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CALORIMETRY
IN
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CALORIMETRY
IN
MEDICINE

PREFACE

The contributions of calorimetry to medicine have been reviewed from the standpoint of one who believes that the least valuable of these contributions is that by which it is best known to the majority of physicians, namely, the use of calorimetry in diagnosis. The review of the extensive literature of the basal metabolism in health and disease can serve no better purpose than to emphasize the pitfalls and dangers of mechanical methods of diagnosis, especially when exactly controlled scientific procedures are degraded to simplified clinical laboratory tests, simplification consisting chiefly in elimination of checks and controls.

The author has attempted to point out the broader fields of usefulness of calorimetry in medicine, in the belief that those contributions are of most lasting value, which add to the better understanding of the mechanism of symptoms and of the action of therapeutic agents. To this end the interrelationships of heat production, respiratory exchange, the respiratory function of the blood, and the circulatory mechanism must be kept constantly in mind. Furthermore, it has become apparent that the study of the total energy transformations in disease should no longer be confined to the post absorptive state, but that the effect of the ingestion of foods and the cost of muscular work should receive further investigation.

CALORIMETRY IN MEDICINE

WILLIAM S. McCANN

From the Medical Clinic of the Johns Hopkins Hospital

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INTRODUCTION

In the Aphorisms of Hippocrates occur the following interesting statements:

The aged endure fasting most easily; next adults; next young persons, and least of all children, especially such as are most lively.

Growing bodies have the most innate heat; they therefore require the most nourishment, and if they have it not they waste. In the aged there is little heat, and therefore they require little fuel, for it would be extinguished by much. Similarly fevers in the aged are not so acute because their bodies are cold. (Charles Singer (274).)

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INTRODUCTION

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After more than twenty-three centuries the correctness of the observations of the Father of Medicine is attested by numerous measurements of this innate heat, which the Greeks recognized as a fundamental condition of life.

The foundations of our modern knowledge of the processes involved in the production of animal heat were laid by Lavoisier when he discovered that the amount of ice melted by a guinea-pig parallels the amount of carbon dioxide given off by the animal. He drew the analogy between the emission of heat, the absorption of oxygen and the production of carbon dioxide by a burning candle and by a living animal, and recognized the identity of the processes involved. The plan was broadly conceived by Lavoisier and the foundations firmly laid.

The structure which has been erected on the work of this great Frenchman, though still incomplete, has reached enormous proportions. The history of its development has been admirably told by Lusk. Except for the mention of a few of the principal events this review will not be concerned with the history of normal metabolism. The discovery of the mechanical equivalent of heat by Joule in 1842, of the law of conservation of energy in 1845 by Mayer and Helmholtz, studies by Liebig of the composition of foods and of the tissues into which they are converted, and the final correlation of these discoveries in the masterly work of Carl Voit and Pettenkofer; these events mark the principal epochs in the history of calorimetry.

Curiosity as to the significance for medicine of this new knowledge was evinced very early. The respiratory exchange of phthisical patients was studied by Nysten (228) in Paris in 1811. Regnault and Rieset (249) about 1850 expressed a desire to install suitable apparatus in the hospitals of Paris for the study of the respiration of man in pathological states. Among the earliest studies of Pettenkofer and Voit (241) was that of a man with leukemia. These sporadic efforts yielded little or nothing to medicine because of their prematurity. Before one could measure or detect the abnormalities of the metabolism in disease it was necessary to have a clear definition of the nature and limits of magnitude of the normal metabolic processes.

It is within only the most recent years that the definition of normal values in metabolism has been sufficiently clear to permit the widest use of calorimetry in medicine. The time is now ripe for the practitioner to sum up the knowledge in this field in order to see how he may use it.

Much important information is available concerning the quantitative changes in the heat production in disease. Fever is an every day problem of the physician and calorimetry has much to offer in knowledge of the regulation of temperature. Valuable contributions have been made concerning the effects of drugs and of the secretions of ductless glands, as for instance, in exophthalmic goitre. The treatment of myxedema may be accurately controlled as never before.

The interrelationships of the metabolism with the functional demands on the heart and lungs are of the utmost importance to the practitioner of medicine. Because the demands of the metabolism determine the volume output of the heart and the rate of ventilation of the pulmonary alveoli the physician should know something of the metabolic cost of muscular effort, the mechanical efficiency of his patient. If he understands these things failure of the heart in exophthalmic goitre will lose much of its mystery for him. The proper dietaries in various diseases, long a matter of guess work or subject to individual whims or fads, may now be prescribed with definite knowledge. Most important of all, the energy demands of growing children may be definitely determined. No less fascinating or important is the view unfolded by indirect calorimetry of the intermediary processes of metabolism in a disease such as diabetes.

So far nothing has been said of the diagnostic use of calorimetry, though this use is the chief one by which it is known to the profession at large. In the writer's opinion the measurement of metabolism for diagnosis is the least valuable of all the contributions of calorimetry to the clinic, the most abused and the most dangerous.

Apparatus and methods

It is not considered to be within the scope of this article to enter into a description of the numerous forms of apparatus used in animal or human calorimetry. As sources of such information the reader is referred to articles by Murlin (218), Lusk (166), Carpenter (59), and Krogh (151a). In general three methods have been employed: (*a*) direct calorimetry; (*b*) respiration calorimeters; (*c*) indirect calorimetry.

Direct calorimetry has been carried out by the use of apparatus such as that of Reichert (250), Ott (230), Paschutin (156) and others (80). Concerning the Paschutin type of calorimeter very little has appeared in the English, German or French literature. A considerable bibliography of the Russian literature of calorimetry has been compiled for the writer by Dr. William A. Perlzweig.

Direct calorimetry involves the physical measurement of heat eliminated from the body by means of radiation, conduction, convection, and the vaporization of water from the skin and lungs. It must take into account corrections for heat stored in the body if the body temperature rises during the period of observation: a corrrection of positive sign, or a similar correction of negative sign if the body temperature falls. For these corrections the specific heat of the body should be known accurately. The heat production is the algebraic sum of the heat eliminated and the correction for change in body temperature.

Another phase of direct calorimetry is that of determination of the heat of combustion of foodstuffs burned in a bomb calorimeter. (Riche (255).) If the heat of combustion of 1 gram of pure dextrose be determined directly, and if from the chemical formula for dextrose a calculation be made of the amount of oxygen required to completely burn 1 gram of dextrose to CO_2 and H_2O, then one may calculate the heat value of any given quantity of oxygen used in oxidation of dextrose. Similar calculations have been made for the other foodstuffs, but in the case of protein a deduction is made of the heat value of end products of protein metabolism found in the urine and feces. A. V. Hill, Meyerhof and others have used minute and very accurate differential calorimeters, which are capable of measuring the heat of small isolated muscles, ova, small animals, and even of the heat produced in the agglutination of bacteria by an immune serum. (Bayne-Jones.)

Indirect calorimetry is the method of calculating heat production by the measurement of the carbon dioxide and oxygen exchanged in the respiration. The validity of the method has been established beyond a doubt by the simultaneous measurement of heat by physical means, and of the gas exchange in a respiration calorimeter. Such calorimeters exist in this country in the laboratories of Graham Lusk, of the Russell Sage Institute of Pathology in Bellevue Hospital under the direction of DuBois, at the Nutrition Laboratory of the Carnegie Institution directed by F. G. Benedict, in the department of Agriculture in Washington, and at Pennsylvania State College. Abroad there is the respiration calorimeter of Rubner in Berlin, the first successful apparatus of its kind. All of these employ the principles of Regnault and Rieset for the measurement of respired gases.

DuBois (95) recorded the accuracy of the Russell Sage Calorimeter as follows:

> In observations lasting three or four hours the heat production, carbon dioxide elimination and oxygen consumption, as determined by alcohol and electrical tests can be measured with an average error of 0.9, 0.6, and 1.6 per cent, respectively. Such a comparison of the direct and indirect methods establishes the validity of indirect calorimetry beyond a doubt, so that is possible by the use of much simpler apparatus to measure the respiratory exchange alone as a basis for calculating the energy transformations of life.

For the principles of the calculation of the heat production indirectly from the respiratory exchange and urine nitrogen excretion the reader is referred to Zuntz and Schumburg (304), Lusk (166), Benedict and Carpenter (25), and other sources (95, 151). For the complete and accurate calculation of heat production the measurement of both respiratory gases is essential, because the heat value of a unit quantity of either carbon dioxide or oxygen varies with the nature of the foodstuff being oxidized. When fat is burned the caloric value of 1 liter of oxygen is 4.686, whereas when carbohydrate is oxidized 1 liter of oxygen is equivalent to 5.047 calories. Thus the heat generated as calculated from the oxygen consumed or carbon dioxide excreted varies with the non-protein respiratory quotient, which normally lies between the limits of 0.71 (fat) and 1.0 (carbohydrate).

Recently numerous forms of simple apparatus for clinical use have been devised (35). For most of these only one of the respiratory gases is measured. Usually when a single gas is the basis of calculation the one selected is oxygen, because the absorption of oxygen is less affected by abnormalities of respiration than is carbon dioxide. This latter gas exists in such labile combination with bases in the body fluids that overventilation of the lungs will result in an excretion of CO_2 at a rate greater than the actual production of the gas by the oxidations of the body. If overventilation occurs during a period of observation with any apparatus which determines CO_2 alone an erroneous measurement of the heat production will be obtained, which will be much higher than the true value.

In all methods of measuring the respiratory exchange there are inherent difficulties of great magnitude. If one gas alone is measured it is much more difficult to detect an error. If both gases are determined the measurement of one checks the other. In the hands of well trained workers reliable results may be obtained with simple apparatus. The great danger arises from the results of poorly trained or careless observers, who neglect to take adequate precautions to insure the accuracy of their determinations. To base a diagnosis upon the results of such metabolism tests, in which innumerable sources of error may remain undetected, is an abuse of science, an insult to the clinical art, and a crime against the patient.

Total energy requirements in disease. Physiologists have made available for the economist data of the utmost importance, upon which depend the solution of the problems of food supply so vital to a nation in the grip of modern warfare. These problems are becoming steadily more significant for a world at peace as the growth of population makes it approach the limit which the earth is capable of supporting. The same data, which are so useful to the economist, afford points of departure for the investigation of the energy requirements in disease. Such investigations determine not only the dietary needs in sickness, but furnish a more complete understanding of many of the faulty mechanisms of the diseased organism.

In a study of the effect of any given disease upon the total energy requirement it is necessary to have some means of comparing that of individuals suffering with that disease with that of normal individuals of the same size, shape, age and sex. For this comparison it has been found that the determination of the *basal metabolism* serves best. This furnishes a measure of the overhead cost of maintenance of the individual. In addition to the "overhead" it is necessary to know the effect of food on the energy transformations, the *specific dynamic* action of food, and what may be the cost to the individual of the performance of muscular work, a cost which depends upon the *mechanical efficiency* of the individual.

PART I. BASAL METABOLISM

The term *basal metabolism* was introduced into English by Lusk as the English equivalent of the German "Grundumsatz." It was originally intended to mean the metabolism of an individual at the lowest ebb of functional activity. However, as the minimal heat production probably occurs during sleep in the early morning hours, in practice measurements have come to be made at a more convenient time of day on subjects who are awake. The *standard basal metabolism* is the heat production of an individual at complete muscular rest in the "nuchtern" or post absorptive condition (fourteen to sixteen hours after the last ingestion of food), in an external environment of about 33°C. (comfortable clothing). These are the conditions under which most of the measurements have been made upon which normal standards are based.

a. Surface area and the surface area law

From the beginning investigators have sought to find some physical measurements of an individual with which the observed heat production could be correlated in an attempt to predict with accuracy the metabolism of other normal individuals. For this purpose metabolism has been referred chiefly to the body weight and to the skin surface area. The idea that the basal metabolism is proportional to the body surface area is an old one, having been proposed by Sarrus and Rameaux as early as 1838. (Harris and Benedict (118).) It originated in the conception that the heat loss is proportional to the body surface and that, since the body temperature is kept approximately constant, there must be a causal relationship between the extent of body surface and the heat production of the body.

Almost simultaneously, about 1883, Rubner and Richet presented experimental evidence tending to show that the basal metabolism is proportional to the body surface. Following this an immense amount of confirmatory evidence was brought out in support of the so called "Surface Area Law," not only as applied to man, but to small and large animals of all kinds. (E. Voit; Armsby, Fries, and Braman (118.))

The study of the applicability of the surface area law made it necessary to have an accurate means of determining the area of the skin surface. For adults the most commonly used formula for this purpose was that of Meeh, which stated that body surface was proportional to the two-thirds power of the weight. Other formulae like those of Lissauer and of Rubner and Heubner which differ from Meeh's only in the constant term, have been used for the surface area of children. Howland and Dana (133) have likewise developed a formula from the data of Meeh's original measurements. D. DuBois and E. F. DuBois (72) after making a series of the most careful and painstaking casts of the body, weighing the paper patterns, were able to compute the skin area from a series of measurements of the body by dividing it up into geometrical figures. This work was known as the Linear Formula, which is the most accurate means of determining body surface, and one which should still be used for very obese persons or for individuals of extremely abnormal shape. It has been found to hold for children over two years of age by Sawyer, Stone and DuBois (265). The average error for the *Linear Formula* is somewhat under 2 per cent. It is a time consuming procedure to make all of the required measurements.

Later DuBois and DuBois (73) devised an easier though slightly less accurate means of predicting surface area from the height and weight. This formula is as follows:

$$A = \text{weight}^{0.425} \times \text{height}^{0.725} \times 71.84$$

where A = area in square centimeters the weight being in kilograms and the height in centimeters. This formula has been found by DuBois to be accurate within the limits of ± 5 per cent.

Following this Benedict (34) in 1916 described a photographic method of determining surface area. By this method the subjects are photographed in suitable positions and the photographs are measured by means of a planimeter. The area of the body determined in this way agrees closely with the results obtained by the DuBois height-weight formula.

These methods have shown how totally inadequate was the formula of Meeh, with which the average error is 16 per cent, with a maximal variation of 36 per cent. In view of this fact it seems highly improbable that the Lissauer formula for the surface area of children is any more accurate than that of Meeh to which it is entirely similar. (Meeh's formula is $A = 12.3 \times \sqrt[3]{w^2}$ Lissauer's $A = 10.3 \times \sqrt[3]{w^2}$). Benedict and Talbot (38) found that Lissauer's formula could be used for obtaining the surface area of children provided that the value of the constant term was varied with different weights.

Faber and Melcher (86) have tested the DuBois height-weight formula in the measurement of area of infants under two years of age. In a series of 100 newborn babies, the area could be computed from a slightly modified height-weight formula with an average accuracy of ± 2.5 per cent. The modified formula is $A = \text{weight}^{0.425} \times \text{height}^{0.725} \times 78.50$.

b. Normal standards for the basal metabolism of adults

As work was done with the more accurate measures of surface area it became apparent that the original statement of the Rubner-Richet law would require modification, for it was found that age and sex had distinct effects upon the metabolism of man. Aub and DuBois (10) reviewed the available data on normal subjects up to 1917 and from these came to the conclusion that age and sex should be taken into account. They proposed a tentative series of standards for the average heat production per square meter of skin area per hour for normal individuals from fourteen to eighty years of age. From these average figures the normal metabolism was found to vary between the limits of ± 10 per cent.