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ABSTRACTS OF PAPERS

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The ballistocardiograph, a new means of investigating the heart and circulation of man: ISAAC STARR (introduced by A. N. Richards). When physics and chemistry changed from descriptive and qualitative methods to quantitative methods, the rate of advance was tremendously accelerated. The investigation of disease has been largely descriptive and qualitative up to the present time, but there has been an ever-increasing group of workers attempting to design and apply quantitative methods to the host of problems encountered in the clinic. This presentation is a progress report of an attempt to get quantitative information about one of the commonest problems in medicine, the question of the strength or of weakness of the heart and circulation. The heart is a pump and to properly assess its function the amount of blood pumped per unit of time must be known. Methods designed to estimate the cardiac output of man have been developing since 1909. The field has been handicapped by the impossibility of testing methods by estimating known quantities, but the best methods now yield consistent results, and agree fairly well with one another. But all these methods, either because of the need for cooperation on the part of the subject, or because they incited fear or caused discomfort or pain, or because of the laboriousness of the procedure, have not been suitable for routine use in the clinic. The ballistocardiograph is suitable for such use, for it requires nothing of the subject save that he lie relaxed on the table and rough estimations of cardiac output can be made by the operator in a few minutes. The apparatus consists of a table suspended from the ceiling on wires and braced to prevent motion in any but the longitudinal direction. Motion in that direction, opposed by a strong spring, is magnified several thousand times and photographed. When a subject lies on the table it moves in time to the beating of his heart. The forces producing this motion are chiefly the recoil as the blood starts headward when the heart contracts, and the impact as this headward motion is arrested at the aortic arch and pulmonary bifurcation. Unfortunately the resultant of these forces is not perfectly reproduced in the record, for they pass through body tissues which, jelly-like, quiver for a brief instant after receiving a single blow. Therefore after-vibrations warp the latter part of the record, but they have much less effect on the early waves and from this part reasonably reliable data can be obtained. For this and other reasons I do not believe that the method will ever be one of the highest precision; its importance is in the ease of its application and in the fact that it gives to clinicians some knowledge of fundamental facts of cardiac function about which the ordinary clinical methods leave them ignorant. Evidence has been secured that the size of the early ballistic waves is related to the output of the heart, that their shape is conditioned by the changes in the velocity of blood during its ejection from the heart. Normal standards have been ascertained by examination of over 300 normal subjects. The method makes possible the routine examination of patients and provides evidence of cardiac health or disease of a type not available before. It will also detect abnormalities of the circulation not associated with heart disease, a condition which has often entirely escaped detection heretofore. The method is particularly adapted to assessing changes in cardiac function in single individuals. Experiments have been carried out on the effects of exercise, drugs and other therapeutic agents on cardiac function, and also on the development and healing of disease.

The interaction of tones in the ear: ERNEST G. WEVER. When two or more tones are applied simultaneously to the ear they interact in a complex manner and give rise to phenomena not represented in the physical stimuli. Some of these phenomena—beats, combination tones and masking—have already been recognized in subjective observations. A new phenomenon, called tonal interference, is revealed by the electrical responses of the cochlea. Tonal interference appears as a reduction in the magnitude of response to a given tone due to the presence of another tone. It is distinct from masking: it has a different locus in the auditory mechanism, and it occurs for tones of any frequency. An experimental analysis shows the character of the interference process and its relations to the stimuli; and, more generally, it gives insight into the nature and order of events in the cochlea in response to sound. The experiments were carried out in collaboration with C. W. Bray and M. Lawrence.

The rôle of the carotid and aortic bodies in the defense of the mammalian organism against oxygen lack: CARL F. SCHMIDT and JULIUS H. COMROE (introduced by A. N. Richards). The carotid and aortic bodies consist essentially of glomus tissue, *i.e.*, they are structures in which arteries break up into thin-walled sinusoidal spaces devoid of muscular coat and in which the pressure must be close to the arterial level. The walls of these spaces contain abundant nerve endings, and the specialized function of the structures depends on the fact that these nerve elements are stimulated by certain changes in the chemical composition of the blood, giving rise to reflexes that strongly stimulate the medullary centers (respiratory, vasomotor, cardioaccelerator, cardioinhibitory); under some circumstances generalized motor activity of the central nervous system (convulsions) may thus be produced. The stimuli by which the chemoreceptors are stimulated include all the conspicuous changes produced in the blood by increased metabolic activity, *i.e.*, increased carbon dioxide tension, decreased oxygen tension and increased acidity. A considerable number of drugs can also stimulate them; most of these can be grouped in two categories: first, those that turn the balance between the demand of tissues for oxygen and the available supply of it in the direction of a deficiency of oxygen (inhibitors of oxidations such as cyanides and sulfides; stimulators of metabolism such as dinitrophenol and dinitrocresol); second, those that have "nicotinic" actions (nicotine, lobeline, coniine, choline and its derivatives, etc.). The significance of these reflexes to the organism probably depends on their being relatively primitive and undifferentiated survivors in an air-breahting mammal of a reflex system originally intended for orienting a gill-breathing

forbear in an aquatic environment. The neurons of the medullary centers (particularly the respiratory) of terrestrial mammals have developed a highly specialized sensitivity to carbon dioxide, but although some observers have claimed that the chemoreceptors are even more sensitive, the balance of experimental evidence now available indicates that in the normal mammal the chemoreceptors are distinctly less sensitive than the center to carbon dioxide. On the other hand, recent evidence indicates that the center is much less sensitive to H^+ ions, and the chemoreceptors considerably more sensitive to them, than had been supposed; it now seems possible that the H^+ ion does not stimulate the respiratory center directly, the responses to this stimulus being due to the effects of the increased CO_2 tension on the center and to the action of the H^+ ions on the chemoreceptors. One of us (J. H. C.) is now investigating the sensitivity of the respiratory center to carbon dioxide and to acids introduced directly into its tissues; so far, although carbon dioxide has regularly stimulated the center, acids (hydrochloric, lactic) have shown no signs of a similar capacity, but the experiments are still in progress and no final statement can be made at this time. The chemoreceptors are definitely responsible for most if not all of the stimulant effects of oxygen deficiency (the hyperpnea, hypertension and tachycardia and perhaps the convulsions also); this is also probably true of the corresponding effects of nicotinic drugs, excepting the hypertension that such drugs can produce by ganglion stimulation. Thus these reflexes are responsible for most of the organism's defense against anoxia; as far as is now known, the direct effects of anoxia on structures other than the chemoreceptors is a depressant one; resistance to the depressant effects of anoxia is probably the most important attribute of this reflex system, and this is probably referable to the relatively undifferentiated state of the chemoreceptors. When the specialized sensitivity of the central neurons is reduced (as by anesthesia) the control of breathing may revert to the primitive aquatic type and be carried out by the chemoreceptors, responding to deficiency in the oxygen tension of arterial blood rather than to increase in the CO_2 tension; under such circumstances relief of anoxemia may cause respiratory failure. In some cases of sudden relief of long-standing tracheal obstruction and perhaps of sudden increase in the oxygen intake by aviators at high altitudes, collapse and unconsciousness ensue, perhaps for a similar reason.

Some effects of low concentrations of copper salts on the mammalian red blood cell: MERKEL H. JACOBS and W. D. JONES. It was previously reported by Jacobs and Corson that concentrations of copper salts of the order of magnitude of 10^{-5} molar, or even considerably less, have a highly characteristic inhibiting effect on the hemolysis, in solutions of glycerol, of the red blood cells of certain mammals, especially man. This effect has been further investigated by a non-hemolytic method involving osmotic volume changes of the cells under more normal conditions, and has been shown to be essentially one of cell-permeability to glycerol. Though it can be imitated in some respects by salts of mercury, in others it seems to be unique, and it suggests a possible delicate non-chemical method which might be used under certain conditions, yet to be exactly defined, for the detection of traces of copper. The available evidence indicates that the action of copper is at the surface of the cell rather than in its interior; the minimum amounts required are so small that only a fraction of the cell surface could be occupied by copper atoms at any one time. Within the limits of accuracy of the method, the effects of copper seem to be practically instantaneous; by photographic recording the full degree of inhibition of osmotic swelling can be shown to appear in less than a second. At the concentrations used the effects are also rapidly reversible, either by washing the cells, diluting the external medium beyond a certain critical point, raising the pH (with results that differ with different species) or, most conveniently, by the addition of a trace of serum or of hemolyzed cells. The latter method is well suited to photographic recording, and permits the demonstration of a restoration of the normal permeability of copper-treated cells in as short a time as one second.

A comparison between splenic and normal erythrocytes: ARTHUR K. PARPART (introduced by E. N. Harvey). One of the chief functions of the spleen is the storage of blood cells. Previous experimental work has suggested that erythrocytes, thus stored, undergo degenerative changes. The nature of these alterations was not known. Recent investigation has clearly demonstrated that erythrocyte degeneration in the spleen is associated with marked changes in the red cell membrane. A comparison has been made between the permeability of erythrocytes from the splenic reservoirs and those from the normal circulation. The permeability to lipid-soluble and lipid-insoluble compounds and to ions has been found to be much greater in the case of red cells stored in the spleen. These observations suggest that there must be some changes in either the chemical composition or the molecular configuration of the red cell membrane, or both. Lipid analyses have shown that the total lipid content of the membrane decreases. At the same time the lipoprotein complexes in the membrane are decreased. These data have an interesting bearing on the relation between permeability and the chemical composition of the red cell membrane. They are the first records of a normally occurring change in the membrane composition which is correlated with a change in permeability. Previous experience with variations of lipid content of red cell membranes in relation to their permeability made it reasonable to expect that the decrease in lipid content of splenic red cells would not have affected their permeability so markedly. There remains the, as yet uninvestigated, possibility that the orientation of the molecules in the red cell membrane is an important factor in the altered permeability of splenic red cells. Investigations are in progress concerning the enzymatic agent which is responsible for the changes in the chemical composition of red cells stored in the spleen.

Pituitary diabetes in the cat; recovery after insulin treatment: F. D. W. LUKENS and F. C. DOHAN (introduced by A. N. Richards). Pituitary-diabetes is the permanent diabetes produced by the injection for a few weeks of crude saline extract of anterior pituitary glands.

This was first described by Dr. F. G. Young, of London, who used normal dogs; he could not make normal cats diabetic. We have likewise failed with the intact cat, but have found that by the removal of part of the pancreas (leaving enough to prevent any signs of diabetes), this species is rendered susceptible to pituitary extract. A number of permanently diabetic cats have thus been prepared. They manifest the same type of diabetes observed in the dog as measured by the blood and urine sugar, but the pancreatic islands (the source of insulin) present a type of abnormal appearance (hydropic degeneration) which is different from that in the dog (atrophy). In the cat anatomical and functional restoration of the islands takes place under insulin treatment, and the recovery of the animal is maintained after the withdrawal of insulin. Recovery does not occur in animals in which the diabetes has lasted for five months, and no recovery has been reported in pituitary diabetic dogs treated with insulin. The relation of various factors to the recovery of damaged islands of the pancreas in the diabetic animal can thus be studied. Species difference, the type of anatomical disorders, the duration and severity of the diabetes and the variations of treatment are under investigation.

The tetramite stage of Orthopteran auxocytes: C. E. McCLUNG. During the development of the male germ cells of the grasshopper a critical stage is reached during which equivalent contributions by the male parent and the female parent are brought into intimate physical contact and there react upon each other so as to bring about new combinations in the character controls of the two. This seems to be the most significant feature of biparental reproduction, and every detail of the phenomena of germ cell production at this time is of great theoretical importance. Because these details concern very minute elements of the cell exact determinations of their behavior are difficult to arrive at. It is, however, now generally agreed that the chromosomes, the cell elements which carry the material genetic controls, are greatly elongated and lie parallel with homologous regions apposed. Just how the exchange of units, representing genetic controls, is accomplished, is not completely understood. One significant stage of the process is of very short duration and has not previously been described. At this time the four strands of each chromosome, two from each parent, lie extended and parallel with each other, without the presence of any of the so-called chiasms which have been credited by some as the means by which these threads are held in contact. Various other assumptions of "attraction" and "repulsion," "precocity," etc., are definitely disproved by the existence of the "tetramite," a chromosome in the form of four parallel threads.

Biographical memoir of Harvey (Williams) Cushing: W. G. MACCALLUM.

Biographical memoir of Calvin Blackman Bridges: T. H. MORGAN.

Biographical memoir of Arthur Edwin Kennelly: VANNEVAR BUSH.

Biographical memoir of Floyd Karker Richtmyer: HERBERT E. IVES.

Biographical memoir of Albert Sauveur: REGINALD A. DALY.

SPECIAL ARTICLES

ATTENUATION OF CELL STIMULATING BACTERIA BY SPECIFIC AMINO ACIDS[1]

FACTORS influencing virulence have been studied as part of a larger program aimed at clarifying the means whereby the crown gall organism, *Phytomonas tumefaciens* (Smith and Town.) Bergey *et al.,* incites diseased growth in plants. After a considerable range of toxic substances and unfavorable conditions failed to change pathogenicity, glycine proved effective. Attenuation was accomplished by 20 to 30 transfers in a mannitol nitrate mineral salts medium containing .1 to .3 per cent. glycine adjusted to pH 6.8. The amount of glycine was increased gradually in successive transfers, according to the tolerance of the culture, so that growth was slow. Attenuation was considered complete when puncture inoculations into tomato failed to induce crown gall. Several original strains have been kept in culture for over ten years without loss of virulence. Mechanically picked single cell cultures were isolated at the beginning, at various intermediate stages and at the end to avoid any differential selection in an originally mixed bacterial population.

Some attenuated cultures when placed on yeast infusion mannitol medium regained virulence within a year. Others remained attenuated even after four years. The permanency of attenuation was partially dependent upon the number of transfers in glycine medium after attenuation.

The reaction of the medium affected the rate of attenuation. A medium at pH 8.0 was inhibitory and readily attenuating, while one at pH 5.0 was not.

Various other compounds having structural similarity to glycine have also been employed. Among over 50 compounds most of the amino acids were included. With the exception of dicyandiamid (which gave only partial attenuation) and the dipeptide of glycine, all the attenuating compounds were amino acids. These were: glycine, alanine, serine, alpha amino n-butyric acid, threonine, valine, norvaline, methionine, leucine, norleucine, isoleucine and lysine. Their relative effectiveness in mannitol-nitrate-mineral-salts solution is indicated in Fig. 1. Only racemic mixtures of opti-

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