thought.

(2) And now Nils Larsen in Honolulu supplies the autopsy data summarized in the next slide. The Orientals here are almost all pure Japanese but like the rest of the ^{Oriental} ~~non-whites~~ in Hawaii, they are progressively becoming Americanized, replacing some of their ^{former} native diet with our own rich foods, but continuing their hard work in the plantations. They have less severe coronary atherosclerosis than the local whites but far more than their relatives in Japan.

All of which is good reason why I hope Dr. White will join ^{me} ~~us~~ to collect first-hand evidence in Hawaii and Japan next Spring.

So far I have merely given some of the reasons why the pursuit of international researches on heart diseases is desirable and why we should not hold back for fear that coronary heart disease is pre-ordained by heredity. Now, to put a little more meat in the argument, I shall mention some recent explorations in this field.

This morning I indicated why I believe the diet, and particularly the dietary fat, is important in the genesis of coronary heart disease. The initial concept came from ~~the literature on~~ animal experiments and the analysis of some surveys on Minnesota men that happened to include dietary data and serum cholesterol measurements. These led to controlled laboratory experiments on man which proved tedious and costly but showed that, by controlling the diet fat, we could readily change the cholesterol and beta lipoprotein concentrations in the blood.

All such experiments had two faults besides their necessary artificiality. We could not relate the diet to coronary heart disease except by remote inference and they were too short to tell us about long-time effects of the diet, even if we were only concerned with the blood cholesterol system. Nor could the answers for man be obtained by experiments on animals. But why not look for human population who would provide our dietary experiments naturally?

③ The next slide shows some possibilities for study. Different populations have very different proportions of fats in their diets. We have the most fat and, among us, the soldiers in the U.S. Army break all records. But in Italy, for example, the average diet is only about half as rich in fats as the U.S. average. And so we went to Italy 4 years ago and have returned several times since.

4 Studies on the spot, indicated in the next slide, showed that the Italians, as a nation, get about 20 per cent of their calories from fats. This figure also holds for the general population of Naples but in Bologna and the Region of Emilia, Emilia la Grasse, the "fat Land," the figure is closer to 30 per cent.

5 The next slide summarizes some of the cholesterol data for men of different ages. The Minnesota data come from over a thousand men. The numbers of Neapolitans are shown below each point. At all ages samples of the general population have much lower serum cholesterol values than the Minnesotans. But a sample of 50 Neapolitan bankers and prominent members of the Rotary Club, where they serve juicy steaks, butter with the bread, and ice cream, are much higher. The serum cholesterol also tends to be relatively high in Bologna, as shown by these 56 policemen and confirmed on other classes of men in Bologna ~~last year.~~ *this Spring.*

6 The significance of these findings for coronary heart disease may be indicated by what Dr. White and the clinical team found last year in Naples and Bologna as compared with the United States. Their findings bear out the data in the next slide. These are from the vital statistics. In 1950 in the U. S. A. there were a total of 108,630 deaths among white men aged 50-59, inclusive. If the death rate of our men in the fifties had been the same as for men of that age in Italy, we should have had 20,855 fewer deaths. If we attempt to explain this 20 per cent difference, we find that it is more than accounted for by the deaths ascribed to "degenerative" heart disease. Dr. White does not like the term degenerative heart disease but I use it here to avoid overly precise

implication--it includes all deaths ascribed to coronary heart disease, myocardial infarction, arteriosclerotic heart disease, chronic myocarditis and myocardial degeneration.

(7) In 1954 we were able to make an exact comparison between men in Naples and men in Malmö¹¹, in Southern Sweden, where about 38 per cent of the calories come from fats in the diet and where coronary heart disease is far more common than in Naples. The next slide gives the cholesterol data on 6 samples of 150 men each: Clerical workers, members of the Fire Departments of the two cities, and men engaged in heavy labor, fabricating steel in Naples and building steel ships in Malmö. In each city the men in heavy manual work tend to have the lowest cholesterol values, especially as they grow older, but the consistent difference between the two cities is ^{much more} striking, ^{There} and is in full agreement with what we know of the diet, on the one hand, and of the incidence of coronary heart disease, on the other.

(8) This Spring, as indicated in the next slide, we carried out a study on the Island of Sardinia where the diet is very much like that of Naples but the people are racially somewhat different, ^{They} and have fierce pride in their 3000 year-old lineage, their curious language and even of their small stature. They are the shortest people in Europe. Compared with the Southern Swedes, and still more so with men in the U. S., the Sardinians have low serum cholesterol values, very similar to those in Naples. And again, Dr. White can tell you what he found in the hospitals and clinics. The picture was very much like that in Naples--not much heart disease and almost all of that either rheumatic or hypertensive.

9

By now some of you may be saying that even though we match age and sex and physical activity, there are other characteristics of populations to consider. What about overweight? Are not we and the Southern Swedes more overweight than the Neapolitans and the Sardinians? The next slide shows the frequency of men overweight by 20 per cent or more, on U.S. standards for height and age, in our samples of men in four areas. These are sedentary men, clerks and desk workers. Bologna is an easy winner for obesity.

10

And the next slide compares members of the Police and Fire Departments in five cities. The defenders of civic safety are all apt to be pretty solid citizens but Minneapolis and St. Paul, the Twin Cities, must yield, again, to Bologna. And Malmö, Cagliari and Naples are much alike.

So not much can be blamed on overweight from these data.

Now it would be interesting to ^{Talk about work in} ~~go to~~ England and ~~to~~ Spain, and to note the differences between rich and poor men in Madrid, but I am reminded ^{in December,} that now it is early summer in South Africa ^{where the weather is fine} so let us go to Cape Town and have a glimpse at the Bantu, the Cape Coloured, and their lords and masters, the local Europeans, as they are called.

11

The next slide summarizes serum cholesterol values for 4 age groups, comprising 548 men studied side by side. There is no shortage of food here, all of the men have enough to eat, but the diets of the 3 groups are very different in character. The general average is about 16 per cent of calories from fats for the Bantu, 25 per cent for the Cape Coloured, and 35 to over 40 per cent for the Europeans, the lower figure being for the lower economic class of European.

And I should explain that the Cape Coloured people are not a mixture of Bantu and European; they contain little if any Bantu blood and are legally and socially entirely distinct. The Cape Coloured people are a racial mixture, stabilized for over a century, of Malay, East Indian, Hottentot and some White blood. Note the tremendous difference, 74mg.%, between the middle-aged Bantu and his European counterpart.

(12) As the next slide shows, these racial groups differ in the proportion of the cholesterol which is in the beta lipoprotein fraction of the blood serum. Note how the beta percentage tends to rise with age in the European and in the Coloured men but falls in the Bantu. The result of this, of course, is that the beta lipoprotein cholesterol differentiates more sharply between the groups than does the total cholesterol, though there is a high correlation between these variables.

(13) Again the question of obesity arises and the next slide shows the distribution of relative body weight in the three groups. The Europeans tend to be overweight somewhat more frequently than do the other groups and the Bantu are a trifle heavier, for their height and age, than the Coloured men. But overweight is found in all 3 groups.

(14) The next slide compares the cholesterol values for these men when they are separated according to relative fatness or true obesity by means of measurements of the thickness of the subcutaneous fat. Observe that the fat and the thin Europeans have the same high cholesterol values but that as the Bantu gets fatter his serum cholesterol rises steeply. But the serum cholesterol concentration in the fat Bantu averages some 50 mg.% lower than ⁱⁿ the thin European.

in Cape Town

(15) We noticed that the fat Bantu were almost all in the upper income bracket of their class, [^] ~~and~~ the next slide shows the relationship between money income and serum cholesterol in these men, each group being divided into 3 income classes. So now we have the secret, perhaps, of the basic difference between the Bantu, the Cape Coloured and the European. It is not color or race but simply a matter of money!

The curve resembles an hyperbole, rising sharply at first and then flattening out. And by the time one gets ^{to} /around one hundred dollars a week, which in South Africa would be something like the equivalent of \$10,000 a year, there may be little further change, ^{hereafter,} Having gone that far you may as well try for a million!

(16) But I suppose the only thing wrong with money is what is done with it. And what you do with it, if you are at the bottom of the income ladder, seems to be to buy animal fat to eat. At least that is the way it works in South Africa. The next slide shows the serum cholesterol and the animal fat consumption values for the 9 income classes in the age range 40-49 years. Two points are somewhat out of line. The top income European does not consume any more animal fat than the middle income European but his serum cholesterol is higher. And the lowest income Bantu eats more animal fat than the middle income Bantu though his serum cholesterol value, at this age, is about the same.

These fat intakes are in absolute units--if we divide the abscissa values by 2 the result is, approximately, grams of fat per day. But if, as we think, the proportion of fat calories ^{in metabolism} is more important, then these discrepancies may vanish. Unfortunately we could not get reliable values for total calories for all these men but we note:

and hence have low caloric needs
First, the top income Europeans are all sedentary and this is not true of any of the other 8 groups. *Therefore* Hence his intake of animal fat represents a higher proportion of the total calories than in the other groups.

And, second, the lowest income Bantu are all heavy manual laborers; in fact it is this class of Bantu that does all of the heavy manual labor in Cape Town. And these men certainly burn up many more calories a day than the others so their *absolute* fat intake is a lower proportion of the total calories than if they were moderate to sedentary workers as are the other Bantu and the Cape Coloured men.

I cannot provide any precise figures on the relative frequency of coronary heart disease among the South African populations represented by these samples. The autopsy data at Kampala, in Uganda, and at Johannesburg on Bantu and other Negroes on similar low-fat diets indicate a frequency of severe atherosclerosis or myocardial infarction in middle age of something from one-tenth to one-~~twentieth~~ *fiftieth* of the local Europeans on our type of rich diet. Clinical records and hospital data in Cape Town, Pretoria and Durban indicate even *greater rarity* ~~fewer cases~~ of coronary heart disease among the Bantu. The data of the Groot ^{er} Shuur Hospital at Cape Town, partly given in the November 26 issue of LANCET, indicate that the Cape Coloured are some 15 times more likely to have an infarct than the local Bantu but the ratio of infarcts among the Coloured as compared with the Europeans is only 1 to 4. In other words, coronaries seem to be something like 60 times as frequent among the Europeans as among the Bantu in Cape Town.

(17) Before I leave the Bantu, I must mention a point that struck me forcibly. And as I speak you may look at the next slide, which gives data on thrombo-embolic complications after surgery in Norway. Every where ^{in Africa} I went I talked with surgeons as well as internists. And they all agreed that the natives, living on the native low-fat diet, almost never have thrombo-embolic complications after surgery, childbirth or trauma. ^{These are able British or Europeans} They do a lot of surgery ^{they tell me they} and incidentally, have a fair number of peptic ulcers to remove, ^{from Bantu} contrary to some rumors that these people are immune.

And so to the data in the ~~next~~ slide. This gives the number of thrombo-embolic complications per 1000 equivalent surgical operations in the Oslo hospitals, mostly involving the same surgeons, from 1941 to 1948. During 1941, as you remember, Norway was occupied and ^{in the second half of the year} the diet was restricted, mostly by the stoppage of imports of fats, oils and sugar. The calories decreased somewhat but the fats fell to half the pre-war value and stayed there until mid 1944. By that time foods were more abundant because of less severe German requisitioning and because of better productive and distribution in Norway. Then came freedom and real relief and see what happened. Instead of one case in a hundred with thrombo-embolic complications, as was true in 1943-1945, the figure was more than doubled by 1947. *Back to the good old days!*

Does this mean anything? In other parts of the world, notably Java, it has been reported repeatedly that populations on low-fat diets rarely suffer thrombo-embolic complications though the rich people of these populations, who affected the European manner of life and diet, were not so immune.

18
Now I should like to continue the discussion of international comparisons and to talk about Yemenite Jews and Guatemala Indians and Post-War Germany and regional differences in Yugoslavia. But there are some general propositions that call for international research. The next slide shows what seem to be ~~the~~ general tendencies throughout the world, though perhaps they are not so striking ^{now} in present-day America. *as in most of the rest of the world.*

There is a widespread belief among doctors and public health officials, ~~fully~~ supported by statistics in many countries, that coronary heart disease is more common among rich people than among the poor, ^{usually} more frequent in cities than in rural areas, and that sedentary men are more susceptible than men whose occupations make them more active physically. *(Repeat these points)*

19
The next slide summarizes a report by the representatives of the Food and Agriculture Organization at the World Health Organization meeting in Geneva last month. The F. A. O. study found that there is a general tendency within each of many countries for rich people to eat diets higher in fat than the diets of the poor, ~~for~~ urban dwellers to eat more fat than rural folk, and ~~for~~ sedentary men to get ~~more~~ a larger proportion of their calories from fats than do men who do manual work. Even in the United States there is evidence that men who do heavy work meet their increased calorie demand by eating extra foods that are primarily carbohydrate.

You see I have a hard time getting away from dietary fats. But my purpose in talking here tonight is not merely to add to the thesis that fat is the villain in coronary disease. I wanted to illustrate some of the facts that emerge when we chase problems around the world.

Let us leave fat and turn to Cuyler Hammond's thesis that the cigarette is the cause of our downfall. This idea has much plausibility when we examine ~~it~~ *that is, within a single cultural pattern* it within the confines of the U. S. or Great Britain. But, first, we note that the coronary mortality Hammond found among the non-smokers in the U. S. is considerably less than among the smokers but ^{that} it is still very high compared with

most other countries. That is a little troublesome but then, at least it must be true that we smoke a lot more than anyone else. Or do we?

20 The next slide shows data on smoking in the U. S. and in Italy. Among men aged 50 - 59, which covers most of the men in the Cancer Society Survey, a little more than half of the men in the U. S. are smokers. In our Minnesota long-range study on middle-aged business men the figure is 52 per cent. In Italy our own surveys yield an average of 61 per cent smokers. On the average, these Italians do not smoke so many cigarettes as do American smokers but they smoke them far more completely so the average Italian, who smokes a dozen cigarettes a day, down to the last tarry quarter of an inch, probably gets more nicotine and tars into his system than does the American who smokes a pack and a quarter. In any case, about two thirds of the smokers in both countries are heavy smokers.

21 The next slide shows smoking habits in Cape Town as we found them to be. In all classes/^{heavy}smoking is more common than here. Tobacco and cigarettes are cheap and the standard package is one of 50 cigarettes instead of 20 as here. The Bantu are more apt to be pipe smokers, because it costs less, but the Coloured man almost always smokes cigarettes, partly because he does not want to do what the Bantu does. It is interesting that there are fewer heavy smokers among the ~~old~~ older Coloured men than among their younger counterparts. Perhaps Dr. Hammond would suggest that this reflects the high early mortality of the heavy smokers.

(LIGHTS)

Rudyard Kipling, who used to be popular among the freshmen of my day, wrote a poem about a soldier who, shall we say, "studied" women in many far-flung places. As the soldier recollected each ^{girl} he could say, "An' I learned about women from Mer." Our own studies have been concerned almost exclusively with men - you see my wife often goes with me^l - but we have learned something, I think, in Madrid and Cagliari and Naples and Cape Town and the ^{other places.} rest. And

everywhere, from Mexico to Finland, from Chile to Uganda, doctors and officials and just plain people are friendly and willing to work with us as soon as they learn what it is about. They will stop ~~their~~ work, try to understand our bad attempts at their native language, show us their hospitals, give us their blood, not because they have been swindled into believing we are helping them personally, but because they believe that medical research is good and ~~should~~ ^{have} know no boundaries. Sometimes we teach them new technical tricks but I think we always learn more from them than they do from us.

I think this is another reason why Paul White wanted me to talk about international research in cardiology. Long before I did, he discovered that beyond our domestic horizon we can learn many things undreamt of when we only stay comfortably close to the familiar local scene. He found, too, that this can be great fun as well as extremely hard work. And that ~~working~~ an international team working together for a good that no peculiar ideology can deny is the finest kind of internationalism, the stuff that makes real understanding and fraternity between peoples.

So far we are just scratching the surface in these explorations. We need actuaries and biochemists and cardiologists, pathologists and physiologists, psychologists and technicians. ~~We need for~~ ^{research} This kind of work requires teams and teamwork. And so we need more organization, ~~perhaps a tenth as much~~ money, ~~as now goes into more customary~~ research, and, not least, more energy and intelligence. There is ^{much} plenty to do and I ^{think we can} ~~am willing to~~ guarantee the outcome.

~~will abundantly~~ ^{will abundantly} prove the ~~base~~ ^{theses} that

THANK YOU!

Basically, people are very much the same everywhere but their differing ways of life result in different patterns of burdens of disease. And by studying these contrasts and parallels we can capture the ~~best~~ results of the experiments of nature in all possible variety and reality.

Paul White