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RELATION OF PHYSIOLOGIC CHANGES IN AGING TO MEDICAL CHANGES OF DISEASE IN THE AGED

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> The attainment of old age is easy and only the inquiry about it difficult and so much the rather, because it is corrupted with false opinions and vaine reports.
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> —Francis Bacon

In this paper I wish to discuss a problem which, it is true, has its share of opinions and reports, but "is a subject which no physician has handled in proportion to its dignity"—again to quote Sir Francis. The problem has been stated in various ways, but in essence it is this: Are the morbid, deleterious structural and functional changes that occur with age inevitable, physiologic, and therefore "normal," or are they indistinguishable from the harmful, pathologic effects of disease? Is the end stage, senility, a disease to be prevented if possible, cured if not preventable, or treated if not curable?

Having posed these questions, I now hasten to add that I have no intention of attempting to provide direct answers. They properly belong in the realm of the philosophers who deal with the more abstract aspects of time, aging, and disease. The questions have been stated in order to define more clearly the mundane level of this discussion; that is, we shall consider the practical difficulties that are faced today in dealing with the interaction of age changes with certain specific diseases.

The problem obviously is partly semantic; it is also partly a result of an inadequate background in statistical principles among physicians.

Many physicians abhor the conscious application of statistics in dealing with a specific patient, although in fact they must use that approach in arriving at probable diagnoses and in choosing among alternative courses of therapeutic action. Almost a cliché of current practice is this sort of statement: "What does it matter that statistics show the odds in my patient to be 5:1 in favor of gallstones over coronary disease? If my patient actually has coronary disease, then the incidence of coronary disease in him is 100%!"

Consider for a moment an epidemiologist-statistician's approach to disease. To him there is a certain truth and even

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fatal beauty in a graph of a family of curves of blood-pressure levels at different ages plotted against subsequent mortality rates. There is no difficulty in his understanding that a certain blood-pressure reading at a certain age is associated with a certain chance of dying. Similarly a family of curves relating serum-cholesterol concentrations at different ages to the incidence of myocardial infarction has certain clear implications. The physician, however, will not (perhaps "cannot" would be fairer) carry in his mind a graph or a complex table of probabilities relating these variables. He wishes the scientist to provide him with a serum-cholesterol value that he can easily remember and that will clearly separate "normal" subjects from "abnormal" patients. He would tolerate two numbers in order to define a "borderline" zone if necessary. He could also see the necessity of two sets of values: one for males and one for females. And, of course, separate sets of values might be necessary for children. It is then understandable that we have probably already exceeded the physician's number-rejection threshold. We can sympathize with him if he is asked to accept the fact that there is indeed no clearly defined normal zone for blood-pressure or serum-cholesterol value, that he may be dealing with a complexly increasing likelihood of disease as the level of these variables increases, and furthermore that these probabilities are intricately related to and vary with the age of his patient. He now looks wistfully at the blood-pressure value "140 over 90" that he was taught was abnormal, and bemoans the take-over of his art by scientism.

It has been remarked that it is the goal of the physician to say that disease either is or is not present. Disease tends to become a thing, separate somehow from the patient. Clearly there can be no pneumonia without a lung; the idea of disease as a physical entity floating freely and independently from the patient must seem especially ridiculous to the psychiatrists in our group. Yet this is the way we clinicians tend to think about our clinical problems.

There are rules in this game that physicians play, and it is only fair that if they play according to the rules they should be able to say that disease is either present or absent. We hate gray zones. One is either pregnant or one is not pregnant—there are no gradations. Changes in structure and in physiologic function of organ systems with age, however, do introduce grayness into our lives. Almost any system can serve as an example of the complexities caused by these age changes. Let us return to our previous examples. We know

that in a cross section of the population mean serum-cholesterol levels rise progressively into late life. A level that is very high for a 20-year-old man may be simply average for a 60-year-old man. Does the increase in cholesterol with age signify a normal physiologic accompaniment of aging or does it signify an increasing prevalence of a disease which ultimately becomes very common? Or, should a separate upper limit of normality be arbitrarily set for each decade of life so that the prevalence of the disease is limited in some manner according to the discretion of standard-makers?

Similarly, blood pressure represents a variable which marches with time into the domain of the hypertensive diseases. Here the actuaries have provided us with data on which rational decisions concerning normal standards can hopefully be based.

Another example, more egocentrically chosen, is that which involves (1) the physiologic variable, glucose tolerance, (2) the disease variable, diabetes mellitus, and of course (3) time.

Diabetes is a disease whose clinical incidence is sharply age-related throughout adult life; yet it is a heritable disease, the abnormal gene presumably being present since conception. Time, therefore, is essential in the metamorphosis of the disease from the stage of an undetectable genetic defect to the later disastrous syndrome of the full-blown clinical picture. Certain extrinsic and intrinsic factors have been identified as rate-modifiers in the development of the syndrome (obesity, multiparity, intercurrent stresses, steroid and other drug administration, and so forth).

At one stage in this development, before any symptoms or signs of the disease are evident, a biochemical abnormality may be elicited by testing the ability of the patient to dispose of an administered load of glucose. Physicians who have had wide experience with this disease can point to examples of subjects who are chemically and clinically normal but who are known to be destined to become diabetic (perhaps they are identical twins of known diabetics), who pass into the chemical stage in which glucose disposal is prolonged, and who may, experience teaches, pass into the clinical stage in the near future. The decline in glucose "tolerance" is, then, a hallmark of the disease. A decline in tolerance is, however, also a hallmark of aging, in that deterioration in the ability to dispose of glucose with aging, whether the glucose is given orally or intravenously, is a repeatedly confirmed and, by now, classic age change.

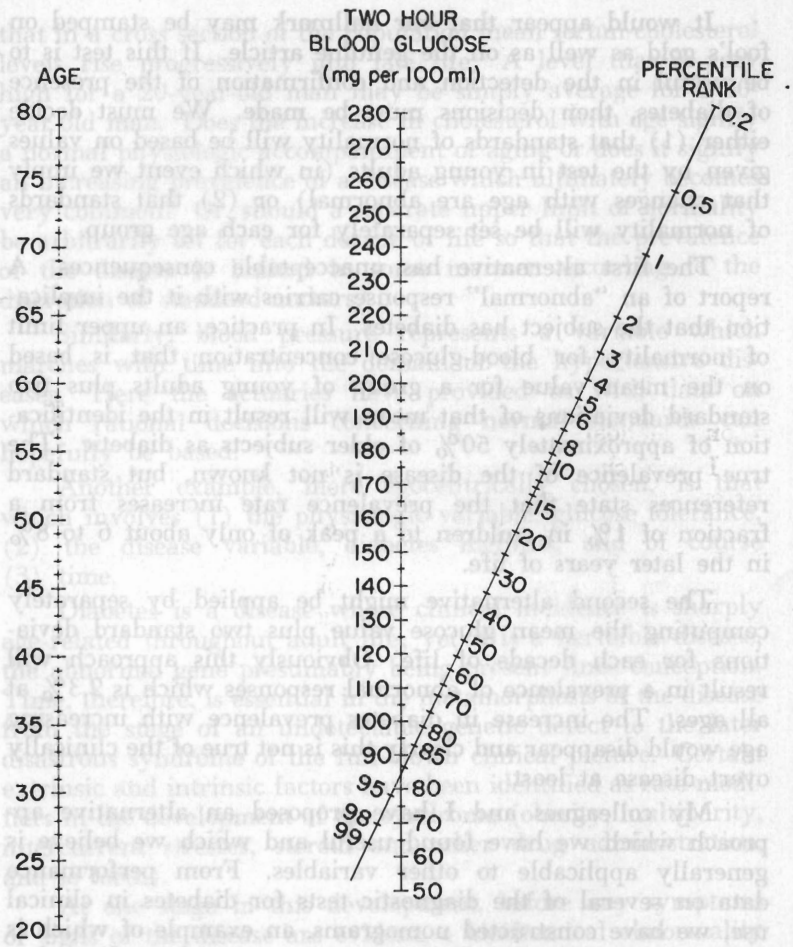
It would appear that our hallmark may be stamped on fool's gold as well as on the genuine article. If this test is to be useful in the detection and confirmation of the presence of diabetes, then decisions must be made. We must decide either (1) that standards of normality will be based on values given by the test in young adults (in which event we imply that changes with age are abnormal) or (2) that standards of normality will be set separately for each age group.

The first alternative has unacceptable consequences. A report of an "abnormal" response carries with it the implication that the subject has diabetes. In practice, an upper limit of normality for blood-glucose concentration that is based on the mean value for a group of young adults plus two standard deviations of that mean will result in the identification of approximately 50% of older subjects as diabetic. The true prevalence of the disease is not known, but standard references state that the prevalence rate increases from a fraction of 1% in children to a peak of only about 6 to 8% in the later years of life.

The second alternative might be applied by separately computing the mean glucose value plus two standard deviations for each decade of life. Obviously this approach will result in a prevalence of abnormal responses which is 2.3% at all ages. The increase in diabetes prevalence with increasing age would disappear and clearly this is not true of the clinically overt disease at least.

My colleagues and I have proposed an alternative approach which we have found useful and which we believe is generally applicable to other variables. From performance data on several of the diagnostic tests for diabetes in clinical use, we have constructed nomograms, an example of which is shown in the Figure. Its construction may be tedious but its principle and its use are simple.* The appropriate points on the age line and on the glucose-concentration line are connected by a straight edge which then intersects the percentile-rank line at a point which gives the centile ranking of the subject as judged against his own age cohort. Thus a 50% ranking is an exactly average performance and a 2% ranking indicates that 98% of subjects of that age would outperform the individual being ranked. We do not know what percentage of subjects at the various ages are truly diabetics. Undoubtedly we are dealing at all levels of rank with probabilities that the subject is now or is to become an overt case.

*Construction and use of two other nomograms are explained elsewhere.[1,2]



Nomogram for judging performance on the oral glucose-tolerance test. Dose of glucose was 1.75 gm/kg of body weight. Concentration of glucose was measured in venous blood by the ferricyanide reduction method using the AutoAnalyzer.

Our decision, which in effect acts as a compromise to the two alternative techniques for handling such data mentioned earlier, has been to classify subjects according to the arbitrary scheme shown in the Table. This plan results (1) in an increase in the prevalence of diabetes with age, (2) in prevalence rates that do not depart too radically from current ideas, and (3) in an equal-sized group of subjects who deserve careful follow-up studies. There has been ready acceptance of these arbitrary rules by the physicians to whom we send

Arbitrary Scheme for Classification of Subjects

Age group, years	% of subjects	
	Abnormal	Borderline
20-29	0-2	2-4
30-39	0-3	3-6
40-49	0-4	4-8
50-59	0-5	5-10
60-69	0-6	6-12
70 and over	0-7	7-14

our test data. No defense of this scheme is possible on any grounds other than those stated above.

Since our subjects are participants in a long-term longitudinal study, eventually objective results will be available which will provide the data necessary to set more rational standards.*

I have chosen in this paper not to attempt an exhaustive or definitive review of changes in physiologic functions with age. Certain selected variables were chosen for discussion as illustrations of an approach which, although not definitive, has general applicability to the problem of judging test performance in subjects of different ages.

*Further discussion of this actuarial approach will be found elsewhere.[3]

DISCUSSION

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Dr. Andres has pointed out an area in which we physicians are quite deficient in standardizing tests. In contrast to a few other laboratory tests such as that for serum calcium, in which we have some independent criteria of normality, we really have no authority to turn to other than the blood sugar itself to say whether a given patient has diabetes. In fact, when we encounter a series of equivocal glucose-tolerance tests, or postprandial or fasting determinations of sugar, we get to the point where we are scarcely willing to accept the diagnosis of diabetes at all until we finally see ketosis with the hyperglycemia or changes in the retinas or kidneys that are specific for diabetes. Of course, it is carrying the point to absurdity to demand such extreme findings. On the other hand, we are faced so commonly with the problem of providing an answer to the question whether a particular patient has diabetes that it is really refreshing to hear Dr. Andres' analysis. In a way it is like the old problem in geometry of trying to trisect an angle. It can be approximated but it cannot be done precisely. Perhaps this may be the answer to our problem of standardizing the glucose-tolerance test. The discussion we have heard does favor the view that we may never find the precise point of separation of the normal from the abnormal. Perhaps we can hope that by massive collection of data and careful analysis we may be able to define the gray zone, and be able to describe the probability that any given set of figures means diabetes.

Perhaps someone may in the future find some means whereby the diagnosis of diabetes may be established other than from blood-sugar measurements and by which we can make comparisons; but at the moment we find ourselves tempted to follow the pattern of circular reasoning—to want to prove that one scheme of doing or interpreting the tolerance test is superior to other procedures based on the results of the test itself. I suspect we are not going to come up with any simple answer.

In addition to the challenge of trying to establish a precise dividing line between the diabetic and the nondiabetic, there is the question, Why is glucose tolerance age-related? I have just read some of Dr. Andres' articles in which he discusses certain interesting items that he did not mention in his talk

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here. One is that the elderly person has a greater resistance to insulin, and another is that the infusion of glucose produces a response of endogenous insulin secretion in the elderly that is at least as great as and perhaps greater than the response in younger persons. This is similar to the situation in pregnancy. Pregnancy is diabetogenic. A woman who shows diabetic tendencies and whose response to the glucose-tolerance test is slightly impaired before pregnancy may develop overt diabetes in pregnancy. A number of investigators have demonstrated that there is an insulin resistance in pregnant women, just as Dr. Andres has shown in the elderly. There is no deficiency of insulin secretion in the women who respond normally to glucose-tolerance tests before and after pregnancy; there is no deficiency in their ability to manufacture insulin, but the diabetogenic changes appear to be the result of an insulin resistance. This is a state of resistance to both exogenous and endogenous insulin, and it seems to depend on the presence of an insulin antagonist called "placental lactogen" secreted by the placenta and similar in its properties to human growth hormone. This raises a question: Is there a specific hormone of aging which in some way is anti-insulin in its effects? It is always easy to speculate and propose the existence of some unknown substance to explain away a discrepancy in one's data. Probably a more ready explanation would be that with aging there are gradual changes in rates of secretion of various hormones and perhaps antibody formation. The insulin resistance in the older person does open the door on a new area for investigation.

I hope that over these next several years Dr. Andres can give us more data which will enable us to tell an individual who has certain figures on a glucose-tolerance test what the probability is that he has diabetes. We find ourselves now having to say to the patient: "The results of the test indicate that your ability to handle sugar is not quite normal but neither is it bad enough to say that you have diabetes. We are, therefore, going to instruct you in a set of precautions and perhaps time will tell us whether you have diabetes." This is satisfactory for the intelligent patient, but it does not work out well for the patient of limited understanding or for the insurance companies, which would like a "yes" or "no" answer.

DISCUSSION

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Since I know little about diabetes, I should like to address myself to some of the interesting methodological issues raised by Dr. Andres' paper. These issues are quite general, but can be directly applied to the study of disease processes of the kind described here.

The first question seems to be, How does one decide where in the statistical scheme to put a cut-off point when there is no real independent objective criterion of what is a normal condition and what is a disease condition? One solution may be to specify an arbitrary criterion such as, say, two standard deviations from the mean. But immediately there is posed the problem of the statistical definition of abnormality, particularly with older people.

In an unimpaired population—one in which practically the total population is available—it may well be justifiable to use the mean as a reference point. When one is talking about an older group, however, in which there is attrition, particularly attrition that by no means is random, but rather systematically related to the variables being measured, it may no longer be proper to use the mean as a point of reference. Some of us would agree to continue to use the mean of the population as a proper reference point. But I would at least want to question, as I have done before in another context,[4] whether it might not be better to use optimal limits, that is, whether one should not indeed specify what the extremes of the population look like.

What do the members of the population look like who remain generally intact in terms of other criteria, say criteria of their own experience of well-being, or in terms of the judgment by independent observers? Can we define the population of those aged individuals who are still well-functioning and then take a look, for example, at their blood-sugar level? Could we have a way of defining optimal limits in this sense and then start working from the mean of the population who came from some kind of an optimal reference group? To this problem I have no specific answer, but do think one ought to consider it.

A second interesting problem raised by Dr. Andres' paper is the perhaps quite well-known fact, to which little attention is paid, that the reaction of an organism under direct stress

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is different from its reaction under indirect stress. We have little information, however, on why this should be particularly important for older persons. Here again we are faced with the great problem that most of our data come from cross-sectional research designs and we must begin to wonder what indeed is the effect of stress on the organism in terms of the specific antecedent experiences of the older organism.

I wonder whether in the increasing complexity of our present life situation there might not be generational differences in our tolerance for stress. I have not seen any very systematic investigations of this kind because they obviously must be long-term. But adequate investigations of this nature might help indicate whether some of the differences observed are related to generational changes in the predisposition of the organism as a species. They might show that persons in the younger age groups will, in their own life experience, remain more tolerant to conditions of stress than did those now in the older age groups. I know of no good data on this point, but if there are any I would like to hear about them.

Another noteworthy point raised by Dr. Andres is the absence of adult plateaus for the functions he measured. Those of us who worry about the psychologic concomitant of physiologic change have been aware for a long time that the adult plateaus reported in the literature are typically nothing but the result of averaging different functions. Indeed, we get plateaus because in measures of composite behavior we find some components that are still developing and others that are already declining. Dr. Andres' failure to find any adult plateaus should reassure him, because it suggests that he must be measuring functions that are relatively pure and not compounded, since measures that compound these functions typically show an adult plateau.

Dr. Andres wonders whether his comparisons between a young population composed of medical students and laboratory technicians and an old population composed of inhabitants of homes for the aged may simply indicate that these two populations differ qualitatively in ways not related to age. This is probably true. On the other hand, even we who think that the gradients presented in cross-sectional studies are probably way off base still must conclude that significant decrement does occur in the last decades of life. My colleagues and I studied a small sample of retired university professors who were still very active, very much intact; in fact, a requirement of the study was that the subjects be able to come to us and that they be discouraged if they felt any discomfort

in participating. Yet we found that this superior sample showed significant decrement in performance. True, the function of these subjects was still somewhat above the mean of the young population. But for an adult sample that educationally and socioeconomically was at the uppermost extreme of the population to perform at the population mean indeed represented serious decrement. Dr. Andres can therefore rest assured that, while he might find some differences if he had more comparable population samples, it would be most surprising if his results were completely demolished.

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