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## ANNUAL DISCOURSE

### GENES, THE HEART AND DESTINY\*

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BOSTON

Our remedies oft in ourselves do lie,  
Which we ascribe to Heaven.

SO said Helena in a soliloquy in the first scene of the first act of William Shakespeare's *All's Well That Ends Well*.

This is my text, much easier for us to subscribe to in this day and age than it was several centuries ago when with highly justified fatalism the same Shakespeare put into Hamlet's mouth the oft quoted lines:

There's a divinity that shapes our ends,  
Rough-hew them how we will.

In the paganism of ancient days the "fates" held sway, as in the case of the three sisters Klotho, Lachesis and Atropos of Greek mythology. The Delphic oracle simply transmitted the prophecy of things to come. Even the dawn of the great religions of the world altered the situation but little. To be sure, a single just God of all creation, sometimes compassionate and loving but often stern and avenging, replaced Zeus and the myriads of lesser gods that had ruled the skies for many centuries, but the One God was supreme and controlled the destinies of man. The leaders of the church often tried to combat the fatalism of the day. Even as recently as two hundred and fifty years ago, in the late winter of 1705 to 1706, in Rome sudden deaths were attributed to the supernatural, in brief to God's displeasure with the Romans. It took the combined efforts of Pope Clement XI and Lancisi, his learned physician, to prove to the world by autopsy that the sudden deaths were the result of natural causes.

In this introduction I should like to give one more apt quotation. It is from Bayard Taylor's *Napoleon at Gotha* and it reads: "Men's lives are chains of chances." Here we are not told the fate of the chances, but surely their fate must vary greatly — some are inevitable under the given circumstances,

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whereas others are open to our choice. We may or may not accept them. The course of our lives depends on the combination of these chances, both inevitable and elective. The more enlightened and vigorous a stand we take when we can control our chances, the happier, healthier and more useful our lives will be.

### EPIDEMIOLOGY

Let me turn now to a discussion of our problem of the day itself, the problem of the person who is sick, in this case the man, woman or child with heart disease. What I shall say will apply quite generally throughout the entire field of medicine, to other diseases of all kinds, the infections, cancer, arthritis and the psychoses. It has long been known that we must take into account not only the agent, whether it is an infectious organism, a poison, a dietary fault, a physical strain or some other external factor, but also the person or host himself. Yet we have paid in large part only lip service to this internal factor of heredity. We have hardly tried as yet to select from the mass of mankind the individuals who are to a greater or lesser degree candidates for any particular disease, to direct, as of course we should, our special programs of preventive medicine at them, thus avoiding a great waste of time, of money and of energy. Here and there with this goal in view some slight progress has been achieved, but very little has been accomplished as yet in the two cardiovascular diseases that have risen to a seriously epidemic level in our midst — namely, hypertensive disease and high degrees of coronary atherosclerosis and thrombosis. Another fairly common type of heart disease that has deservedly attracted increasing attention of late and should also concern us now is that of congenital defects. The heart diseases due or related to infections are in a much more promising state of increased control, but even they, in particular rheumatic heart disease, have been inadequately studied and subjected to preventive measures directed at the host.

After a brief review of heredity itself I shall discuss its possible relation to the more important kinds of heart disease and our needs of future research. I can state at the outset that one of our weakest resources in basic disciplines in present-day medicine is that of genetics. We badly need geneticists.

### HEREDITY AND THE HOST

The nineteenth century was a period of intense interest in human inheritance from the time of Lamarck in 1809 ("Structure follows function") through Darwin (from the *Voyage of the Beagle* in 1837 to the *Origin of Species* in 1859), Mendel in 1866, Hering in 1870, Galton from 1871 to 1889 and Weisman ("immortality of the germ plasm" in chromosomes) in 1893. Galton, a cousin of Darwin, proposed a law of ancestral inheritance, each parent contributing 1/4, each grandparent 1/16, and each great-grandparent 1/128 (later confirmed by Pearson); Galton introduced the term "eugenics." DeVries, Morgan and Jennings supported Darwin's concept of a slow mutation, not the immediate control of man by environmental forces, such as, with Lysenko's help, fitted the Soviet ideology at the height of its authority when freer minds like that of Orbeli still recognized the great elemental force of inheritance. It would, of course, be convenient not only for the dictatorial regime of a Stalin but also for many other doctrines if environment were heavily preponderant and heredity weighed little or not at all in the scales of health and disease. This, however, is not true. Just how much heredity actually counts in any given case remains for future researches to discover, but that it plays a most significant role is a certainty.

Although this is a truism recognized by every practicing physician it is astonishing how little attention is paid to it when we obtain and record the history of the individual patient. Often, though by no means always, we are in the habit of noting the age at and the cause of death, or the current state of health of parents and siblings, but rarely is this information noted for the grandparents or other relatives, despite its importance. To be sure, such information is at times unobtainable, but even when it is obtainable it is not often recorded. Here, I would enter a plea to the public at large. In the first place a family genealogic record or tree would be very helpful for the doctor; it has much more than sentimental value, for it helps to determine the health hazards for descendants for generations to come. We physicians should spread the importance of this far and wide. A second valuable aid concerning the future health of any family is the information to be derived from post-mortem examinations; the natural emotional reaction of the family at the time of death should not obscure the importance of these examinations after death. Even as far back as 1706, two hundred and fifty years ago, the Church, in the

person of Pope Clement XI, urged the carrying out of autopsies to obtain invaluable information, and churchmen and scientists alike still strongly recommend to the public that such examinations be done.

For the sake of argument let us suppose that on the average heredity and environment are equally responsible for both the maintenance of health, the induction of disease and the length of life in mankind as a whole but with very variable influences in any given person. With this as a basis for our discussion let us now take up individually the different kinds of heart disease.

### CONGENITAL DEFECTS

Although congenital defects of the heart and blood vessels do not comprise a very large percentage of all cases of cardiovascular disease, the interest and challenge that they pose actually exceed those presented by the other types or causes. The reasons for this are twofold. In the first place by so-called congenital heart disease we really mean a combination of truly inherited defects and of those acquired in utero. There are no satisfactory terms to indicate this in common use today, but they should be introduced as soon as we are able to distinguish between the two. Both groups together might better be called antenatal rather than congenital; those really inherited in the genes of the germ plasm might be eventually labeled "hereditary" or "inherited" or "intrinsic congenital." By strict definition "congenital" should be the term to apply. The defects acquired during fetal life might be called "acquired in utero, or fetal," or "extrinsic congenital" or even "connate" as suggested by the dictionary. At present, however, we know next to nothing about the etiologic factors actually behind either group or how to distinguish between them, and, indeed, there may be a mixture of the two, even when German measles in the first three months of pregnancy is responsible. In such a case it is conceivable that an inherited resistance to German measles or its lack may be just as responsible for its occurrence as exposure to the infection itself. In laboratory animals various other causative factors, such as vitamin deficiencies, anoxia and exposure to excessive radioactivity, are being tested and studied, but there is a great deal still to be learned.

Among reported cases of congenital cardiovascular defects in which there appear to have been hereditary faults in the genes themselves a few examples may be cited.\* Walker and Ellis noted the presence at autopsy of a high ventricular septal defect identically the same in a mother and a six-month-old fetus, and a patent ductus arteriosus in a man and in 4 of his 8 children.

\*Incidentally in his notable book, *The Aneurysmatibus*, published in 1728, Lancisi referred to a family afflicted by heart disease (quite probably of congenital type) in four generations: great-grandfather, grandfather, father and son.

These authors reported the record in the literature at that time, in 1940, of 48 other families with multiple cases of congenital cardiovascular defects, 15 of which were in more than one generation.

In 1940 and 1947 Murphy, in his book on congenital malformations, reported as follows:

... that 47 of each 10,000 births were children with obvious congenital defects, that 25 per cent of these were stillbirths, and that, as far as his records went, 77 per cent of the children had a defect of one part of the body only. . . . Malformed children were born premature four times as often as others and more often of older than of younger mothers, and children born later in the family were more often defective. When a second defective child was born in the same family it was more likely to be later rather than just after the first one, as might be expected with an environmental cause.

In 1946 Kjaergaard reported a patent ductus arteriosus in 3 sisters, and in 1947 Taussig wrote that she had "seen four families in whose members there were multiple instances of congenital malformations of the heart, in two of these families in more than one generation. The most striking instance was that of a father, two of his three children and one of his two grandchildren, who all showed unmistakable evidence of a patent ductus arteriosus." Some anomaly in the tissue of the wall of the ductus or aorta may have existed to prevent the normal closing of the ductus very soon after birth.

In 1949 Dr. Campbell, of Guy's Hospital, London, studied the case notes of 340 children (185 boys and 155 girls) with congenital heart disease for evidence of genetic or environmental factors in its causation. In 4 cases in the series the congenital heart disease, generally Fallot's tetralogy, was probably related to rubella in the mother during the first three months of pregnancy, but there was no clear evidence of the importance of other environmental factors in the series and Campbell concluded that the causes of congenital heart disease are mainly genetic. However, this is still only a supposition since adequate studies have not been made of very large series of cases.

Nadas, in his recent book on pediatric cardiology (1957), wrote that in his series of approximately 2500 patients there were 15 families in which 2 siblings had congenital heart disease. The same lesions were likely to be repeated in siblings of the same sex, and he had seen patent ductus arteriosus, pulmonary stenosis and tetralogy of Fallot each in 2 siblings, and also patent ductus arteriosus in a mother and daughter, both successfully operated upon. Mongolism was commonly associated with a persistent atrioventricular canal or ostium primum. Coarctation of the aorta was found in conjunction with arachnodactyly and Turner's syndrome. Transposition of the abdominal viscera, with or without dextrocardia, was commonly accompanied by septal defects and transposition of the great vessels.

Dr. Ongley, of the Children's Medical Center in Boston, has very recently told me of two more families each with several members showing congenital cardiovascular defects. One consisted of 3 siblings — a girl of four with patency of the ductus arteriosus cured by operation, a girl of three with patency of the ductus arteriosus, aortic coarctation and the Wolff-Parkinson-White syndrome, to be operated upon later, and a boy who died at eleven days of age, with autopsy findings of patent ductus arteriosus, aortic coarctation and Ebstein's anomaly. In the other family the mother had pulmonic stenosis proved by cardiac catheterization, 2 children had proved pulmonic stenosis, and 2 other children had probable pulmonic stenosis.

I myself have encountered several families in which several members showed a defect in the aorta incident to congenital arachnodactyly.

### RHEUMATIC HEART DISEASE

From the early days of the recognition of rheumatic fever and of rheumatic valvular heart disease it was observed that these conditions tend to run in families. A generation ago several studies were carried out in an effort to obtain some statistical information about the frequency of familial involvement. We ourselves found "that from 32 to 50 per cent at least of patients with rheumatic fever, chorea, or rheumatic heart disease have near relatives with a history of similar trouble" (far more than in any control series). Three factors were considered "responsible for such family incidence: (1) inherited susceptibility to the rheumatic infection, (2) close contact, with the actual spread of the exciting organism from one throat to another, and (3) crowded or unsanitary living conditions, sometimes with inadequate food and clothing."

In 1940 May Wilson, from a study of families with rheumatic fever in New York City, concluded that the disease is inherited according to the mendelian-recessive pattern. She stated unequivocally that if both parents are rheumatic, nearly every child is susceptible to rheumatic fever; if one parent is rheumatic and the other is a carrier (that is, rheumatic fever is present in near relatives) each child has a 50 per cent chance of getting rheumatic fever. After these earlier observations it has been generally agreed that the hemolytic streptococcus is the factor that in certain susceptible persons sets off a chain reaction leading to rheumatic fever in the course of a fortnight, more or less. It has been estimated that a few, up to about 5 per cent, of the inhabitants of almost any given community react in this way, the great majority of persons being more or less immune. This sensitivity is what runs in families. Doubtless, there are many persons considered normal who react in such slight degree, which might be called subclinical, that a clinical diagnosis of rheumatic fever or rheumatic heart disease is never made. In fact Dr. Timothy Leary, skilled pathologist that he was, thought that a touch of

chronic rheumatic heart disease was the most common lesion to be found at autopsy — even more common than minimal scars of healed tuberculosis. If that is true it is a matter of the degree of susceptibility that is inherited.

It is always wise to investigate by history and examination relatives of persons who have or are suspected of having rheumatic heart disease, for it is to such families and not to everyone that one should more particularly apply preventive measures. Here, heredity and environment — that is, host and agent — probably share on the average about equally, but it may well be true that in extreme cases there may be a very high degree of inherited susceptibility with exposure to but little streptococcal infection on the one hand or heavy infection with relatively slight susceptibility on the other. Families with several members involved obviously need more protection than the community at large against the hemolytic streptococcus.

Although there are quite a few other kinds of heart disease to which these principles apply, I shall discuss in some detail only two more, the most important and frequent of all, the hypertensive and the coronary. Before I do so, however, two conditions that are frequently inherited are worthy of special though brief mention: these are a tendency to cardiac irritability, as manifested by arrhythmias, and neurocirculatory asthenia. I have known of many families in which premature beats or extrasystoles, paroxysmal tachycardia and even atrial fibrillation or flutter seemed to be inheritable, and the inheritance of neurocirculatory asthenia is common. I recall a family in which the father was discharged from the United States Army in World War I because of disability due to severe neurocirculatory asthenia and the son was similarly discharged in World War II.

#### HYPERTENSION AND HYPERTENSIVE HEART DISEASE

Hypertension is a most interesting problem for several reasons. In the first place the range of normal is very considerable, and, as Master and Pickering have noted, some families and older persons can have pressures, in particular systolic levels, somewhat above those generally considered normal, with no harm done. A moderate increase in systolic pressure alone with advancing age is a result of loss of elasticity and of sclerosis of the aorta and other great arteries and in the absence of complications can be well borne for many years — this may be a family characteristic. Another common inheritance is that of so-called hyperreactivity with very labile blood pressure whether at normal or at elevated levels. Thirdly, serious hypertension, including the malignant degree, does run in some families, the younger members of which should be investigated, followed carefully and protected, so far as we know how to do so now, before their blood pressures reach high levels. A fourth con-

sideration is that in some families current treatment and protective measures are less effective than in others and, therefore, deserve to be subjected to more investigative study, which may need to include more than dietary regimens, weight control, reduction of stress and a trial of drugs. Finally, some families inherit heart muscle and vascular tissue that can more stoutly resist than can other families the hypertension that they also inherit.

Thomas and Cohen, in studying medical students and their ancestral histories, made several interesting observations. Sons often inherited hypertension from their fathers, and daughters from their mothers; when both parents were affected there was more hypertension in both sons and daughters. High blood pressure was three times more frequent in the siblings of hypertensive persons than in those of persons with normal blood pressure. These authors believed that multiple genetic as well as multiple environmental factors are responsible but that the relative responsibility of genetic and environmental factors in any given case or as an average in toto remains for the future to determine.

#### CORONARY-ARTERY DISEASE

Now let us turn to the most serious problem of all — namely that of coronary atherosclerosis of a degree great enough to cause trouble. Here, we practitioners know from experience the importance of heredity. Thomas and Cohen found in their study, already referred to, that coronary-artery disease was four times more frequent among the children of affected parents than among the children of parents not so affected. A few years ago in a study of our own of coronary-artery disease among 100 young adults (under the age of forty years) compared with 146 controls, it was found that 37 per cent of the fathers in the coronary group died from coronary-artery disease as compared with 18.5 per cent in the control group (of 62 dead fathers of the coronary group, 23 had succumbed to coronary-artery disease in contrast to only 14 out of 76 among the controls); only 4 mothers of the 41 of the coronary group who had died succumbed to coronary-artery disease, and only 3 out of 39 among the controls. Five out of 58 dead siblings of the coronary group died of coronary-artery disease (8.6 per cent) in contrast to but 1 (1.0 per cent) among 98 siblings in the control group. We included only 1 case of recognized familial xanthomatosis or hypercholesterolemia in this series. Only 18 of the patients with coronary-artery disease had serum cholesterol levels of more than 330 mg. per 100 ml. (1, however, was as high as 509 mg.) as compared with 5 of the matched controls. It is, of course, well known that in familial hypercholesterolemia and xanthomatosis coronary-artery disease is common.

In every study of coronary-artery disease in youth and middle age the male sex is represented in high

preponderance — for example, in the ratio of 24 or more to 1 under the age of forty years, though with much lowered ratio in the next two or three decades. The sex factor is much more significant than heredity, of course. Two other characteristics often noted, which are, of course, inherited, are a highly mesomorphic (broad muscular) build and a psychologic and physiologic drive; these are probably but manifestations of the candidate rather than causative factors as may well be a tendency that seems to be commonly found to excesses in many habits that may be aggravating rather than basic factors, such as eating, smoking and the use of alcoholic liquor.

It seems very probable that in the present almost frantic search, which, I might add, is highly important and should go on, to establish a safe program of life for the protection of our citizens from the present devastating epidemic of coronary thrombosis, we should not expect to find one program equally suited to all. It is a very complicated business, for we are dealing with the intricacies of diet, of stress and strain, of physical and mental effort, of climate and of personal habits in addition to all manner of humankind, but the main point I want to make is that we must recognize our duty in the study of the host as well as in that of the agent (or environment), just as we would do in any infectious epidemic. Doubtless, there are general measures of positive health that are good for everyone and certain dangers that are bad and should be avoided, and these are at least in part already evident but the details of both host and agent are still to be added. We can supply, much more than we are doing now, the important ancestral and immediate family history in every case, and this is bound to be helpful at the very start.

#### SUMMARY AND CONCLUSIONS

And so in summary I make the following recommendations:

To stimulate the training of many more human geneticists to help us physicians in both our practice and our research.

To ask families to begin to record again for permanent preservation their family trees, with ages at death and causes of death of all their members, and, for the sake of the protection of the health and the

prolongation of the life of their descendants, to request that post-mortem examination be made at the time of death for vital information as was requested by Pope Clement XI himself back in 1706.

To ask all practicing physicians to record the ages dead or alive, the causes of death and the state of health of the parents, grandparents and siblings of their patients.

And to plan as soon as possible to utilize the programs of the ways of life now being studied to protect the candidates for disease, trying so far as possible to be selective so that what may be useful measures for some individuals may not be discredited ahead of time by mass application.

In closing may I express my confidence that in some oration in the more or less distant future the fatalism concerning the familial inheritance of disease will be dispelled, even before the days of eugenics if such an age ever arrives, through the application of preventive measures in time to save the younger members of families who are susceptible to serious diseases such as are represented by those of the heart and blood vessels. There may then come true the quotation from Shakespeare, the text with which I began this discourse:

Our remedies oft in ourselves do lie,  
Which we ascribe to Heaven.

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