

SCIENCE

VOL. 101

FRIDAY, MAY 11, 1945

No. 2628

<i>Disease of the Heart:</i> DR. ALFRED E. COHN	471	<i>DR. DOROTHY M. HORSTMANN. The Effect of Dietary Protein Intake on the Xanthine Oxidase Activity of Rat Liver:</i> E. B. MCQUARRIE and A. T. VENOSA. <i>The Inhibiting Effect of Quinones on the Growth of Penicillium Notatum:</i> DR. FELIPE GONZÁLEZ	489
<i>Obituary:</i> <i>A. D. E. Elmer:</i> ALBERT W. C. T. HERRE. <i>Recent Deaths</i>	477	<i>Scientific Apparatus and Laboratory Methods:</i> <i>Filtration of Citrated Plasma:</i> DR. LEO RANE and DAVID M. BALDWIN. <i>Efficient Handler for Small Mammals:</i> DR. LYEEL J. THOMAS	494
<i>Scientific Events:</i> <i>The Imperial College of Science and Technology; Conference on Research and Regional Welfare; The Department of Technology of the Carnegie Library of Pittsburgh; The Fiftieth Anniversary of the New York Botanical Garden</i>	478	<i>Science News</i>	12
<i>Scientific Notes and News</i>	480		
<i>Discussion:</i> <i>A Newly Discovered Periodicity of 16 Months in the Sun's Wave Radiation:</i> DR. C. G. ABBOT. <i>Quinine from Bemisia Bark:</i> DR. GEORGE M. HOCKING. <i>Centennial of Wood's "Class-book of Botany":</i> PROFESSOR CHARLES J. LYON. <i>Science and the New Draft Regulations:</i> DR. HARRY GRUNDFEST	483	<i>SCIENCE: A Weekly Journal, since 1900 the official organ of the American Association for the Advancement of Science. Published by the American Association for the Advancement of Science every Friday at Lancaster, Pennsylvania.</i> <i>Editors:</i> JOSEPHINE OWEN CATTELL and JAUQUES CATTELL. <i>Policy Committee:</i> MALCOLM H. SOULE, ROGER ADAMS and WALTER R. MILES. <i>Advertising Manager:</i> THEO. J. CHRISTENSEN.	
<i>Scientific Books:</i> <i>The Climate of Indiana:</i> J. B. KINCER	487	<i>Communications relative to articles offered for publication should be addressed to Editors of Science, 34 Gramercy Park, New York 3, N. Y.</i> <i>Communications relative to advertising should be addressed to THEO. CHRISTENSEN, Advertising Manager, Smithsonian Institution Building, Washington 25, D. C.</i> <i>Communications relative to membership in the Association and to all matters of business of the Association should be addressed to the Permanent Secretary, A.A.A.S., Smithsonian Institution Building, Washington 25, D. C.</i>	
<i>Reports:</i> <i>Technological Manpower</i>	488	<i>Annual subscription, \$6.00</i>	<i>Single copies, 15 cents</i>
<i>Special Articles:</i> <i>Growth-retarding Effect of Corn in Nicotinic Acid-low Ratios and Its Counteraction by Tryptophane:</i> W. A. KREHL, L. J. TEPLY, P. S. SARMA and DR. C. A. ELVEHJEM. <i>Poliomyelitis Virus in Fly-contaminated Food Collected at an Epidemic:</i> DR. ROBERT WARD, DR. JOSEPH L. MELNICK and			

DISEASE OF THE HEART¹

By Dr. ALFRED E. COHN

MEMBER EMERITUS, THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK

AS natural scientists we ought, I think, to seek earnestly and intelligently the place where our science fits in the general scheme of knowledge. Because there has been some measure of carelessness, the need is greater now, when exact methods of thinking are beginning to be used in the study of diseases. So much is usually included in accounts of disease in general, and of any set of diseases in particular, that what constitutes the essential properties in the description of any disease and so of diseases in general is often obscure. These remarks apply with especial relevance to disease of the heart. Folklore, tradition, anatomy, early physiology, contributions of the art of the clinic, bacteriology and therapeutics have all been included indiscriminately in accounts of

¹ Delivered before Alpha Omega Alpha, Tulane University Medical School, New Orleans, March 20, 1945.

the history of knowledge of this organ. How much earlier than Aristotle attention was paid to the heart and circulation is of little importance. The heart was recognized in any event as an organ of very great significance. Aristotle recognized in its performance the existence of rhythm. And rhythm in nature has been a subject which has always compelled speculation—whether this is applied to the daily reappearance of light or whether to the tides in the Euripus, in the case of Aristotle. Mention of Aristotle has value because it indicates when records on this subject began. It was not until about two thousand years later, in the middle of the eighteenth century and the early decades of the nineteenth, that a sensible contribution was made by any one to a recognition, to say nothing of an understanding, of the

existence of any disease of the heart. I pass over the names of Galen and Erasistratus, of Leonardo and Vesalius, of Servetus and Harvey. Whatever contributions to knowledge they made, and many of them were not only striking but of determining importance in anatomy or in physiology, I pass them without further mention because these advances were not additions to a comprehension of the evolution of knowledge concerning disease or diseases. Morgagni, Pitcairn, Wells, Corvisart, Laennec and Hope occupy wholly different positions.

But before I discuss observations, I should define what disease may mean and I should make an effort to discover why a society like ours is concerned with this problem. I have mentioned the word "science." It is by no means clear what subjects are to be included in this term. Investigations on light and magnetism and matter, both inorganic and living, have earned them the right to belong here. They are present everywhere. The most critical thinking and the most rigorous methods of which we are capable have been applied to them. These phenomena have universality. The universe is not to be understood unless they are. They are essence—not accident. But diseases—do they partake of this nature? And if they do not, what special considerations apply to them to separate them off? The answer, I think, is simple. Diseases are not timeless nor are they found everywhere. Some of them have appeared for brief periods only—others are confined to limited localities. Many are accordingly not necessary. Whether certain other ailments are to be designated diseases is not clear but not unimportant either; they appear not separable from the life and growth of the human organism. Some which are accidental are, just now, during wars carried on everywhere on the planet, introduced upon these shores for the first time, brought here by returning soldiers, illnesses never encountered in this country before.

It is desirable to widen this inquiry and to study where diseases are endemic and under what conditions they spread from their original to other regions. Diseases are, in short, linked both to space and time. These characteristics make them different from natural phenomena which have not these limitations but which have continuous and enduring existence. By contrast it makes of diseases something which gives them the appearance of accident. I believe that these elements of difference have far-reaching consequences for the advancement of knowledge, for the education of those who wish to advance that knowledge and for the place of diseases in our scheme of things—social, intellectual and economic.

How long, do you think, will diseases like typhoid fever or malaria continue to be studied when these diseases cease to afflict human beings? Compare the

number of publications on the subject of typhoid fever in the year 1900 with those in the year 1943, in the midst of a great war. Or take the case of malaria. How long will the many problems connected with mosquitoes as vectors or matters connected with the human carriers of this disease or the symptoms that occur in its many forms or the chemotherapeutic investigations now being conducted so energetically survive, after the dusting powder DDT has rid us of the insects which convey this ubiquitous and destructive disease? I wish naturally not to be misunderstood. There is good ground for believing that gifted and curious men will continue to interest themselves in the biology of pneumococci, in the processes of immunity, in the life cycles of plasmodium malariae. These are general problems of enduring interest, come to notice because once they were injurious. Interest in them may survive because they yield occasions for gaining insight into processes of living—a better occasion than when they did so into processes of killing.

In considering disease of the heart these wider generalizations can be applied. It is certain already that this organ is liable to diseases which belong in the category of accident; but the heart gives rise also to ailments in other categories, the meaning, and therefore the classification, of which is far from established. A first rough approach to ascertaining the significance and importance of cardiac ailments can be gained from engaging in so colorless a business as trying to learn the number of persons in this country who are incapacitated by cardiac disabilities—what kinds of persons do they afflict; do they afflict all the victims at every or only at certain ages; and do they do so everywhere or in selected areas only? Answers to these questions will themselves, if given consistently year after year, introduce concreteness and definition into our inquiry, and put us on the road to appreciating more than one fact of great significance. I have inserted the phrase "year after year" not without purpose. We live always in states of transition; nor have the past hundred years escaped this quality. But the last forty suffice to bring into prominence one aspect of change—especially important in this study. In this period the outstanding elements that demonstrate that this is a period of transition can be made evident from an analysis of the population and its illnesses—treated statistically. In the transition, forces have been at work which have modified the composition of our entire population and have brought in their train a variety of consequences in the economic life of the country, the end of which is not yet in sight and a comprehension of which has just begun to engage the national interest.

On what factors have the changes depended? In an era, the beginning of which is arbitrarily chosen at

the year 1900, deaths from infectious diseases such as typhoid fever, tuberculosis, intestinal infections, both in infancy but also at more advanced ages, were rampant and, through death, permitted relatively few people to attain old age. These diseases now have all but disappeared. There is room here for misunderstanding that should by all means be avoided. These diseases still exist. The numbers affected are great. The suffering which is entailed in individuals is not less than it was. But the grand total of persons who are involved in such misfortunes has shrunk to a much lower level. The direct consequence of the significant reduction of diseases which took their great toll of persons in the first two or three decades of life has resulted, naturally, in the survival of those same persons into the sixth, the seventh and the eighth decades. When we say, therefore, that expectancy at birth has increased greatly, emphasis should be placed at the same time on the fact that the phrase—expectation at birth—does not include as a consequence increase in the number of years it is possible to live. It means only that more persons are in position to realize a span of years which, within the range of those variations observable among men, make possible the attainment of natural expectations.

Now, what has been said permits insights into the state of affairs as to diseases of the heart. The names which are given to diseases have very great importance. If as descriptions they are inadequate or inaccurate, their use can be seriously misleading in laying out conceptions of the health of the nation. It is a comfort to realize that the business of using correct nomenclature is now taken seriously and that improvement is demanded. That increases confidence in statistical enumerations. There need be little doubt, therefore, in accepting the statement that certain names, that is diseases, occur with decreasing frequency in the earlier decades. Other ones occur with increasing frequency in the later decades. It is also a fact that during these last forty years, fewer and fewer entries are to be found before the age of forty. Young people, in short, are dying less and less of any cause, certainly of infection. Many, many more older persons, on the other hand, appear in the mortality tables. Of what are they dying—of the same diseases as the young or of other ones? And if of other ones, are those peculiarly appropriate to their age? That is a crucial question, bound up in the phrase “peculiarly appropriate.” In the end, we shall agree there is a difference between the processes which cause death among the young and those which do so among the aged. Concerning those which result in death among the aged, knowledge is far from precise. If they are different there is still opportunity for difference in opinion concerning their nature. About

their occurrence there can be no doubt. They have forced themselves upon our notice.

The whole circulatory system exhibits seemingly natural, evolving processes—in the heart, the arteries, the capillaries, the veins and those parallel and accessory systems which see to the movement of fluids through the body. All these several parts are subject to injuries which create in them something unusual and are therefore abnormal or diseased. The most significant factor in bringing about change in performance or function is often not definitely known even when its nature is suspected, as is now the case in many directions. With this general reservation it is possible to proceed as if what is now known constituted genuine insight into malfunction. It is appropriate to speak of the heart first. It is not as if the heart were composed of a single tissue. The several of which it is composed each requires consideration of its own account. Its bulk consists predominantly of muscle, a fact never to be forgotten. The arrangement of that muscle is far from simple. It is in fact a system of intricate bands which form figures of eight in three dimensions, a very powerful mechanism. The muscle fibers which compose it differ in structure from all other muscle cells in the body, smooth or striated. The life of this mass of muscle depends upon its blood supply—conveyed to it by an elaborate system of coronary vessels. The rich supply of nerves and ganglia play an important role in the behavior of these muscles, whether by dominating its performance or instead of regulating the harmony of that performance, is still not wholly decided. Of another structure which presides over the sequential coordination of the auricles and ventricles there need be no mention now.

But it is important to move into a position of great prominence the endothelial layers which cover both the outer and inner surfaces of the heart, and of that surpassingly ingenious arrangement of valves within, which for several reasons have occupied so large a part of the attention and which eluded so successfully for so many centuries the imagination of men in picturing forth the mechanics of the heart's action. However the whole story may ultimately be written, and in whatever way and on whatever ground they come to be involved, the inflammations of the valves, together with that of the endothelial lining of the heart, constitute processes in this organ which are to be found almost exclusively in younger persons—the infectious diseases predominantly but not exclusively of the endocardium of the heart.

In young people, rheumatic fever is the disease which stands at the head, indeed far in the lead, of all the diseases of the heart. It is, at that age, the out-

standing disease of the endocardium. All the anatomical features of this disease are not yet known, and although there are theories aplenty concerning the bacterium or bacteria which occasion this disease, and concerning the other very intricate immunological principles which are at work, definitive knowledge on its etiology, although it does not exist, seems, will-o-the-wisp-like, to be beckoning just around the corner. Presumably there are weaknesses or local chemical attractions in the endocardium, or defects in the structure of the valves, a point on which Thomas Lewis has laid stress, that dispose these structures to invasion by bacterial and perhaps virus diseases.

Now the course of events, after rheumatic fever has been acquired, is various and unpredictable. A first attack may last a brief time only, but be overwhelmingly severe, so that a patient dies in the first one, in a matter of days. Or, even after having suffered a series of recurrences, not too severe perhaps, a patient may survive and may actually fill out his expected days. In any case a further account of this subject is not relevant here.

It is for the sake of completeness worth recording two other diseases which belong in this class and affect younger persons predominantly even if not exclusively. These are cardiovascular syphilis and bacterial invasions by streptococci, pneumococci and rarely, gonococci.

These then are the ecological, the environmental, diseases. They are of two classes; first those in which the host is an opportunity for parasites, mostly living—the bacteria. Second, in very recent years, since the dividing line between living and non-living things has become much more sharply drawn, structure alone being decisive in determining the existence of livingness, quasi-living things also may play a role. Such entities, viruses, can, it is now certain, take on the function of being agents inciting disease. This conception is the consequence of Stanley's discoveries beginning with the virus of tobacco mosaic. All this concerns the milieu exterieur, though the problem of susceptibility, the corresponding reaction of the milieu interieur, may naturally not be ignored.

The dependencies on time and place give to the study of ecological diseases a peculiar accidental appearance, different from the universal nature which characterizes the steady march of inherent ailments. Concerning ecological diseases we do what we must—not what scientific curiosity dictates. All the so-called infectious, communicable, contagious diseases belong in the ecological group. Since they vary with time and place, that is to say with climate or geography, it has been customary, and indeed imperative, to study only those diseases which threaten or actually disturb or endanger us. It is a matter of common

sense, therefore, that we devote ourselves only to those which are upon us.

When they exhibit wide-flung biological principles which reward exacting study, the situation is different and we change our attitude.

In addition there are diseases which depend not on the milieu exterieur but on the behavior of the whole organism as an expression of harmonious existence. They depend, I am suggesting, upon the milieu interieur. It requires only a cursory glance at a graphic record of mortality to notice that the number of persons who succumb to attacks of infectious diseases in early years is, relatively speaking, insignificant in comparison with the great number of individuals, now to be discussed, who die in ever expanding numbers after age forty-four. It is almost as if, having survived the struggle of the first year of life and having established one's right to live, the chances are very good that you can go on until old age, and good perhaps even to advanced old age. This statement is almost correct. It needs, however, a few modifications. One is important enough to be singled out to the neglect of the others. The record shows that there is one cause of death which begins to take its toll already in the fourth and fifth decades, that it increases in destructiveness decade by decade until it becomes dominant, and in the end overwhelming. Here is an arresting observation; it may yield information of importance.

Because cardiac deaths begin so early in life it seems unlikely that those which take place in the fourth and fifth decades are identical with those which occur later—in the sixth, seventh and eighth. Supporting evidence that they are different begins to emerge. The whole story needs still to be unfolded. If there were no ecological or accidental reason for dying in the earlier decades, there may be, and in all probability are, other reasons connected either with one's inheritance or with some other form of subtle injury, exposure to which has long been going on, but has not been recognized.

In this milieu, the milieu interieur, at least two different kinds of process are distinguishable—hormonal ones which for some reason, often not identified, disturb the balanced life of the body and result in disharmony and so, in disease. But much more important, indeed overwhelmingly important, in these interior disturbances are the ones which are recognizable as the ailments and disabilities of the aging process. These phenomena are, it seems, intimately associated with the evolution of the body and may be called disturbances inherent in its natural history.

It is necessary to call attention, in passing, to differences in the liability of diverse races to suffer

from ailments or disabilities peculiar to themselves and that these are occasions for assembling information concerning duplicate natural histories. They need not be described in detail here.

In this background, free choice can and should be exercised in deciding what researches come first. In making a selection the quality which we call statesmanship becomes determining. And the technique which statesmen employ turns out to be statistics. That technique applied to phenomena expressive of the condition of the public health gives the clue to what it is urgent to investigate. "In early use (A.D. 1787) (statistics was) that branch of political science dealing with the collection, classification, and discussion of facts . . . bearing on the condition of a state or community." (O.E.D.) That early use of the word statistics deserves to be reintroduced, at least to common comprehension.

It is desirable now, to be definite. The heart is a large organ. Its weight depends, except for a few per cent., on its muscle. The fate of the muscle is to be taken with great seriousness. But it is unlikely that the muscle lives unto itself alone. Its arrangement is complicated, the fibers branching in all directions, so forming a syncytium. The coronary system of vessels is so arranged as to supply at least one capillary to every fiber. The number of muscle fibers probably does not change from birth to death. But the intimate structure of the fibers alters considerably. Roughly, very roughly, a fiber at the beginning of life appears not to contain very much aside from its nucleus, not much even in the way of sharply defined cross striations. But later on, certainly at middle age, a fiber seems to contain a good deal. Beside a nucleus, cross striation is conspicuous and curious structures called cement lines, intercalated discs, step-like concentrations like boundaries, make their appearance. The nucleus itself, instead of looking a simple featureless ovoid globule, begins to look like an angry cumulus cloud. In youth cross striations are everywhere evident, running like bars to the very edge of a nucleus. But later, outside both nuclear poles there are spaces, become vacant of striations and now filled with lipochrome pigment. The meaning of all these changes from youth to age is not obvious. But one thing may be taken for granted: there is an inescapable relation between the form of a structure and its function. What that relation is, is far from having been worked out. Here enter two important problems. One concerns the nutrition of the muscle; and the second, its essential function, its motion, the business of contraction. One question which needs to be asked of the muscle fiber is this—is the alteration in its form connected with its nutrition? If, other things being equal, and the other things are

difficult even to define—if the composition of the blood remains uniform throughout life, would any change in the form of the muscle take place? In one sense this is an idle question because it is already known that the organs of the body do not develop synchronously. Evidence for that is to be seen in the decrease in size of the thymus gland in childhood and in continuous changes in the structure and function of the genital tract both in males and females. Whenever an organ or a tissue changes, there must go with that a discharge into the blood stream of modified and perhaps of new substances, each of which plays its role. Clearly with changes such as these, whether cyclical or otherwise, reflections of these changes must and do occur in the blood. What is obvious in these examples has counterparts in the behavior of many or all the other organs and tissues of the body, each after his kind.

The blood, which is our common supply and disposal system, accordingly changes. What else changes? How the endothelial reticulum lining the capillaries does and how the other elements in their walls, lying between the blood stream and the muscle fibers, is not known with particularity. But there begins to accumulate evidence to show that this is so. There are, it seems, then, changes of three kinds; in the blood, in the capillary wall and in the muscle. All change, but to what end no one knows.

There need be no question about the labor of the heart; that is carried on by its muscle. What concerns or damages the muscle, other things like the valves being equal and uninjured, concerns a man's strength and indeed concerns his very life. What function limits the power for work so that after thirty-four or thirty-five a man is not as fit an instrument for military service as he was formerly? That same function is the limiting factor also in his athletic performance and in the expression of his vigor in general. It is not necessary to believe that the lessening of physical power is dependent solely upon the muscle of one's heart. Undoubtedly, owing to the togetherness of the whole organism, all his structures participate in his performance. But the muscle of the heart certainly participates as one of them.

The word contraction serves to denote that power of the cardiac muscle fiber on which the development of vigor depends. If that decreases what can there be in that increasingly intricate structure of a fiber which spells, as it were, the decline of its power. It is of course not necessary that the most significant contribution in a system should be that element of which there is most bulk. Nor is it obvious as yet which constituent of a muscle fiber plays the outstanding role in the act of contraction. The intricate arrangement of the lines of cross striation and the vary-

ing height of the discs between the recurring main ones suggest that they may not be ignored. But so far they have not been studied successfully, either chemically or otherwise, to this end. Such a study presents for the time being too great a challenge to current technological refinement. Instead, advantage has been taken, especially by Mirsky, of the opportunity to study, as such, the proteins that occur in muscle. It turns out that they constitute the most important bulk (19 per cent.). And of them, myosin is the protein which is present in largest amounts (two thirds). Reversibility of denaturation is now recognized to be an important function at least of certain proteins. This study, after having made progress for a while, has recently slowed down. That is unavoidable. Such episodes suggest an analogy with military operations, which teach that a salient can not safely be thrown forward indefinitely without collateral support. The shoulders must be consolidated. In the slow advancement of knowledge it is necessary to await from time to time for the study of neighboring subjects to come abreast. But sometimes you stop, even in mid-career, just short of success, for reasons not dictated by the experimental situation. Moses you remember did not enter the Promised Land.

In assigning reversibility as a property of a protein, myosin for example, underlying the act of contraction in a given structure and as responsible for that act, certain considerations must be satisfied. Among them it is necessary to know how many times a minute the action takes place. A number of years ago, in 1911, Hertz and Goodhart encountered a case in which the speed of the heart, that is of the ventricles, was recorded at 236. They thought the number 236 represented the speed limit. Later, rates as high as 313 have been found. What cardiac muscle can do is, of course, not limited to such observations. The bearing of fibrillation and flutter on this function is not yet obvious. But it is clear that if reversibility of denaturation of myosin or of any other protein determines the act of beating, the rate of reversibility which is possible in that protein is basic to a conception that the rate and rhythm of the heart depend on this substance.

That there exist muscles, change in the state of which can occur several hundred times a minute, is obvious in the speed of the wings of insects and of humming birds and in the hearts of canaries. Something accomplishes this trick and does so, obviously through the mechanism of a particular structure, situated undoubtedly in muscle. It seems almost inescapable that this something is basically protein, provided this has the faculty for accomplishing such continuous rapid changes. The responsible substance may, of course, wear away and so may need rapidly to be replenished. But it seems less likely that the

result should be accomplished by using up a substance, rather than that a substance should exist, poised in unstable knifelike equilibrium to be set in motion, from lengthening to shortening, by some master mechanism. Whether reversibility of denaturation is capable of such rapid oscillation is, of course, still unknown. But if this is the direction in which search for the basic mechanism of rhythmic contraction is to be instituted, some such process as the reversibility of denaturation seems a possible conception to explore.

There are good reasons for wanting to get on speedily with advancing knowledge in this direction. If contraction is essentially a chemical reaction, then here as everywhere, to be able to control such a reaction, a knowledge of the chemical mechanism which constitutes that reaction is essential. And if, furthermore, the means at hand to establish control are inadequate, an attempt to alter a detail in the structure of a controlling agent and so to bring about a useful result is eminently desirable. These have been the considerations which underlie the plan of investigation that has been going on in exploring the chemistry of the immune processes and in the pharmacological studies which are devoted to furthering those objectives. And so, the disinterested (chemical) study of the mechanism of contraction leads on to further analyses having a practical value in therapeutics. But there is even a further reason for this investigation. Understanding the behavior of the substances which engage in the act of contraction has theoretically, and for many people preeminently, the great advantage that it may facilitate not only comprehension of an important subject but may actually assist in illuminating that most subtle process, among the many subtle ones in nature, called growth, which in a special sense is the same as the process of aging. The structure of muscle and its functions and the changes both in structure and function which take place with time have, therefore, decisive importance in securing a better comprehension of the ailments of the heart at all ages, but especially those at the far end of life.

Turn now to the coronary vessels. They themselves, aside from their function of being channels for carrying blood and so of facilitating the nutrition of the muscle, have life histories of their own. The newly identified disease, of which the observations of James Herrick have made us aware, is intimately dependent on occurrences in the walls of these vessels. That these vessels, especially the arteries, are subject both to microscopical and then to gross alterations, beginning almost at birth, metabolically in the form of cholesterol deposits and structurally in splitting of the internal elastic lamina, has long been known. Having begun with the discovery of changes in the

elastic tissue, designated arteriosclerosis, and having learned of the subsequent introduction of fat and calcium in the ground substance, designated atherosclerosis, investigation has proceeded further. It has now been learned which vessels in the coronary system suffer earlier from these processes, which vessels represent major importance from the point of view of site, and what the consequences are to given areas of muscle to which the vessels large or small are distributed when these same vessels become impassable. Whether passage is interrupted gradually or suddenly has, of course, clinical bearing. It is not too much to say that knowledge of the processes to which the coronary vessels are subject and the ultimate damage to which they give rise can not be too minute. The fate of the very smallest and seemingly insignificant capillary constitutes an important part in the mechanism of damage. But occlusion of a vessel, even of a capillary vessel, does not tell the whole story. That is only the end of the drama. Larval processes must have been going on continuously in the walls of capillaries and of arteries, perhaps in the vasa vasorum, which constitute changes of such a nature as to alter their structure and so to interfere with the passage of metabolites. These processes injure the walls further, and so impair the nutrition of the muscle beyond. The ground substance, where Aschoff thought the basic metabolic disturbances take place, deserves furthermore the most thoroughgoing research. It is necessary to think only of the capillaries in a glomerulus of the kidneys or in an island of Langerhans or in the convolution of Broca to appreciate the extent to which health depends upon the integrity and consequently upon the successful performance of these very small structures. So far, exact studies of the larger arteries, but less of the smaller vessels in the coronary system, have had rewarding results. There is a difference, it is now known (Ehrlich, de la Chapelle and Cohn) in the vulnerability, or perhaps it would be better to say in the viability of various coronary arteries. The branch which supplies the back of the heart (the posterior descending ramus) survives intact, without lesions, for a decade longer

than the one which courses down the front. Besides, there are sites along both these vessels and along the trunks from which they originate, which seem especially exposed to deformity. Why these sites? And when in a man's life are they affected? Is there a difference between men and women in the development of particular kinds of lesions? Blumgart, Schlesinger and Davis have carried on the search further and have shown that it is not only vessels at different locations but societies of vessels in several, perhaps special regions which under certain circumstances fall victims simultaneously to an underlying, far-reaching process.

These studies must go further. It is necessary to know what compromises the expectation of long duration in the competent life of vessels of different orders of size and in different locations and of whether a recognizable element exists, in metabolism perhaps, which accounts for what we observe. Is there a difference among the races of men, yellow, black and white, or in the conditions under which they live and nourish themselves, that brings about differences not only in the length of life they may reasonably anticipate but, to pass from the very important to the very minute, in the evolution, in the growth of their smallest blood vessels. These may be the differences, the growth and nutrition of their blood vessels, on which the health of their surviving years depends. We begin to appreciate the fact that on the mechanics of the infinitely small depends the mechanics of the great machine—electrons, valence, the very granules in cells, and genes in chromosomes, upon these depend the morals and intelligence of individual citizens in the highest and in the humblest places. To learn about such matters is not to go too far afield if we are to gain badly needed insights. What takes place in our later decades and what hope we may entertain in developing ability to manage the course of our lives may depend, not improbably, on our managing to live so that pain and disability is reduced and that we approach our appointed ends with a maximum of joy in living and with a minimum of dependence and decrepitude.

(To be concluded)

OBITUARY

A. D. E. ELMER

FROM a friend recently released from the Santo Tomas prison camp in Manila word has been received of the death in July, 1942, of A. D. E. Elmer, the distinguished Philippine botanist. Working under great handicaps, Mr. Elmer published ten volumes of Leaflets of Philippine Botany, and distributed sets of Philippine and Bornean plants to all the principal

herbaria of Europe and America. Mr. Elmer was a plant collector of extraordinary ability. He graduated from the State College at Pullman, Washington, in 1899, and received a master's degree from Stanford University in 1904, leaving shortly after for Manila, where he made his home until his death. It was my privilege to know Mr. Elmer for over forty years. To hear him tell in his quiet way of fantastic but