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Monographs on Biochemistry

THE RESPIRATORY EXCHANGE OF ANIMALS AND MAN

BY

AUGUST KROGH, PH.D.

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THE RESPIRATORY EXCHANGE

OF

ANIMALS AND MAN

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GENERAL PREFACE.

The subject of Physiological Chemistry, or Biochemistry, is enlarging its borders to such an extent at the present time, that no single text-book upon the subject, without being cumbrous, can adequately deal with it as a whole, so as to give both a general and a detailed account of its present position. It is, moreover, difficult, in the case of the larger text-books, to keep abreast of so rapidly growing a science by means of new editions, and such volumes are therefore issued when much of their contents has become obsolete.

For this reason, an attempt is being made to place this branch of science in a more accessible position by issuing a series of monographs upon the various chapters of the subject, each independent of and yet dependent upon the others, so that from time to time, as new material and the demand therefor necessitate, a new edition of each monograph can be issued without reissuing the whole series. In this way, both the expenses of publication and the expense to the purchaser will be diminished, and by a moderate outlay it will be possible to obtain a full account of any particular subject as nearly current as possible.

The editors of these monographs have kept two objects in view: firstly, that each author should be himself working at the subject with which he deals; and, secondly, that a *Bibliography*, as complete as possible, should be included, in order to avoid cross references, which are apt to be wrongly cited, and in order that each monograph may yield full and independent information of the work which has been done upon the subject.

It has been decided as a general scheme that the volumes first issued shall deal with the pure chemistry of physiological products and with certain general aspects of the subject. Subsequent monographs will be devoted to such questions as the chemistry of special tissues and particular aspects of metabolism. So the series, if continued, will proceed from physiological chemistry to what may be now more properly termed chemical physiology. This will depend upon the success which the first series achieves, and upon the divisions of the subject which may be of interest at the time.

R. H. A. P.
F. G. H.

PREFACE.

THE subject of the respiratory exchange of animals is not one of physiological chemistry but rather of chemical physiology. It deals with very few substances, and with their quantities not their qualities. The relations between respiratory exchange and functional activity have been excluded from the scope of the present monograph, which deals therefore with one very limited problem only: the quantitative aspect of the catabolic activity of the living organism as living.

To give an exhaustive account of the work done even in this restricted field has not been attempted, but I have endeavoured to trace out the essential lines of study, to state the fundamental problems, and to indicate the solutions of them so far as such solutions appear to have been reached—with what amount of success it is for the reader to judge.

For my own part I have felt the difficulties of my task so acutely that I cannot doubt but that they must have been very imperfectly overcome, and I shall be very grateful to have errors and omissions pointed out to me.

AUGUST KROGH.

COPENHAGEN, *September*, 1915.

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RESPIRATORY EXCHANGE OF ANIMALS AND MAN

INTRODUCTION.

THE respiratory exchange of an animal in the widest sense of the term means the exchange of gaseous substances taking place between the organism and the surrounding atmosphere, and it is defined not by any physiological difference between the part played within the body by these substances and others but solely by practical considerations of convenience. The investigation of the gaseous exchange requires special methods and a technique which is rather different from that employed in other branches of biochemical work. In most cases quantitative determinations of gaseous exchange can be made only by means of more or less complicated respiration apparatus, the manipulation of which is supposed to require a great deal of special training.

The study of the gas exchange of organisms dates back very far, but the difficulties in dealing with gases delayed progress for a very long time and are responsible to a certain extent for the present unsatisfactory state of our knowledge regarding some of the fundamental problems encountered.

It was first shown by John Mayow [1668] that a gas—spiritus nitro-aereus = oxygen—is constantly absorbed by animal organisms. Nearly a hundred years later [1757] Black discovered that "fixed air," what we now call carbon dioxide, is produced and eliminated during expiration; but Lavoisier [1777] was the first to understand the significance of the respiratory exchange as the result of a process of combustion going on within the body, and by which the carbon and hydrogen of the animal tissues are combined with oxygen to form carbon dioxide and water. Lavoisier was the first also to make quantitative measurements of the oxygen absorption and CO_2 elimination, and so to determine the respiratory exchange in the sense in which this term is usually employed.

Lavoisier and Seguin [1817] stated expressly that the nitrogen of the atmosphere does not take part in the respiratory processes, and for a long time these were taken to consist exclusively in the exchange of oxygen and carbon dioxide. By the famous researches of Regnault and

Reiset [1849] it was found incidentally that hydrogen and methane are sometimes exhaled from the animal body, and these authors concluded further from their experiments that the atmospheric nitrogen was not completely inactive but did take a certain, though very variable, part in the respiratory processes. A few other gases have since been supposed or shown to be regularly or occasionally exhaled from the body; but while the exhalation of carbon dioxide in all animals and the absorption of oxygen in almost all belong to the fundamental functions of the organism the other gases are of comparatively minor importance.

These latter are briefly dealt with in a special chapter, the third, of the present monograph.

The respiratory exchange in the strict sense of the term comprises only the oxygen intake and the elimination of carbon dioxide, and with the quantitative aspect of these processes it is intended to deal more fully, treating first their general physiological significance (Chapter I), then the methods of studying the respiratory exchange quantitatively (Chapter II), and finally attempting a review of the results obtained (Chapters IV to IX).

A comprehensive treatment of almost the whole of this field (excluding the results obtained on invertebrate animals) has been given before by Jaquet in 1903 [Ergebn.],[1] and parts of it have been treated repeatedly. Reference must be made especially to Oppenheimer's "Handbuch der Biochemie" [Op.][1] in which Loewy has written an account of the respiratory exchange of man and warm-blooded animals, while Cronheim has treated the cold-blooded vertebrates and Weinland has brought together the literature concerning the biochemistry of the invertebrate animals. R. Tigerstedt has described respiration apparatus and methods in his "Handbuch der physiologischen Methodik" [T.M.],[1] and in Winterstein's "Handbuch der vergleichenden Physiologie" [W.][1] he has given a very useful review of the temperature and heat production of animals both warm-blooded and cold-blooded.

The writer feels greatly indebted to these predecessors and to several others. Only by constant reference to them has it been possible to trace out a course, more or less satisfactory, through the ocean of literature.

[1] The abbreviations here given are used in the following chapters for reference to "comprehensive treatises," the titles of which are given in the bibliography on p. 151.

CHAPTER I.

THE PHYSIOLOGICAL SIGNIFICANCE OF THE EXCHANGE OF OXYGEN AND CARBON DIOXIDE.

LEAVING out of account the mechanism by which the gas exchange is brought about, its physiological significance lies in the catabolic processes of which the gas exchange furnishes quantitative evidence.

The study of the gas exchange has been utilized in three main directions:—

(1) To establish the carbon balance of the organism;

(2) to determine the nature of the substances catabolized;

(3) to measure the total catabolism.

In many cases the respiratory exchange appears to have been in itself the object of quantitative physiological research, without further thought about its significance. It will be shown, however, that such determinations fall in reality under the third and sometimes the second of the above heads, and are to be considered as more or less approximate determinations of the amount of energy transformed from a potential to a free state.

The Carbon Balance of the Organism.

In order to establish the carbon balance it is necessary only to measure the output of carbon dioxide, which simplifies considerably the technique of the respiration experiment. On the other hand the experiments must be of long duration, and cover at least the greater part of the twenty-four hours or any longer period for which it is desired to establish the balance. The results of short experiments are sometimes very misleading as pointed out repeatedly by Rubner. The amount of carbon excreted in twenty-four hours is found from the respiration experiment and analyses of urine and fæces, and is compared with the intake of carbon in the food.

Experiments of this sort were first made by Ranke, using Pettenkofer's respiration apparatus [1862], and have since been extensively used by Pettenkofer, Voit, Rubner, and their pupils. They have

rendered excellent service by the clearing up of various problems, but more complete determinations are now largely taking their place.

The Respiratory Quotient.

A determination of the nature of substances catabolized is possible within certain limits by means of the respiratory quotient, the relation by volume of the carbon dioxide eliminated to the oxygen absorbed or by weight of the O_2 contained in the eliminated CO_2 to the O_2 absorbed, as first shown by Regnault and Reiset.

This possibility depends on the fact that a definite relation exists for each substance between the oxygen consumed and the carbon dioxide formed in its catabolism.

For all carbohydrates the respiratory quotient is 1.

$$C_6H_{12}O_6 + 6\,O_2 = 6\,CO_2 + 6\,H_2O.$$

For fats the respiratory quotient is not absolutely the same for all as the composition varies, but the differences are small. The average composition of fat is 76·5 per cent. C, 12 per cent. H, and 11·5 per cent. O. The catabolism takes place according to the equation—

$$100 \text{ gr. fat} + (76{\cdot}5\tfrac{32}{12} + 12\tfrac{16}{2} - 11{\cdot}5) \text{ gr. } O_2 = 76{\cdot}5\tfrac{44}{12} \text{ gr. } CO_2 + 12\tfrac{18}{2} \text{ gr. water,}$$

or

$$100 \text{ gr. fat} + 288{\cdot}5 \text{ gr. } O_2 = 280{\cdot}5 \text{ gr. } CO_2 + 108 \text{ gr. water.}$$

The 280·5 gr. CO_2 contain $280{\cdot}5\tfrac{32}{44} = 204$ gr. O_2 and the respiratory quotient is therefore $\frac{204}{288{\cdot}5} = 0{\cdot}707$.

Similar computations can be made for proteins, but as the percentage composition of different proteins is not the same, and as the catabolism is incomplete and to a certain extent variable, the results may vary from about 0·78 to 0·82. The average respiratory quotient of protein is generally taken as 0·80.

The respiratory quotient of alcohol is 0·667.

The respiratory quotients met with in animals usually lie between 0·97 and 0·72. When nothing further has been determined a low respiratory quotient will indicate qualitatively that the material catabolized is chiefly fat and protein, and a high that it is chiefly carbohydrate and protein; but quantitative results cannot be obtained. When the amount of protein catabolized is known, generally in the form of the quantity of nitrogen in the corresponding urine, the corresponding quantities of O_2 and CO_2, which have been given by Zuntz as 8·471 gr. = 5·923 litre O_2 and 9·347 gr. = 4·754 litre CO_2 per gr. N

in the urine,[1] are subtracted from the measured respiratory exchange. The respiratory quotient for the remaining "non-protein" gas exchange is thereupon formed, and can be utilized for a quantitative computation of the distribution of the metabolism on fat and carbohydrate. Zuntz and Schumburg [1901] have compiled the following table, showing the distribution directly from the non-protein respiratory quotient :—

TABLE I.

R. Q.	Per 1 Litre Oxygen.		
	Glycogen Catabolized, gr.	Fat Catabolized, gr.	Heat Produced, cal.
0·71	0·0000	0·5027	4·795
0·75	0·1543	0·4384	4·829
0·80	0·3650	0·3507	4·875
0·85	0·5756	0·2630	4·921
0·90	0·7861	0·1753	4·967
0·95	0·9966	0·0877	5·012
1·00	1·2071	0·0000	5·058

I give as an example the calculation of one 8-hour period from a series of determinations made on two Eskimo subjects by A. and M. Krogh. They found

Nitrogen in urine gr. 34·93 corresponding to a respiratory exchange of 34·93 × 5·923 = 206·9 litres oxygen and 34·93 × 4·754 = 166·0 litres CO_2

The total gas exchange during the period was	405	lit. O_2 and	331	lit. CO_2
The protein metabolism corresponded to	206·9	,, ,,	166	,,
The non-protein metabolism therefore to	198·1	,, ,,	165	,,

The respiratory quotient of the non-protein metabolism was $\frac{165}{198{\cdot}1} = 0{\cdot}833$. By interpolation in Table I we find that this corresponds to 0·510 gr. glycogen and 0·293 gr. fat per litre oxygen. The quantities of the different foodstuffs actually catabolized by both subjects during the period have been therefore

Protein	34·93 × 16 = 218 gr.
Glycogen	198·1 × 0·510 = 99 ,,
Fat	198·1 × 0·293 = 58 ,,

Calculations such as these rest upon the assumption that no substances are catabolized except carbohydrates, fats and proteins, and further that no syntheses of these substances or others take place.

[1] This computation is valid only for man and for those mammals in which urea is the chief product of the protein catabolism.

While the first condition can generally be taken as fulfilled in normal higher animals fed on a normal diet, or fasting, the occurrence of synthesis, especially of fat, is by no means rare.

The formation of fat from carbohydrate is a process which takes place regularly by the fattening of herbivorous animals. In this case an oxygen rich substance (containing 53 per cent. O and 40 per cent. C) is converted into another which is very poor in oxygen (11·5 per cent. O and 76·5 per cent. C), and it is obvious that some oxygen must be liberated by the conversion. This oxygen will replace the corresponding amount of absorbed oxygen in the catabolic processes going on simultaneously, and the quotient will rise. As a matter of fact the quotient does often rise above unity as first observed by Bleibtreu on geese (quotients up to 1·38) and since confirmed in a number of similar cases.[1]

Low quotients may be produced, on the other hand, by the formation and storage of carbohydrate from protein as in diabetes. Magnus-Levy [1894] has calculated, however, that when carbohydrate is formed from protein the respiratory quotient cannot become lower than 0·68. When lower quotients are observed as in hibernating animals (p. 124) they must, when not due to experimental errors, indicate either formation of carbohydrate from fat, incomplete oxidation by which organic acids are formed to a certain extent instead of CO_2, or some other metabolic process of an unknown nature.

It is obvious that the processes mentioned may go on to a certain extent even when the quotient remains within the limits 0·72 to 0·97, and a certain caution is therefore necessary when the distribution of the metabolism on the different food-stuffs is deduced from the respiratory quotient.

Such caution appears doubly necessary when it is remembered that the respiratory quotient, as determined from an experiment, depends on the elimination of carbon dioxide and not directly on the production of this gas in the animal economy. As will be shown below (p. 16) carbon dioxide is very apt to become stored in the tissues and the blood for some time, while on the other hand it may under certain conditions be washed out by the ventilation of the lungs in excess of the production.

[1] It should be borne in mind, however, that in herbivorous animals a considerable amount of carbon dioxide is often produced by fermentation in the gut, thus producing an apparent increase in the respiratory quotient, which has nothing to do with the metabolism of the animal itself (see later, p. 53).

The Measurement of Total Catabolism. Direct and Indirect Calorimetry.

The adequate term for expressing total metabolism is the calorie, and the standard method of measuring it is the biocalorimetric. Biocalorimetry alone will give perfectly reliable determinations of the sum total of the energy transformation independently of the nature of the metabolic processes.

The biocalorimetric method has until recently been rather difficult to manipulate, when accurate results were aimed at. It has required and does generally require costly and complicated apparatus, and there has been therefore and still is a wide field for indirect calorimetry by means of measurements of the respiratory exchange. With the recent advances in calorimetric methods due to Atwater and Benedict, Rubner [1911], and especially A. V. Hill, there is every reason to think that direct determinations of the total metabolism will be preferred to indirect in many cases, and for all classes of animals, as it is undoubtedly preferable theoretically.

On certain points, however, the determination of the respiratory exchange possesses advantages over the direct calorimetry which should secure its application.

The determination of absorbed oxygen is distinctly more sensitive than the determination of heat produced by organisms of very small size. 2 cub. m.m. of oxygen absorbed in ten hours is at present about the limit at which fairly accurate determinations can be made. This corresponds to 10 mg. calories in the same time, or 1 per hour. The limit of accuracy in the calorimetric measurements of Bohr and Hasselbalch [1903] on the embryo of the fowl was about 100 mg. calories per hour.

In experiments on warm-blooded animals the determination of the respiratory exchange possesses this advantage over the direct calorimetry that it is not affected by changes in body temperature which may cause considerable errors in results obtained calorimetrically over short periods. This has been well shown by Williams, Riche and Lusk [1912] who found that in the second and third hour after a large meal of meat there was in the dog a discrepancy between the calorimetric results obtained directly and indirectly. During this period the body temperature and the increase in heat stored by the organism could not be accurately estimated from the increase in temperature in the rectum, because the temperature increment was not the same in all

organs, and was, especially, larger in the skin than in the rectum. Where rapid changes in metabolic activity are to be studied the respiratory exchange method is therefore distinctly preferable to the calorimetric, and for a large number of problems involving such changes the calorimetric method cannot be used at all.

The reliability of the respiratory exchange as an index of heat production in the body is variable and depends upon the nature of the metabolism.

As mentioned above the amount of oxygen necessary for the catabolism of 1 gr. carbohydrate, fat, or protein can be determined as well as the amount of carbon dioxide resulting from the process. On the other hand the amount of heat liberated can be measured calorimetrically *in vitro* or *in vivo* and compared with the gas quantities. The figures obtained by different investigators agree fairly well.

According to Loewy [Op.]

			Or 1 gr. CO_2 to	Relative Figures.
1 lit. CO_2 from	carbohydrate (starch)	corresponds to 5·047 Cal.	2·56 Cal.	100
,, ,, ,,	fat	,, ,, 6·629 ,,	3·37 ,,	131
,, ,, ,,	protein	,, ,, 5·579 ,,	2·84 ,,	110

The caloric equivalent of 1 litre of carbon dioxide is very different for the three principal sources of energy in the animal body, and it follows that determinations of CO_2 production can only be used for calculations of heat produced when the nature of the substances catabolized is known and does not vary during the experimental period.

For oxygen Loewy [Op.] finds that

			Or 1 gr. O_2 to	Relative Figures.
1 lit. O_2 from	carbohydrate	corresponds to 5·047 Cal.	3·53 Cal.	100
,, ,, ,,	fat	,, ,, 4·686 ,,	3·28 ,,	93
,, ,, ,,	protein	,, ,, 4·485 ,,	3·14 ,,	89

While all practically agree with regard to the caloric value of oxygen used for the catabolism of carbohydrate or fat, and the differences between the several carbohydrates and fats are insignificant, the results obtained for protein are not so concordant but vary from 4·3 (Magnus-Levy, 1894) to 4·75 (Pflüger, 1899) or 4·7 (E. Voit, 1903). As usually only a small fraction of the total heat is derived from protein the uncertainty with regard to the caloric value is not so serious as it might appear, and the differences between the caloric values of oxygen when used for the different processes are so small that an estimate of the

heat production of an animal, which is accurate to within some 3 per cent., can be obtained from determinations of the oxygen consumption alone, provided always that the catabolic processes comprise only the usual oxidations of carbohydrates, fats and proteins, and that syntheses of any of these substances do not take place or can be considered as quantitatively insignificant.

When both the oxygen consumption and the production of carbon dioxide are determined, and the protein metabolism is either estimated or measured from the nitrogen excretion, the respective amounts of carbohydrate and fat catabolized can be calculated from the respiratory quotient of the non-protein metabolism as mentioned above (p. 7, Table I); and as the caloric value of each of these substances is pretty accurately known the total heat production can be calculated with considerable accuracy. In the table by Zuntz and Schumburg given above, the caloric value of oxygen corresponding to the different respiratory quotients of the non-protein metabolism is included.

A number of experiments have been made on dogs (Rubner, 1894) and man (Atwater and Benedict; Benedict, 1907; Benedict and Milner [1907]), both during rest and during muscular work, in which the results of direct and indirect calorimetry were compared, while the quality and quantity of material catabolized were varied within very wide limits. The results, of which a typical example is given in Table II from Benedict's paper, usually agree to within 1 or 2 per cent., and on an average for a large number of experiments the difference is in most series only a fraction of 1 per cent. With higher animals the indirect calorimetry is therefore in almost all circumstances completely justified, when the respiratory quotient remains within the limits 0·71 to 0·99.

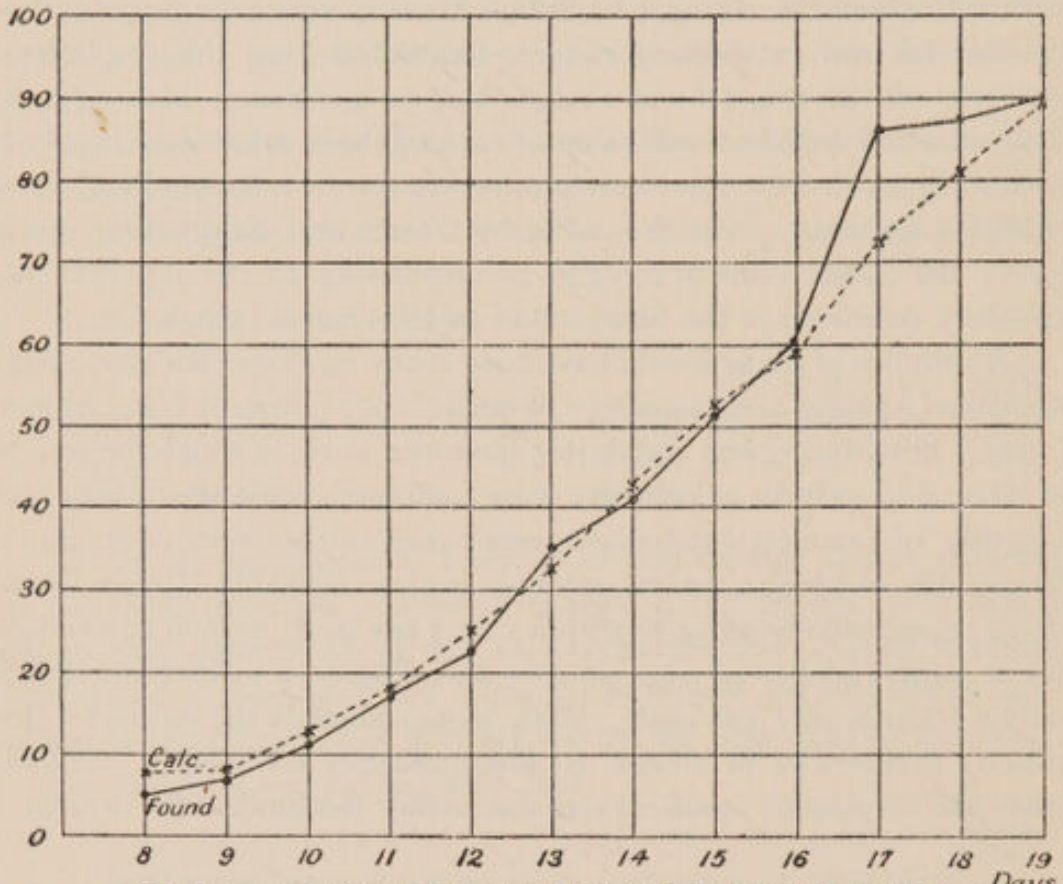
TABLE II.—Inanition Experiment on Man Lasting Seven Days.

Day.	N in Urine, gr.	O_2 Absorbed, gr.	CO_2 Eliminated, gr.	R.Q.	Heat Production from			Total Heat		Diff. Calc.-Found, Cal.	Diff. per cent. of Found.
					Protein, Cal.	Fat, Cal.	Carbohyd., Cal.	Calculated, Cal.	Found, Cal.		
1	12·24	533·6	569·9	0·78	318	1206	272	1796	1765	+ 31	+ 1·75
2	12·45	534·3	550·6	0·75	286	1407	97	1790	1768	+ 22	+ 1·24
3	13·02	535·7	545·1	0·74	303	1459	23	1785	1797	− 12	− 0·67
4	11·63	519·6	534·2	0·75	248	1381	105	1734	1775	− 41	− 2·31
5	10·87	491·0	496·4	0·74	221	1381	34	1636	1649	− 13	− 0·84
6	10·74	466·1	477·4	0·75	218	1238	91	1547	1553	− 6	− 0·39
7	10·13	466·4	475·6	0·74	204	1264	78	1546	1568	− 22	− 1·40

Bohr and Hasselbalch have compared the heat production and respiratory exchange of the embryo of the common fowl during almost

the whole period of incubation. The respiratory quotient shows that practically the only substance catabolized in this case is fat (R.Q. = 0·71). Though there are occasional discrepancies, especially at first, when the heat production and the respiratory exchange are both very slight, the agreement for the whole period is remarkable.

In one experiment, covering the period from the eighth to the nineteenth day of incubation, the measured total heat production was 12·16 cal. and the calculated 12·11. Fig. 1 shows the agreement



The heat production of the embryo measured directly and indirectly.

FIG. 1.

obtained in the single determinations. In all the experiments taken together they find a total heat production, from the third to the nineteenth day, of 12·58 cal. observed by direct calorimetry and 12·21 calculated from the respiratory exchange. This shows that no energy is stored by the synthesis of living tissues from dead protein, and that the indirect calorimetry can, therefore, be safely employed in growing organisms, where such syntheses take place.

In cases in which the catabolism is incomplete, or in which endothermic processes are taking place to a quantitatively appreciable extent, an agreement between the results of direct and indirect calori-

metry is not to be expected; it is just in such cases that a comparison would probably be very valuable, and might furnish a clue (*a*) to the nature of the processes taking place, when these are unknown, or (*b*) to a quantitative estimation of their extent in cases in which their nature was completely established. All those types of metabolism, common enough among invertebrate animals, which deviate from that accepted as normal for mammals ought, therefore, to be studied both directly by biocalorimetry and indirectly by respiration experiments. Several instances in which such an investigation is essential to the understanding of the processes taking place will be mentioned in the following.

An attempt in this direction has so far been made only by Meyerhof [1911] who studied the eggs of sea urchins and determined the absorption of oxygen as well as the heat production. The Calories produced per gr. oxygen absorbed (or small calories per mg.) are denoted by Meyerhof as the caloric quotient of the oxygen. With the ordinary catabolism of fats, carbohydrates and proteins the caloric quotients vary, as shown above, between 3·5 and 3·15.

In experiments on aquatic animals in which the oxygen is presented in a dissolved form, while the CO_2 liberated remains in a dissolved state and enters into combination with the carbonates of the sea water, certain corrections have to be applied to the observed caloric quotients in order to make them comparable to those obtained on air-breathing animals. The corrections amount, according to Meyerhof, in the case of the Echinoderm eggs, to – 0·176 Cal. per gr. O_2, but in the opinion of the writer the estimation is somewhat arbitrary.

Meyerhof found on eggs during segmentation caloric quotients of 2·6 (average, corrected), which is much below any of the possible quotients for normal catabolism. For the spermatozoa of the same animal (*Arbacia*) the quotient was about 3·1 or possibly normal, and for the eggs of *Aplysia* about 2·9. Meyerhof points out that in all cases a catabolism of fat (quotient 3·3) takes place, but assumes that this must be accompanied by other oxidations of an unknown nature and having a much smaller caloric quotient.

CHAPTER II.

THE METHODS EMPLOYED FOR MEASURING THE RESPIRATORY EXCHANGE.

General Principles.

BEFORE entering upon a review and discussion of the numerous methods and technical appliances used for the purpose of studying the respiratory exchange, it is desirable to emphasize certain principles which are, perhaps, more easily overlooked in gas exchange work than in any other; they are not peculiar to the study of the gas exchange, but are common to all scientific measurements.

It is a general principle that the accuracy of the measurements and the definition of the experimental conditions should correspond to each other.[1] In determinations of the respiratory exchange the conditions are usually very difficult to define. Determinations are usually made on "normal" animals, but a "normal animal" is an extremely vague definition. In a normal animal the respiratory exchange may often vary 100 per cent. and more, and to use methods, the results of which are reliable to within 1 or 5 per cent., in such a case is obviously waste of time. In most cases, however, the fault lies not so much in the methods being too fine, as in the definition of conditions which might be made more precise.

It is well known that muscular movements increase the metabolism considerably, and it is obvious that the investigation of the influence of other less potent factors must be made when muscular movements have been excluded. In experiments on animals this principle has very often been disregarded, and one of the most important improvements in technique is undoubtedly the introduction by Benedict and Homans [1911] of the recording cage (fig. 2 and fig. 6), which is put up in the animal chamber of a respiration apparatus, and which will record any shifting of the centre of gravity of the animal under experiment. Periods can then be selected during which the animal keeps quiet.

[1] Ostwald-Luther, "Physiko-chemische Messungen," 3 Aufl., Leipzig, 1910.

Several improved models of this arrangement have been described in later publications from the Nutrition Laboratory.

When muscular movements and tone must be absolutely excluded during a definite series of measurements the use of an anæsthetic or of curari becomes necessary. Tangl has introduced the regular use of curari for respiratory exchange purposes, and the results fully bear out the importance of this step in improving the definition of conditions.

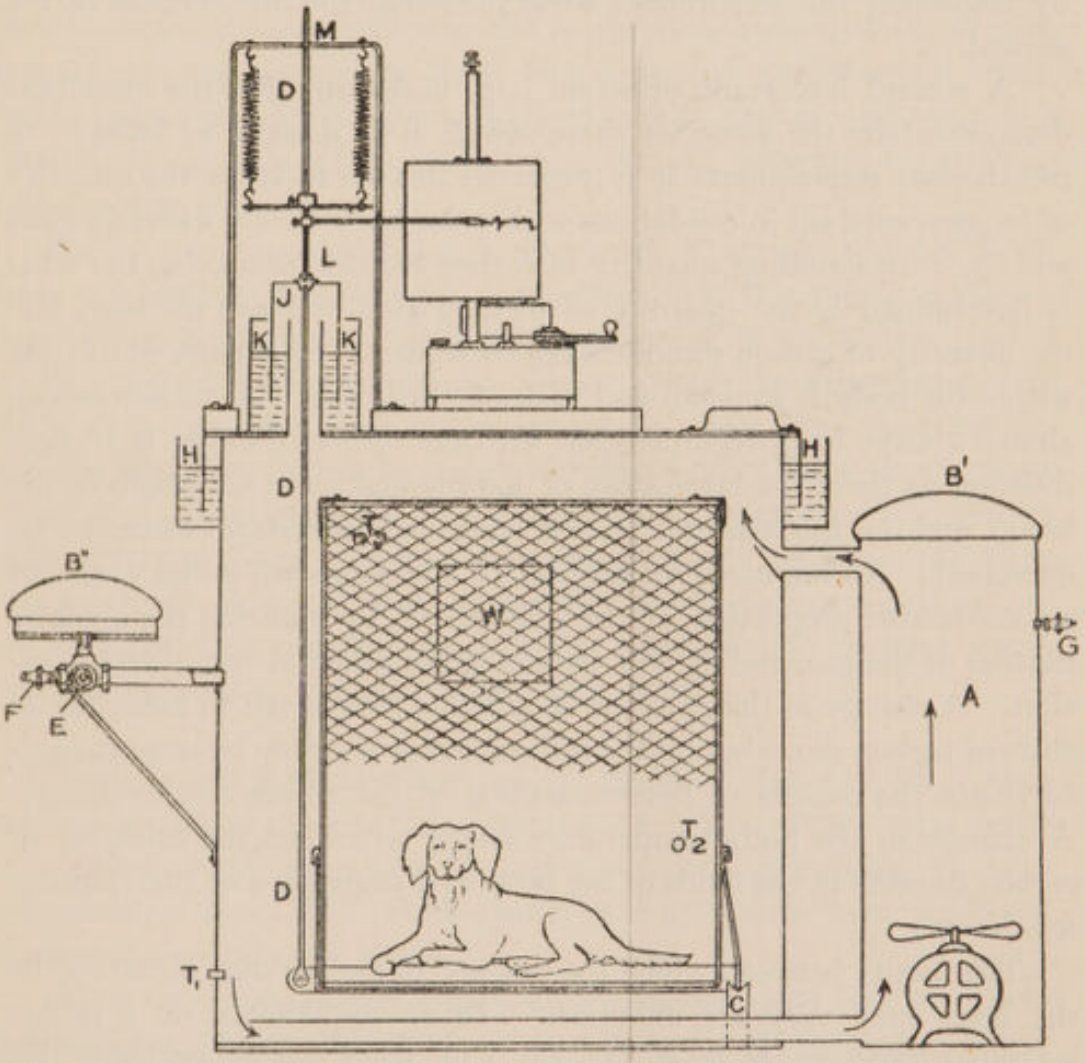


FIG. 2.—The recording cage. After Benedict and Homans. "Amer. J. Physiol.," **28**, 33.

Recently Raeder [1915] has substituted a prolonged urethane narcosis instead of curari for experiments on mammals. By putting off the experiment proper until a number of hours after the narcotization he obtains results of wonderful regularity.

For ordinary experiments involving the determination of the metabolism under "normal" conditions the rule initiated by Seegen and Nowak [1879]: never to begin an experiment just after the intro-

duction of an animal into the respiration apparatus, should be rigorously adhered to. The behaviour of an animal just after it has been handled and transferred is never normal, but becomes so only after a certain time, differing greatly of course with different animals. As pointed out by Krogh [1908], most respiration apparatus require also a certain period of accommodation, especially with regard to temperature, and serious sources of error in the determination itself are excluded by beginning the experiment some time after the introduction of the animal.

A second important principle is to make sure that the quantities determined are the same as those which it is desired to know. In metabolism experiments it is generally desired to know the quantity of oxygen used up in oxidations within the body during a certain time and the corresponding quantity of carbon dioxide produced, but what is determined is the quantity of oxygen absorbed into the body and the quantity of carbon dioxide exhaled from it. The store of oxygen within the body is so small and varies so little that the variations can almost always be disregarded, but with the carbon dioxide it is very different as there is a large store of loosely combined CO_2 both in the blood and in the tissues. Great care has therefore often to be exercised. An increased ventilation of the lungs will often wash out a considerable proportion of the stored CO_2 by lowering the alveolar tension of the gas, and it will then be replenished at some later occasion. A change in the reaction of a tissue cannot fail to influence its store of carbon dioxide, and the influence may possibly be large enough to vitiate the results of determinations of the respiratory exchange. A change in the body temperature finally will affect the solubility of carbon dioxide in the fluids of the body and probably also their affinity for the gas.

The limits between which the amount of carbon dioxide stored in the body may vary are unknown.[1] In an experiment on a rabbit weighing 1800 gr., at least 250 c.c. CO_2 were washed out from the body in excess of the production by artificial ventilation of the lungs during 1·5 hours. The observed respiratory quotient remained above unity all the time, rising to 1·8 at last, and the quantity washed out

[1] In a series of experiments which will shortly be published in "Skand. Arch. Physiol." Liljestrand has found that men of 60 kg. may wash out as much as 3-4 litres CO_2 during 30-40 minutes by increasing the ventilation from the normal to 13 litres per minute. A decrease of 1 per cent. in the alveolar CO_2 tension corresponds to a surplus elimination of 1 litre CO_2 or a little less.

per minute decreased slowly from 3·40 c.c. to 2·86 c.c. and then dropped suddenly to 1·6 c.c. in the last ten minutes before the animal died.

It follows from the above that when artificial respiration is performed the respiratory quotient is very apt to become abnormal and must vary with the amount of ventilation. In experiments with spontaneous breathing through cannulas, mouthpieces, or masks these instruments will often influence the ventilation, especially in subjects who are not accustomed to them and abnormal quotients will result. It has been found by Becker and Olsen [1914] that mental work of a certain type produces increased ventilation and consequently washing out of carbon dioxide.

As the possible variations in the store of carbon dioxide in the body are limited it is obvious that errors from this source must become proportionately smaller in experiments of long duration, and in 24-hour determinations they can almost always be disregarded. In many cases, however, it is impracticable to make long experiments, and the best plan then is to compare series of quite short experiments. When it is found that the CO_2 output either decreases or increases independently of the oxygen intake the quotients found are not to be relied upon as indices of the catabolic processes going on. It cannot be concluded with certainty on the other hand that a quotient which remains constant is the true catabolic quotient.

When repeated determinations of the same quantity have been made it is customary to average the results. An average ought never to be given, however, unless the necessary data for judging its value are published also. This fundamental rule has often been neglected in respiratory exchange work.

When only few determinations have been made the best plan is to publish them all, but when they number more than five the elements of the statistical theory of errors ought always to be applied, because it will often allow definite conclusions to be arrived at in cases where nothing can be seen from the untreated figures. Usually it will be sufficient to figure out what is called the mean "error" or "standard deviation" of a single determination (denoted μ) and the mean error of the average. To do this the average is formed and the deviation (d) of each result from the average calculated. The algebraic sum of these deviations must obviously be 0. The deviations are squared and the squares added together. Let the sum be Σd^2 and the number of deter-

minations n. The mean deviation of a single determination or the "standard deviation" [1] is then

$$\mu = \sqrt{\frac{\Sigma d^2}{n - 1}}$$

and the mean error of the series

$$\frac{\mu}{\sqrt{n}}.$$

As an example I have treated in this way some of the results obtained by Benedict and Carpenter in their study of the influence of mental work upon metabolism.[2] They found in twenty-two double experiments on twenty-two subjects that during 3-hour periods of mental

TABLE III.

	Mental Work Experiment CO_2 in 3 h. g. (a)	Control Experiment CO_2 in 3 h. g. (b)	$\frac{100\,a}{b}$. (c)	c − A. (d)	d^2. (e)
	101·13	84·51	119·9	+ 17·5	306
	94·00	111·99	83·9	− 18·5	343
	81·94	83·61	97·9	− 4·5	20
	106·09	97·11	109·3	+ 6·9	48
	101·60	97·63	104·0	+ 1·6	3
	113·94	105·14	108·2	+ 5·8	34
	89·07	85·73	103·8	+ 1·4	2
	116·87	120·39	97·0	− 5·4	29
	92·14	101·98	90·3	− 12·1	146
	98·48	99·44	99·1	− 3·3	11
	85·66	89·51	95·8	− 6·6	43
	95·07	104·80	89·8	− 12·6	159
	124·21	108·68	114·2	+ 11·8	140
	102·56	91·59	112·0	+ 9·6	92
	143·61	133·37	107·6	+ 5·2	27
	82·67	78·26	105·4	+ 3·0	9
	114·88	112·58	102·0	− 0·4	0
	92·76	82·75	112·0	+ 9·6	92
	100·08	110·14	90·8	− 11·6	135
	91·81	87·75	104·6	+ 2·2	5
	108·78	116·14	93·5	− 8·9	80
	103·17	91·58	112·8	+ 10·4	108
Average	101·84	99·76	A = 102·4		$\Sigma d^2 = 1832$

$$\mu = \sqrt{\frac{\Sigma d^2}{n-1}} = \sqrt{\frac{1832}{21}} = \pm 9{\cdot}3. \quad \text{Mean error of series } \frac{\mu}{\sqrt{n}} = \frac{9{\cdot}3}{\sqrt{22}} = \pm 2{\cdot}0.$$

$$A = 102{\cdot}4 \pm 2{\cdot}0.$$

[1] A much better name which has not yet come into general use is the "dispersion" of the series of determinations.

[2] U.S. Dep. of Agriculture, 1909. Bull. 208.

work and rest respectively, the quantities of carbon dioxide given in columns (*a*) and (*b*) of Table III were eliminated. These figures show rather wide variations and the question to be decided is: can it be concluded from them that the elimination of carbon dioxide is increased during mental work. The simplest way to treat the figures is to form the ratio between the CO_2 elimination during work and during rest. This has been given in column (*c*) and shows that on an average the excretion is 2·4 per cent. higher during mental work than during rest. The deviations of the individual results from this average are given in column (*d*) and squared in column (*e*). The sum of the squares is 1832, the standard deviation therefore $\mu = \pm 9{\cdot}3$ per cent., and the mean error of the series $\pm 2{\cdot}0$ per cent., which shows that it can not be concluded that there is any increase in carbon dioxide elimination during mental work though there may possibly be one amounting to anything from 0 to 6 per cent. Double the mean error is usually taken as the limits between which the true result must fall, provided always that the deviations are of a purely "accidental" character.

The units employed for expressing the respiratory exchange of animals are rather various and no definite usage has so far become established. The most rational plan, and that which is best adapted for comparisons with other quantitative work on metabolism, probably is to give the weights of gases absorbed or eliminated in a given time. This possesses the advantage, moreover, that the figures require no further qualification and that no doubt can arise about their meaning.[1] Usually, however, the quantities of gases are expressed by their volumes. The volume of a gas being absolutely indefinite, the expression by volume requires a further statement of conditions regarding temperature and pressure. In gas exchange work it is customary to give the volume measured dry at 760 mm. mercury pressure (temperature of mercury 0°) and 0° temperature, and when no other conditions have been definitely mentioned quantities given by volume must be presumed to have been reduced to 760 mm. and 0°. The actual measurements are practically always made at higher temperatures, at varying barometric pressures, and with gases either completely or partially saturated with water vapour. A very convenient table for reducing gas volumes measured moist (that is saturated) at pressures from 740 to 775 mm. and temperatures from 10° to 25° has been given by Hal-

[1] When gas quantities are expressed by weight the definition of the respiratory quotient must be slightly modified. The respiratory quotient is then the ratio of the weight of O_2 in the CO_2 produced to the weight of O_2 absorbed.

dane.[1] When the saturation is incomplete the pressure (in mm. Hg) of the water vapour present must be determined (usually indirectly) and subtracted from the total pressure. The further reduction is then carried out by means of the formula

$$V_{(0^\circ\ 760)} = V_{(t^\circ, p)} \cdot \frac{p}{760} \cdot \frac{273}{273 + t}$$

or corresponding tables.

Gas volumes measured dry at 760 mm. and 0° are reduced to weights by means of the following figures :—

1 litre	oxygen	weighs	1·429	gr.
1 ,,	carbon dioxide	,,	1·965	,,
1 ,,	nitrogen	,,	1·255	,,
1 ,,	hydrogen	,,	0·0895	,,
1 ,,	methane	,,	0·715	,,

The units of time most often employed in gas exchange work are, 24 hours, 1 hour, and 1 minute. Experiments on "normal" animals, in which no special definition of conditions is attempted, are usually calculated on the basis of 24-hour periods, and this is always the case when the carbon balance is the object under investigation. The 1-hour unit is employed in most cases, while the statement of results per minute is practically confined to short experiments on the pulmonary gas exchange of man and mammals. Some writers calculate the results of experiments made under special conditions such as complete muscular repose on the 24-hour basis. This appears to be irrational and misleading.

Classification of Methods.

The methods described for the determination of the respiratory exchange of animals are very divers as are indeed the problems to be solved. It is obvious that the same apparatus cannot be used for an ox and a mouse, and it would be strange if the same type of apparatus would be suitable. Between the mouse and the egg of an insect the difference in size is as great again and the methods employed must obviously differ. The time factor is equally important. Certain problems involve the determination of the respiratory exchange in long periods up to twenty-four hours or even more, while it is essential for the solution of others that determinations be made over very short periods, down to a few seconds. Methods must differ accordingly. There is finally the difference in respiratory medium to be considered.

[1] J. S. Haldane, "Methods of Air Analysis". London, 1912.

Respiration experiments on aquatic animals breathing dissolved oxygen differ greatly in technique, though not in principle, from the corresponding experiments on air-breathing forms. I shall make this last difference the basis of my classification and describe :—

1. The methods for studying respiratory exchange in air, and

2. The corresponding methods to be used with water as the respiratory medium.

I do not propose to describe in technical detail the large number of respiration apparatus constructed,[1] but I shall endeavour to characterize the different types of apparatus and to indicate their proper sphere of usefulness and their limitations.

Within each type we have a number of instruments, composed of essentially the same principal parts (e.g. air circulators, CO_2 absorbers, etc.). Each part exists in a variety of forms which differ greatly in their technical appearance, though they are intended for the same purpose. I do not propose to describe all or nearly all such forms but to select those which in my judgment are best adapted for their purpose and to indicate as far as my experience goes the most useful combinations. My descriptions are intended throughout as guides for the selection of instruments but not for their technical construction.

The methods for studying respiratory exchange in air fall naturally into two groups :—

1. A. The methods by which the total gas exchange is determined while the animal under experiment is enclosed in a suitable respiration chamber but otherwise not interfered with, so that the conditions may approach the normal life as nearly as possible. These methods can be applied to air-breathing animals of all classes and all sizes. They are especially suitable for experiments of rather long duration from about an hour upwards.

1. B. The methods by which the specific respiratory organs only are connected with a respiration apparatus. These methods will almost invariably interfere greatly with the freedom of movement of the animal. They are suitable therefore for determinations involving definite experimental conditions, e.g. narcosis, operations, etc. In practice they can be applied only to vertebrates of a certain size and over comparatively short periods only. A number of these methods

[1] Such descriptions must be sought in the original papers referred to and in Tigerstedt's "Handb. der physiol. Methodik".

are specially adapted to the study of the pulmonary gas exchange of man.

In both groups of methods we have two essentially different types of apparatus :—

(*a*) The closed space or Regnault type, and

(*b*) The air current or Pettenkofer type.

A Regnault apparatus consists of a closed vessel or system of vessels which must be absolutely airtight and in which the animal breathes the same air over and over again. Arrangements are provided for absorbing the carbon dioxide liberated and generally also for adding oxygen to replace that which is absorbed by the animal. The carbon dioxide is determined generally in the absorbing system, and the oxygen added is measured. For both gases a correction must in most cases be introduced to account for changes in composition or quantity of the air enclosed in the apparatus. The influence of this correction depends upon the volume of the apparatus which is therefore made as small as possible.

In the air-current apparatus atmospheric air is conducted in a uniform current through the animal chamber, and the changes produced in the air by the respiration of the animal are determined either

a in the outgoing air as a whole by absorption of the total quantity of carbon dioxide produced, or

β in a certain fraction of the outgoing air, in which case the total air current must be measured.

In most apparatus of the air-current type it is not essential that the animal chamber is absolutely airtight.

It follows from the above that each of the two types *a* and *b* has its own special sphere of applicability, and that they cannot be used indiscriminately without sacrificing the special advantages.

A closed-space apparatus is the only one which can be used with advantage for experiments involving a composition of the air breathed differing from the atmospheric, e.g. for experiments on the influence of varying oxygen percentages, and it must be used further for experiments in which it is desired to measure the exhalation of small quantities of gases other than carbon dioxide from the body.

In the closed-space apparatus a very accurate determination of the oxygen absorbed can be obtained with comparative ease and over short periods, and it is therefore indispensable, especially for the determination of the oxygen intake of very small animals.

The difficulty of making a large Regnault apparatus absolutely

airtight renders this type unsuitable for experiments on large animals,[1] in which also the difficulty and cost of dealing with the large quantities of carbon dioxide produced constitutes a very serious drawback.

In experiments of a long duration the excretions of the animal may render the use of a Regnault apparatus very difficult.

The air-current apparatus are in general much less complicated and much cheaper both initially and with regard to working expenses than closed-space apparatus of corresponding dimensions. They are therefore, and also because they need not be airtight, absolutely to be preferred for experiments on large animals (from the size of man and upwards) and also for experiments on smaller animals which have to last long. When it is desired to determine only the carbon dioxide produced the air-current apparatus can be of an especially simple and cheap construction.

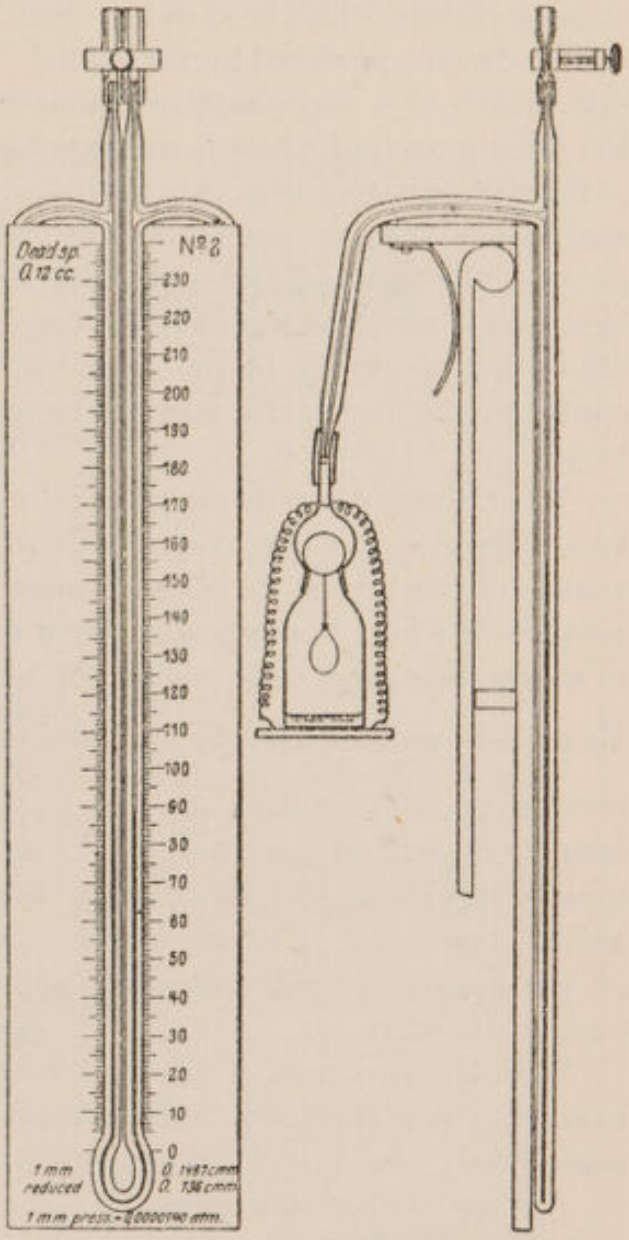


FIG. 3.—Krogh's micro-respiration apparatus. From "Biochem. Zeitschr.," **62**, 267.

1. A. (*a*) Closed Space Respiration Apparatus.

The simplest form of a closed-space respiration apparatus is the micro-respiration apparatus shown in fig. 3 (Krogh, 1914). It consists

[1] In the Regnault apparatus at the Landwirtschaftliche Hochschule in Berlin of 80 cub. metres a volume of 500 lit. air will often leak in (or out) during an experiment of twenty-four hours in spite of every precaution being taken to keep the inside pressure as near as possible the same as the atmospheric.

of a glass vessel, the size of which is selected according to the size of animal (not exceeding 1 or 2 gr.) experimented on. The bottom of the vessel is covered with a layer of 2 per cent. NaOH, which will absorb the carbon dioxide produced by the animal. The vessel is connected with one branch of a very sensitive manometer of narrow bore ($\frac{1}{2}$ mm.), the other branch of which is connected with an exactly similar vessel —the compensating vessel[1]—charged with the same volume of 2 per cent. caustic soda but without any animal. When an experiment is in progress the two vessels are placed in the same water-bath which is kept well stirred, and the whole is shut off from the atmosphere. The absorption of oxygen by the animal will then become accurately recorded by the manometer, and can be read off at intervals of suitable length.

When the two vessels are of equal or nearly equal volume a pressure difference of 1 mm. corresponds to $Vp + v$ where V is the gas volume of the animal chamber (= absorbing fluid and animal), p the pressure of 1 mm. of the fluid in the manometer (kerosene) expressed in atmospheres, and v the volume of 1 mm. of the manometric tube. Vp must be reduced to 0° by multiplication with $\frac{273}{273 + t}$ in which t is the temperature of the water-bath; v, which is very small compared with Vp, is reduced once for all to 0° and 760 mm. from the ordinary room temperature and the average barometric pressure. With an animal chamber of 25 c.c. each mm. variation in the pressure read off on the manometer will correspond approximately to 2 cub. mm. of oxygen absorbed.

With an instrument of this kind the oxygen absorption of a single insect egg weighing about 2 mg. has been followed in 10-hour periods from shortly after it was laid until the hatching of the larva.

A very similar apparatus was constructed earlier by Winterstein [1912]. The manometer consists of a drop of kerosene in a horizontal tube. This drop is set at 0 and the level of the mercury in the **U**-tube to the left (fig. 4) which is graduated in cubic millimetres is read. By the absorption of oxygen in the animal chamber the drop of kerosene is caused to travel, and whenever a reading is to be taken it is

[1] The use of a compensating vessel was introduced into the gas analysis by Petterson and adopted for respiration apparatus by Thunberg [1905] and Krogh [1906]. So long as the temperature of the compensating vessel remains the same as that of the animal chamber, the effects upon the manometer of all changes in barometric pressure or in the temperature of the bath in which both vessels are immersed are automatically compensated and have no influence upon the measurements.

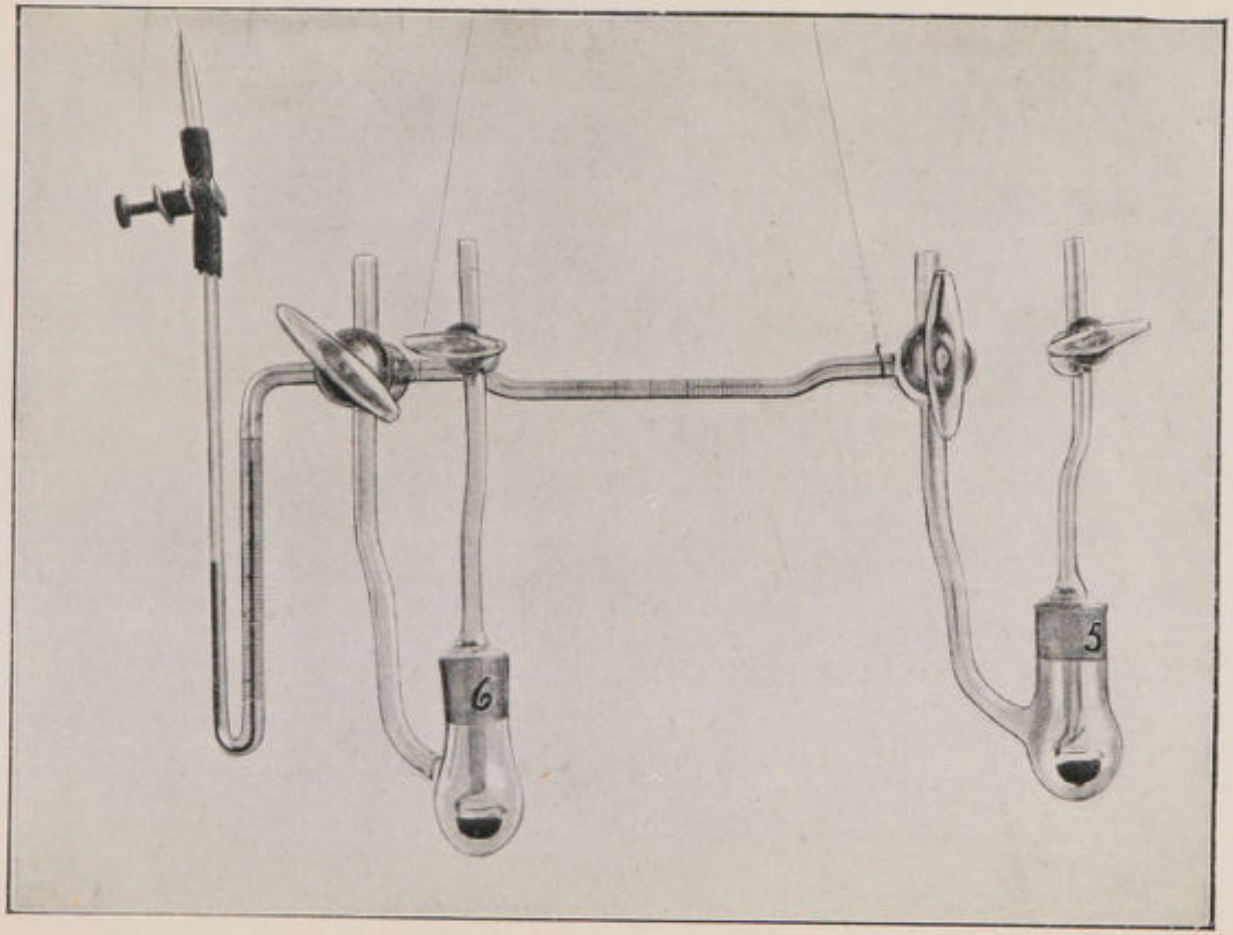


FIG. 4.—Winterstein's micro-respiration apparatus. From Bayliss's "General Physiology".

brought back to 0 by means of the screw. The volume of mercury added is equal to the volume of oxygen absorbed, but this volume must, of course, be reduced from the temperature and barometric pressure at the moment of closing the apparatus to 0° and 760 mm. In Winterstein's apparatus it is not necessary to measure the volume of the animal chamber or the bore of the manometric tube. The calculation of the results is, therefore, greatly simplified. The apparatus can be made still more sensitive than Krogh's, but is not well adapted for prolonged experiments. A later model [1913] of Winterstein's apparatus is shown in fig. 4. It is provided with four taps and connections, which render possible the filling of the vessels with definite gas mixtures differing from the atmospheric.

Both these instruments show only the oxygen absorption. The production of carbon dioxide can be determined indirectly if the animal chamber is charged with a drop of water instead of the absorbing soda lye. The pressure (or volume) change will then correspond to the difference between the volume of oxygen absorbed and of carbon dioxide liberated, and if the oxygen absorption is determined just before and just after such an experiment, the CO_2 production and the respiratory quotient can be found by combining the results.

Krogh's apparatus is a modification of Barcroft's blood gas apparatus. Winterstein's is an improvement on various earlier types (Thunberg [1905, 2], Winterstein [1905, 1906], Widmark [1911]), which were not suitable for accurate quantitative measurements.

Thunberg's original micro-respirometer [1905, 1] was a gas-analysis apparatus of the Petterson type for the determination of very small percentages of CO_2, in which the animals to be experimented on could be introduced into the gas-measuring pipette. The change in volume of the enclosed air would indicate the difference between the volume of oxygen absorbed and of carbon dioxide produced, and when that had been read off the air could be carried over into the potash pipette and the CO_2 absorbed. The change in volume after absorption would then give the carbon dioxide produced. This apparatus is too costly and complicated for general use. The introduction of mercury into the animal chamber is also to be deprecated, even if it has not been directly demonstrated that mercury vapour is harmful to the invertebrate animals in question.

All the instruments so far mentioned can be used only for very small animals up to 1 or 2 grm. weight. The surface of the CO_2 absorbing fluid which cannot be renewed must be comparatively large

to maintain a low and practically constant percentage of carbon dioxide in the air. This involves a gas volume which is large compared with the animal experimented on (not less than 100 times its volume), and when the gas volume exceeds a couple of 100 c.c. it will no longer be sure to possess a uniform temperature and composition throughout.

In the micro-respiration apparatus the oxygen absorbed is not replaced, but on account of the comparatively large volume of enclosed air the changes in composition are always very slight.

In all larger closed-space respiration apparatus we have a separate absorbing system for the carbon dioxide connected by tubing with the animal chamber. This involves further a ventilating arrange-

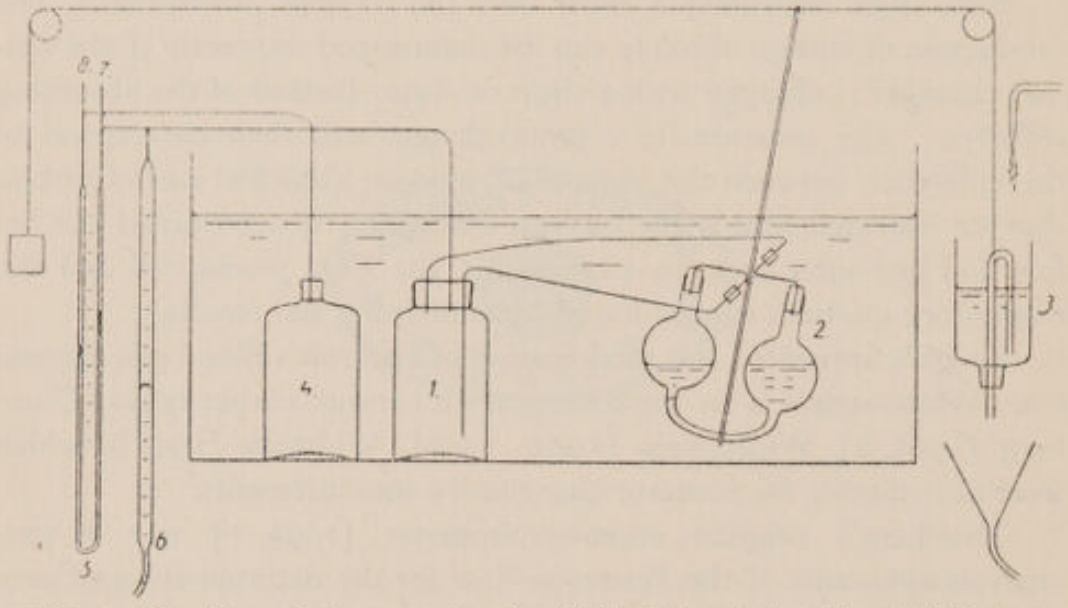


FIG. 5.—Krogh's respiration apparatus for cold-blooded animals. From "Zeitschr. f. Physik. Chem. Biologie".

ment to bring the air from the animal chamber to the absorber and back again.

The simplest form which is at the same time very convenient and accurate is Regnault-Reiset's apparatus for small animals [1849], especially when combined with a compensating vessel (Krogh [1914]), as shown in fig. 5. In this instrument the CO_2 absorbing and ventilating arrangements are combined into one (2). The oxygen absorbed is measured in the burette (6) when the manometer (5) has been brought back to its zero point just as in Winterstein's micro-respiration apparatus. When the mercury has reached the top of the burette, oxygen is added through (7) and the mercury brought back to the 0 mark on the burette. The use of a water current as a source of

power (3) to produce the oscillations of the CO_2 absorber is not, of course, essential, but has been found to be very satisfactory because of its absolute uniformity. The CO_2 absorbing efficiency of the arrangement described is very limited, and that is why the apparatus can be used only for small animals such as frogs or small reptiles and possibly mice.

In all larger closed-space respiration apparatus the ventilating and CO_2 absorbing appliances are separate, and there is moreover a separate, usually more or less automatic, device for adding oxygen. As a compensating vessel cannot be used to advantage on large apparatus the internal pressure and also the composition of the air will vary, and it becomes necessary to make analyses of the air in the chamber at the beginning and end of each experimental period. We have therefore in a complete closed-space apparatus of a large type the following distinct parts :—

1. The animal chamber.
2. The air-circulating pump.
3. The carbon-dioxide absorbing system.
4. The device for adding oxygen.
5. The air-sampling arrangement.
6. The arrangements for measuring temperature, humidity, and pressure of the enclosed air.

A considerable number of closed-space apparatus have been described since the prototype of them all was published by Regnault and Reiset in 1849, notably by Hoppe-Seyler, Zuntz, Oppenheimer, Atwater and Benedict, Benedict and his collaborators and Tangl, but none of them is satisfactory with regard to all details. It will be most convenient therefore to describe the modifications of each of the essential parts separately, in order to bring out the principles, which should guide the construction, instead of describing the instruments one by one. A complete instrument of recent type is shown diagrammatically in fig. 6.

The essential point with regard to the animal chamber of a large closed-space apparatus is absolute tightness. There is abundant evidence in the literature of the trouble which it has cost to attain this end, though most of the difficulties encountered are never mentioned in the publications. Zuntz and Oppenheimer [1908] have adopted the plan to immerse the whole of their animal chamber (for dogs) into a water-bath. This no doubt facilitates the temperature control and the detection of leaks, but the whole becomes very cumbrous and the construction must

be very rigid to withstand the water pressure. Moreover, the connections must be made movable when the animal chamber has to be lifted in and out of the bath, which certainly does not make for tightness. The best general form of an animal chamber is undoubtedly that described by Grafe [1909] for his Jaquet apparatus, which has been adopted also by Benedict [1912] and by Fridericia [1913]. It consists of a thin-walled metal box of suitable dimensions. Such a box can be made of tinplate, zinc, or tinned brass, and made airtight by soldering. The aperture for introducing the animal is closed by means of a fluid seal which is always absolutely effective. The fluid

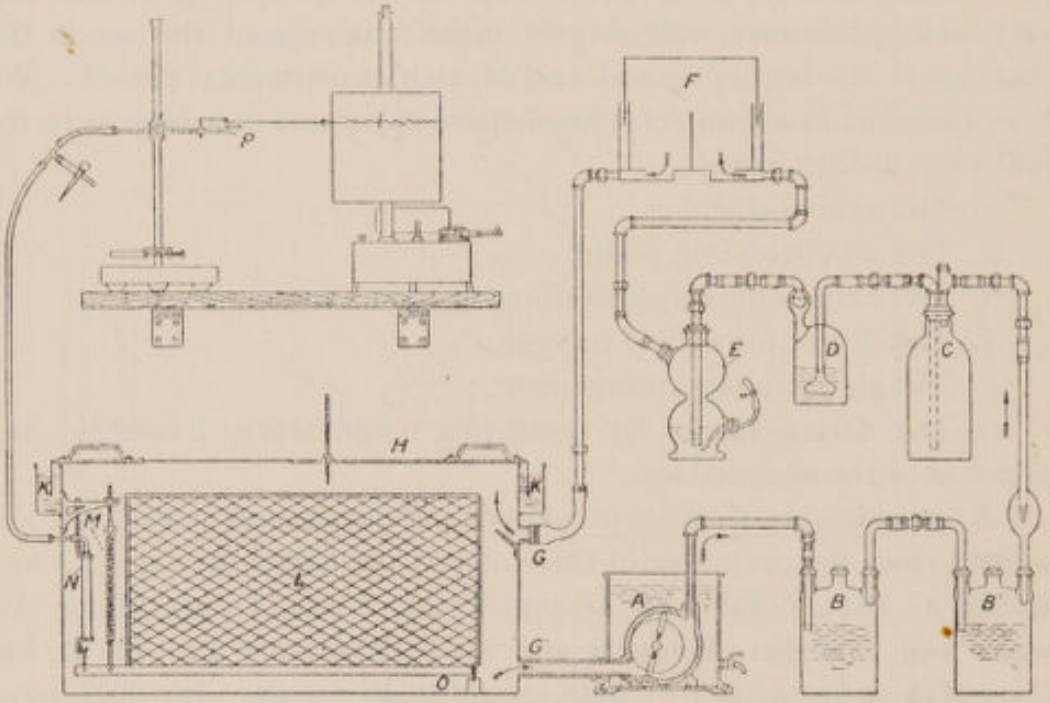


FIG. 6.—Benedict's respiration apparatus for small animals.

seal can be at the top of the box (fig. 6, H, K), which is the best plan for smaller animals, or around the floor, in which latter case arrangements must be provided to lift the whole of the box.

The volume of the animal chamber and indeed of the whole respiration apparatus must be determined, but the accuracy need not be particularly great. It is best therefore to give it a simple form which can be easily measured. Heide, Klein, and Zuntz [1913] have described a method by which the volume can be determined by introducing a measured volume of a gas which can be analysed accurately (carbon dioxide will usually be most suitable), mixing and analysing the resulting mixture.

As circulating pumps rotary blowers, as introduced by Atwater and

Benedict (fig. 6, A), have in later years superseded all other forms. They are very effective and can easily be made airtight. In many earlier closed-space respiration apparatus mercury was used in the circulating pumps. Mercury should, however, be absolutely avoided in any part of a closed-space respiration apparatus. The confined quantity of air will rapidly become saturated with mercury vapour, and will cause pronounced toxic symptoms as found by Krogh [1906] in experiments on birds and incubated eggs, and by Carpenter and Benedict [1909] in experiments on man. It has been attempted by Seegen and Nowak [1879], and later by Krogh [1906], to purify the circulating air by the application of a red heat at some point of the circuit. When mercury is avoided this precaution would appear to be superfluous and against mercury it is not in all cases effective.

The CO_2 absorbing devices at present in use in large closed-space respiration apparatus are not very satisfactory. Zuntz and Gerhartz [1913] employ a strong potash solution which is circulated by a special pump through an absorbing tower in which it presents a very large surface to the air. This method has the very important advantage of presenting no resistance to the passage of air and therefore of minimizing the danger of leakage; but the strongly alkaline fluid must be very disagreeable to handle, and the determination of the carbon dioxide taken up becomes very complicated. Samples of the solution are taken out and analysed for CO_2 at the beginning and end of each experimental period, but the volume of the potash solution is continually changing from absorption both of CO_2 and water and this factor also has to be taken into account.

Atwater and Benedict dry the air current completely by blowing it through a specially constructed absorber with sulphuric acid (fig. 7). The CO_2 is thereupon absorbed by moist soda lime and the air dried again in a sulphuric acid absorber. The amount of CO_2 absorbed is determined by weighing the soda lime can and the second water vapour absorber. The resistance of the H_2O absorbers is very considerable, and the pressure of the air in this part of the apparatus therefore so high that very elaborate precautions have to be taken against leakage.[1] The absorbers are very heavy, so that it requires a large and at the same time very sensitive balance to weigh them with sufficient accuracy (0·1 gr.). It has been alleged by Morgulis [1913] that they cannot be relied upon to absorb the last traces of moisture

[1] It ought to be possible, however, to construct efficient H_2O absorbers with a large surface over which the air could pass freely.

from a rapid current of moist air—e.g. in experiments involving heavy muscular work.

The oxygen supply has to maintain the inside pressure as near as possible to the atmospheric in order to minimize the danger of leakage. When it fulfils this purpose it will at the same time maintain the composition of the atmosphere in the apparatus sufficiently constant.

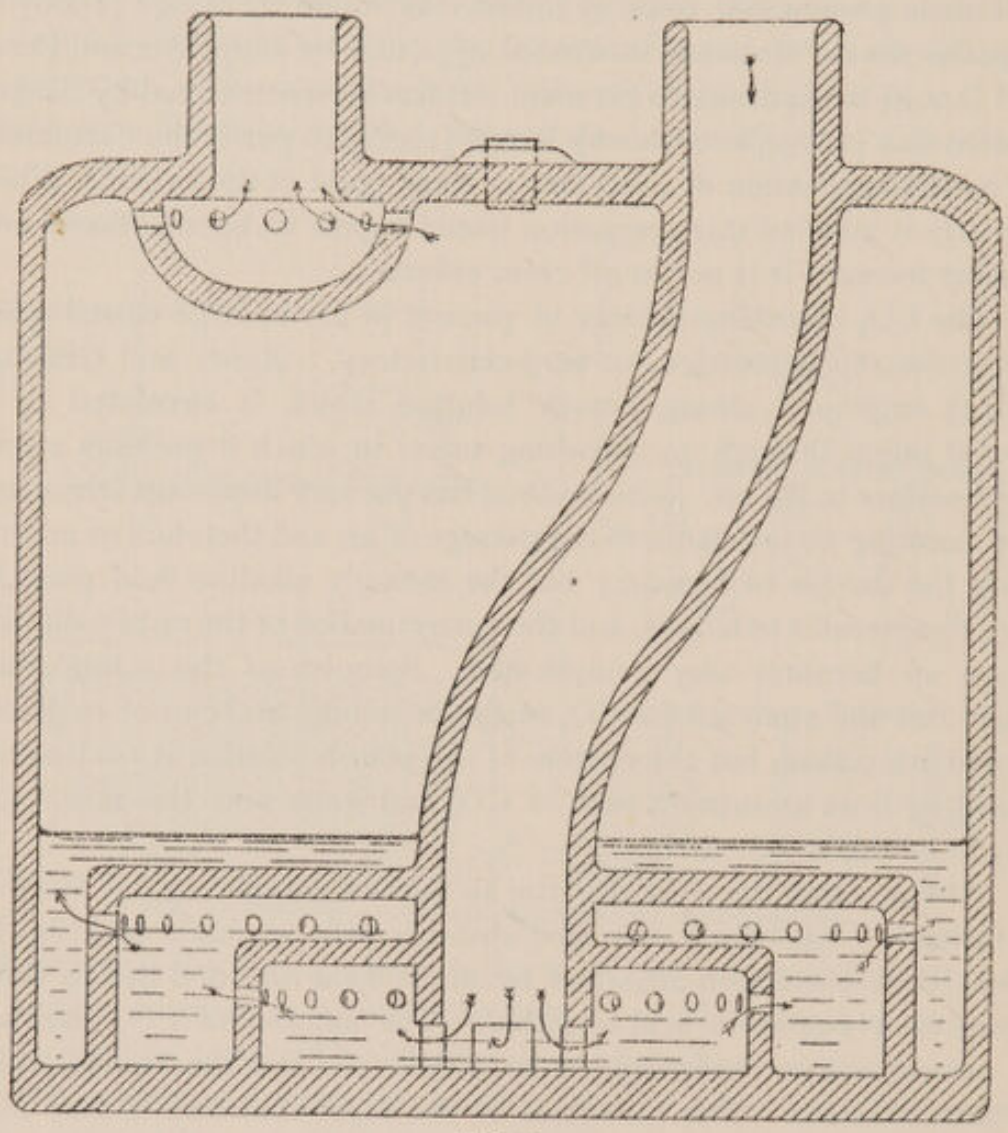


FIG. 7.

Various devices are in use. The simplest plan is undoubtedly to arrange a volume recorder connected with the chamber which will at a certain point close an electric circuit and admit oxygen from a cylinder and reduction valve, or an oxygen generator through a meter as shown in fig. 15. With a sensitive volume recorder the pressure in the chamber can be kept equal to the atmospheric within less than 0·1 mm. of water. Leakage can then take place by diffusion only.

Usually the oxygen for feeding a respiration apparatus of large dimensions is taken from a cylinder. This oxygen is never pure and generally contains as much as 2 per cent. of nitrogen. In an experiment of long duration the nitrogen percentage in an apparatus may therefore rise appreciably. Oxygen from oxylith generators is pure but expensive, and the generators are inconvenient and wasteful. By special arrangement with the manufacturers of oxygen it is often possible to obtain cylinders with less than ·5 per cent. of nitrogen, a percentage which will be small enough for almost all purposes.

It is impossible on account especially of the variations in temperature and barometric pressure to maintain the internal atmosphere in a large closed-space respiration apparatus constant with regard to quantity and composition. The oxygen admitted is not therefore an accurate index of the oxygen absorbed by the animal, nor is the carbon dioxide absorbed in the purifiers an accurate index of the quantity produced. The larger the apparatus compared with the respiratory exchange of the animal and the shorter the duration of the experiment, the greater is usually the influence which variations in the internal atmosphere are likely to have. Sampling and analysis of the air at the beginning and end of each experimental period are therefore practically always necessary. Most investigators take small samples of a 100 c.c. or less and use gas-analytic methods, and in the opinion of the writer this procedure is undoubtedly the safest as well as the simplest. Benedict and Carpenter [1910] have devised a method by which gas analysis is avoided. Before and after each experimental period they allow air to go through a bypass from the piping in front of the large absorbers. They absorb and determine by weight the moisture and CO_2 in this air current, measure the volume by means of a gas meter, and let the air enter the chamber again. When the whole apparatus is absolutely airtight they are justified in assuming that the quantity of free nitrogen in it remains constant except for the known volume of nitrogen which is admitted as impurity with the oxygen. When therefore the total enclosed quantity of air at the beginning and end of each period is calculated, and the corresponding quantities of CO_2, water vapour and nitrogen subtracted, the rest represents the oxygen, the variations of which can thus be determined without actual analysis. Except for the rigorous tests of tightness to which every part of their apparatus is subjected before and after each experiment this ingenious method of calculation would be very unsafe.

The results of the analysis, however made, must be multiplied with

the quantity of enclosed air to give the quantity of each separate gas. The quantity of enclosed air is the known volume of the apparatus reduced to standard conditions (0°, 760 mm. dry pressure). Zuntz and Oppenheimer [1908] carry out the reduction automatically by means of a so-called thermo-barometer, in which 100 c.c. of dry air at 0° and 760 mm. have once for all been enclosed. The apparatus consists of a long tube arranged in the animal chamber. The inside of the tube is moistened, and the volume of the enclosed air at the pressure obtaining can be read off from outside. 100 divided by the observed volume gives at once the reduction factor. As pointed out by Krogh [1908] this apparatus is very unreliable. The chances are against its representing the actual average temperature of the chamber, and the moisture will in the course of time condense at the point where the temperature is lowest and leave the warmer parts more or less dry. There can be no doubt that the best plan is to mix the air in the animal chamber thoroughly and continuously by means of an electric fan, as done by Grafe and by Benedict and Carpenter, and to measure the temperature on thermometers in one or more places. The degree of humidity can be measured on a pair of wet and dry bulb thermometers placed in the tube, by which the ventilating air current leaves the chamber, as done by Stähelin and Kessner and by Zuntz [1913] in his new 80 cub. metre Regnault apparatus. The pressure should always be kept absolutely equal to the barometric.

1. A. (*b*) Air-Current Respiration Apparatus.

As mentioned above, the air-current respiration apparatus fall naturally into two groups:—

α. Those in which the ventilating air current is not measured but treated as a whole with absorbing reagents. These are obviously suitable for comparatively small animals only.

β. Those in which the ventilating air current is accurately measured, while only a representative sample is drawn off and subjected to analysis. These are suitable for animals of the largest size.

α. The simplest form of an air-current apparatus is that which is suitable for measuring the CO_2 output of very small animals and which is extensively used in experiments with plants (fig. 8). The air current which can be provided by an aspirator is deprived of carbon dioxide by means of soda lime and tested with baryta solution. After passing through the animal chamber it is taken through baryta bottles or Pettenkofer's baryta tubes in which the carbon dioxide pro-

duced is absorbed. The amount of CO_2 is determined usually by titration of an aliquot part with very weak hydrochloric acid.

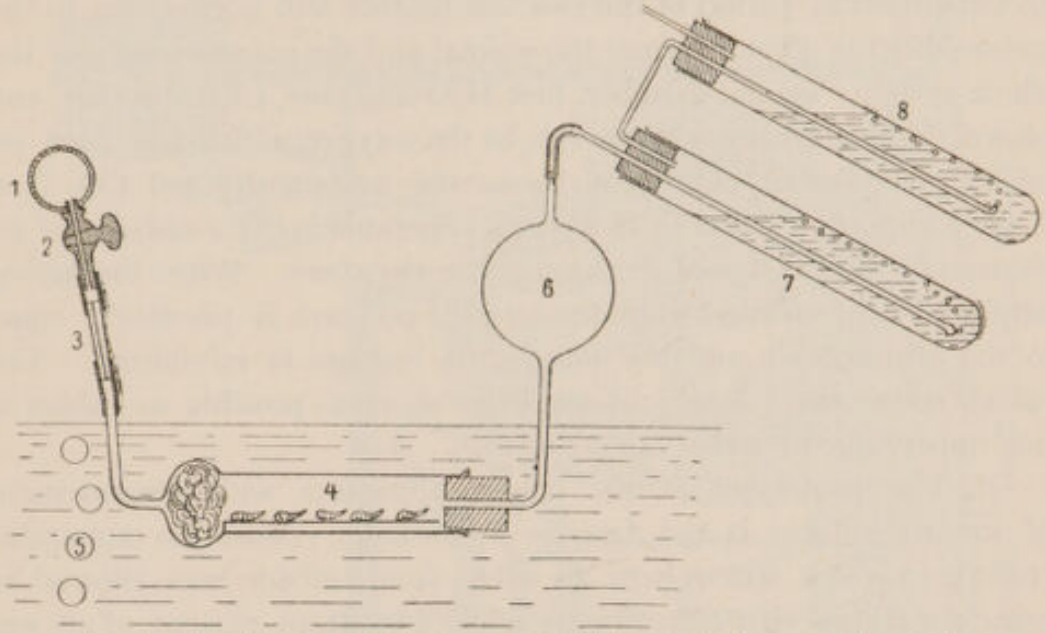


FIG. 8.—Krogh's apparatus for measuring CO_2 output of very small animals. From "Zeit. f. Allgem. Physiol."

For somewhat larger animals, and especially for small mammals up to the size of a rabbit, the Haldane apparatus (fig. 9) [1892], which allows the determination both of carbon dioxide and oxygen, is extremely

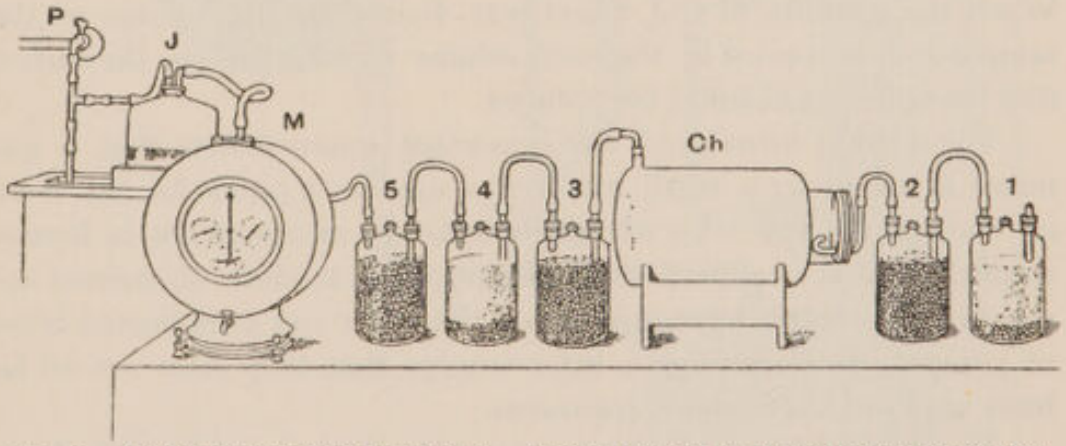


FIG. 9.—Haldane's respiration apparatus. From "Journal of Physiology" (Cambridge University Press).

convenient and accurate. The air is deprived of carbon dioxide and moisture by means of soda lime (1) and pumice stone soaked in sulphuric acid (2). The dry and CO_2 free air is taken through the animal chamber (Ch), which is so arranged that it can readily be weighed with the animal enclosed. From the animal chamber the air passes again through a water absorber (3), a carbon dioxide absorber with soda lime

(4), and a third vessel (5) with sulphuric acid on pumice stone to absorb the moisture given off from the soda lime. The gain in weight during an experimental period of the two last bottles will correspond to the carbon dioxide given off from the animal and the gain in weight of the whole system: animal chamber, first H_2O absorber, CO_2 absorber, and second H_2O absorber corresponds to the oxygen which has been retained, since the air enters and leaves this system dry and CO_2 free. A very important point in Haldane's apparatus is the avoidance of resistance to the passage of air through the absorbers. When the tubing employed is of sufficient bore the internal pressure is practically equal to the atmospheric and the danger of leakage is minimized. The rubber connections should be made as short as possible as rubber is not impervious to water vapour or CO_2.

β. The prototype of the larger apparatus with measurement of the air current is the famous Pettenkofer respiration apparatus [1862], in which atmospheric air taken from outside was allowed to enter the animal chamber directly while a constant current of air was drawn out by a large pump and measured by a gas meter. Two small pumps were at the same time continuously taking samples of the atmospheric and of the outgoing air. These samples were measured in gas meters and pressed through baryta water contained in Pettenkofer tubes, in which the carbon dioxide was absorbed and afterwards titrated. When the quantity of CO_2 found was divided by the volume of the sample and multiplied by the total volume of outgoing air, the carbon dioxide elimination could be deduced.

Voit [1875] introduced the important improvement that a gas meter actuated by a small motor was used as a pump for the main air current (fig. 10). An extremely accurate measurement is hereby secured as Voit's calibrations show, and in all modern air-current apparatus gas meters have superseded the older and complicated types of pumps. It is perhaps a little strange that they have not so far been used in closed-circuit apparatus.

The Pettenkofer-Voit apparatus could only be used for CO_2 determinations.[1] The same is the case with Tigerstedt-Sondén's apparatus [1895] which is ventilated in the same way as Voit's, but in which only a small sample of the air (60 to 100 c.c.) is analysed in the extremely accurate Petterson-Sondén gas-analysis apparatus for CO_2. It is

[1] Though the determination of oxygen is theoretically possible by weighing the subject before and after the experiment and determining the excretions and the output of water vapour it has never become accurate enough for practical use. (See Benedict, 1910.)

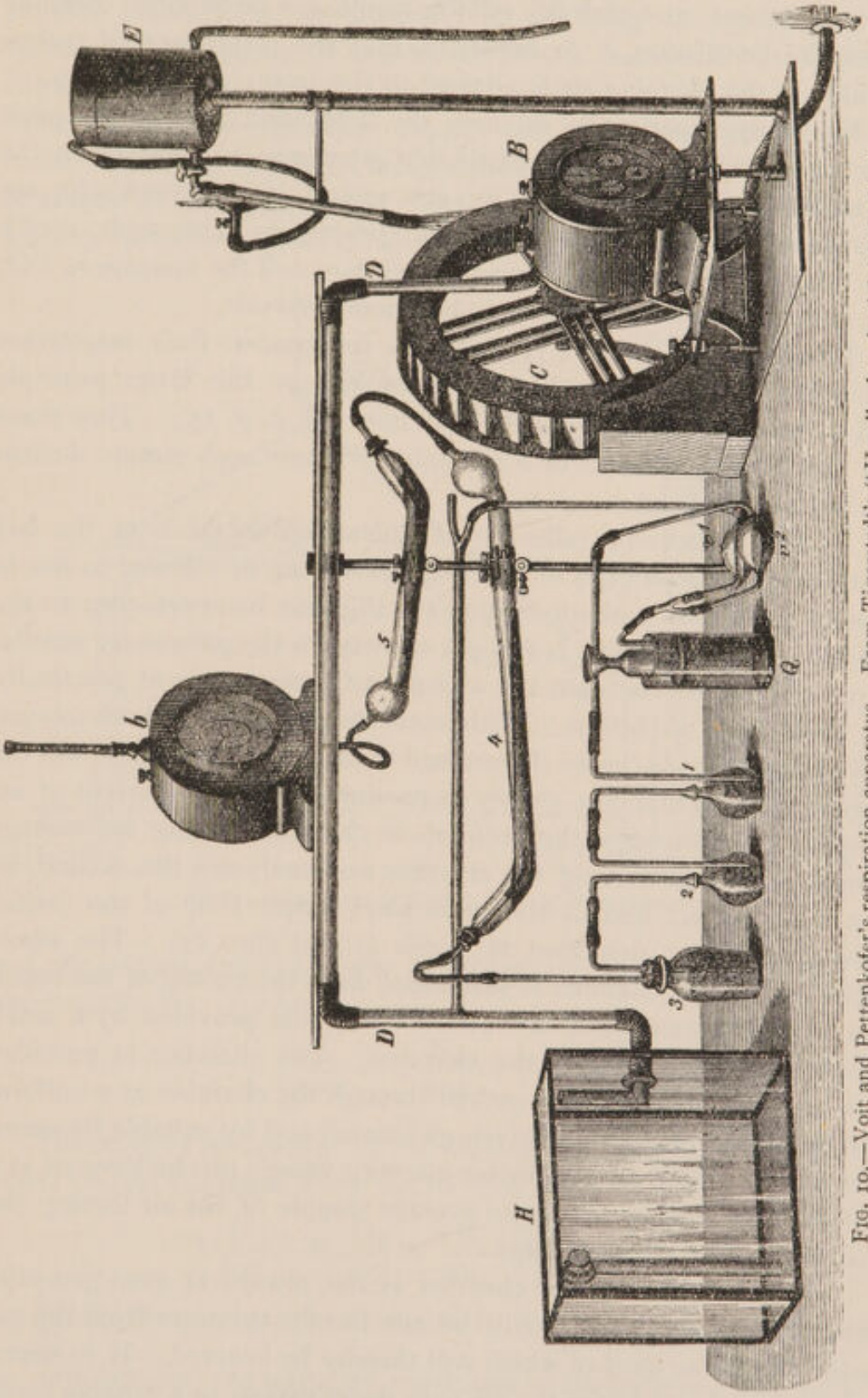


FIG. 10.—Voit and Pettenkofer's respiration apparatus. From Tigerstedt's "Handb. der physiol. Methodik".

possible with this instrument to determine CO_2 with an accuracy of 0·0004 per cent., and perfectly reliable results can be obtained therefore when the ventilation is so regulated that the percentage of carbon dioxide in the outgoing air is allowed to rise to 0·1 per cent. only.

For many experiments on man the Tigerstedt-Sondén apparatus has been used without any ventilation whatever, but the air in the chamber which is very large (100 cub. metres in the Stockholm apparatus and 76 cub. metres in that at Helsingfors [Tigerstedt, 1906]) has been mixed continually by an electric fan, and the increase in CO_2 per cent. measured by analyses in half-hour intervals.

Benedict and Homans [1911] have constructed their respiration apparatus for small animals (dogs of 5 kg.) on this latter principle and without any provision for ventilation (fig. 2, p. 15). They point out that for experiments of a preliminary nature such simple devices are often very useful.

In the Jaquet apparatus [1903] advantage is taken of the fact that the CO_2 percentage of the inspired air can be allowed to rise to at least 1 per cent. without causing the slightest inconvenience to the subject. The only effect is a slight increase in the pulmonary ventilation sufficient to maintain the alveolar CO_2 percentage at practically the same level as before. With accurate gas analysis both oxygen and carbon dioxide can be determined to about 0·01 per cent., and the method consists therefore simply in passing a measured current of atmospheric air through the respiration chamber, taking an average sample of the air leaving the chamber and analysing this accurately. The most perfect and at the same time simple form of the Jaquet apparatus is that described by Grafe [1910] (fig. 11). The whole upper part of the chamber is suspended from the ceiling of the room, and can be lowered into a water (or oil) seal provided by a small trough round the floor of the chamber. The chamber is provided with an electric fan. Air is sucked through the chamber at a uniform rate by means of a motor-driven gas meter, and by suitable transmission from the shaft of this meter mercury vessels can be lowered at a uniform rate, thereby taking an average sample of the air leaving the chamber during a certain time.

As the air leaving the chamber is not always or even generally saturated with moisture it will be apt to take up water from the gas meter, the water level of which will thereby be lowered. It is necessary therefore to saturate the air with water vapour in a suitable vessel (Stähelin) or to maintain a constant level in the meter by having a slow current of water through it.

In the Jaquet apparatus, and in practically all the air-current apparatus presently to be described for studying the pulmonary respiration, the outgoing or expired air only is measured. In order to calculate the absorption of oxygen it is necessary in this case to assume that no other gas than oxygen and carbon dioxide is involved in the respiratory exchange, an assumption which is practically justified in almost all cases (see p. 53). On the basis of this assumption the ingoing quantity of air (I) can be calculated from the outgoing (E),

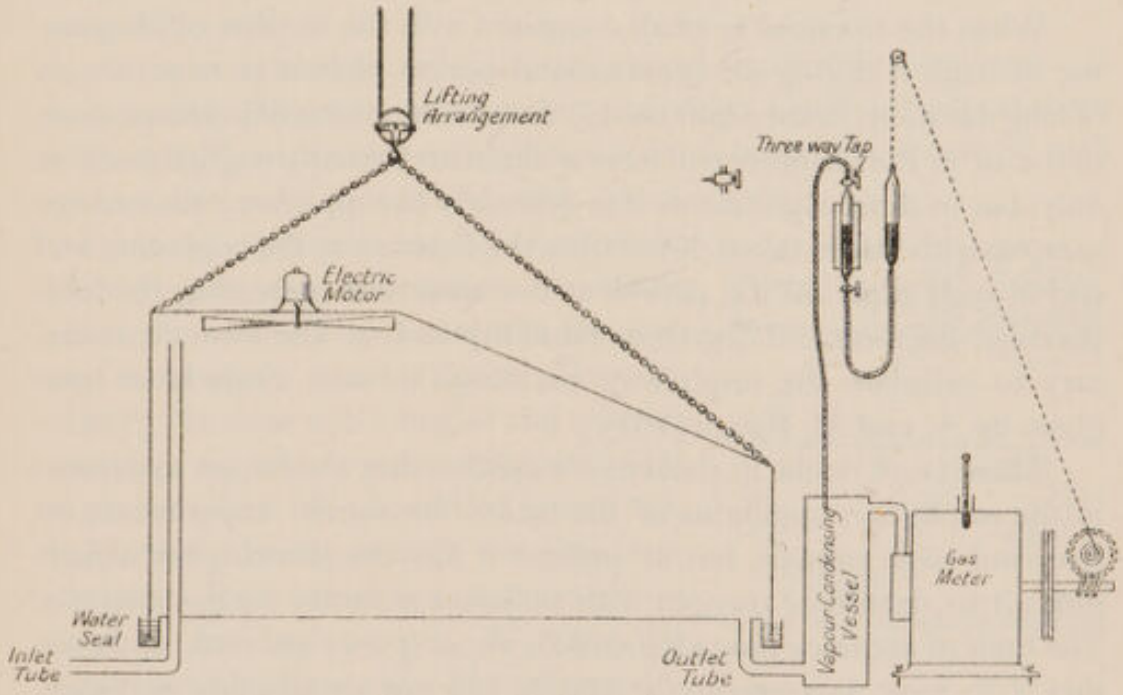


FIG. 11.—Diagram of Grafe's respiration apparatus.

and the percentages of nitrogen in the ingoing (N_I) and outgoing (N_E) air respectively. We have

$$I \frac{N_I}{100} = E \frac{N_E}{100} \text{ or } I = E \frac{N_E}{N_I}.$$

The oxygen percentages in the ingoing and outgoing air being denoted O_I and O_E respectively the oxygen absorption is

$$I \frac{O_I}{100} - E \frac{O_E}{100} \text{ or } \frac{E}{100}\left(\frac{N_E}{N_I} O_I - O_E\right).$$

$\frac{N_E}{N_I} O_I$, the percentage of oxygen in the ingoing air multiplied by the ratio between the nitrogen percentage in the outgoing and ingoing air, is called the corrected oxygen percentage.

EXAMPLE.

	Ingoing Air.	Outgoing Air.	Ingoing Air Corrected $\times \frac{79{\cdot}23}{79{\cdot}04}$	Difference.
O_2 per cent.	20·93	20·02	20·98	0·96
CO_2 ,,	0·03	0·75	0·03	0·72
N_2 ,,	79·04	79·23		

When the chamber is small compared with the volume of air passing through it during an experimental period, that is in experiments of long duration (twenty-four hours), the possible changes in composition of the air in the chamber will have a slight and usually negligible effect only, but in short experiments it is necessary to supplement the average samples with others taken direct from the chamber at the beginning and end of each experimental period, at the same time measuring the temperature, pressure and degree of humidity in it. The formulæ necessary to calculate the respiratory exchange in such cases have been given by A. and M. Krogh [1913].

There is no doubt in the writer's opinion that the Jaquet apparatus is the respiration apparatus of the future for normal experiments on man and large animals, but at present it has this drawback that it is difficult to determine oxygen with sufficient accuracy by gas analysis. The limit of accuracy now attainable is about $\pm$ 0·01 per cent., and even this is in most instruments a relative and not an absolute accuracy. A short series of analyses of the same air may agree within these limits, but unless the burette is always kept scrupulously clean, which takes much time, analyses of the same air made at longer intervals are apt to differ several hundredths. Though the composition of the atmospheric air even in towns is constant as shown by Benedict [1912] to within 0·01 per cent., it is therefore generally necessary in work with Jaquet's apparatus to analyse both the ingoing and the outgoing air and to let these analyses alternate regularly (A. and M. Krogh).

1. B. Apparatus for Measuring the Pulmonary Gas Exchange.

Special researches (Schierbeck [1893], Krogh [1904], Franchini and Preti [1908]) have shown that the gas exchange taking place through the skin in higher animals is very insignificant, as it is generally 1 per cent. or less of the total gas exchange. Quite apart therefore from the use of pulmonary respiration apparatus to study the processes taking

place in the lungs, their application for determinations of the total respiratory exchange is completely justified.

All forms of apparatus for measuring the pulmonary gas exchange possess some arrangement for connecting the measuring instruments with the air passages of the man or animal experimented on, and almost all possess valves which determine the direction of the air current to and from the lungs. Before describing the different types of apparatus in detail, it will therefore be useful to discuss the different methods of connecting with the air passages and the different forms of respiration valves.

In animals tracheal cannulas are almost exclusively employed. It is extremely difficult to put a mask or anything like it airtight on to an animal, and the results which have been obtained by means of such devices can only be utilized with great caution, as pointed out by Tigerstedt [T.M.]. On man mouthpieces of rubber which fit between the teeth and the lips are extensively used (Zuntz, Geppert [1887], Haldane and Douglas and others), and they are sometimes supplemented by an extra piece of rubber tied round the head and pressing against the lips from outside. This precaution appears, however, to be unnecessary. To close the nose suitable nose clips are universally employed. Several persons feel it as a considerable inconvenience to breathe through the mouth, and in such cases the nosepieces constructed by Benedict [1909] may be very useful (fig. 12). They can easily be fitted tightly by inflating the rubber cushion. The diameter of the tubes must necessarily be so narrow, however (7 mm.), that a considerable resistance is inevitable when the breathing is increased.

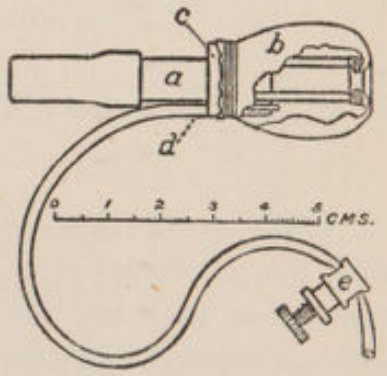


FIG. 12.—Benedict's nosepiece.

Masks of rubber which can be fitted on the face and enclose the mouth and nose are far more convenient than mouthpieces or nosepieces, but it is extremely difficult to avoid leakage. Bohr constructed masks which were specially fitted to each person on whom it was intended to experiment. These masks (fig. 13) consist of a funnel-shaped piece of tinplate coated on the edge with a substance used by dentists and known commercially as Stent's composition. This substance becomes soft at a temperature about 50°, and can then easily be moulded on the face of a person and can be made to fit absolutely

airtight when greased with lanoline, causing at the same time a minimum of inconvenience. These masks are much used in Danish laboratories for all experiments which have to last more than a few minutes at a time.

Valves such as Müller's and other fluid valves, generally filled with water or mercury, were formerly used extensively. They have the advantage that leakage backward is impossible, but their resistance is generally considerable. Zuntz uses the "Darmventile" invented by Speck. These are certainly effective and the resistance very slight, but the valves are large and cumbrous. Reliable metal valves with a minimum resistance have been constructed by Chauveau (Tissot, 1904) and by the firm of Siebe, Gorman (Douglas, 1911). Bohr constructed rubber valves which, slightly modified, have given entire satisfaction in Danish laboratories (fig. 14).

1. B. (*a*) Pulmonary Ventilation Apparatus of the Closed-Circuit Type.

While closed-circuit respiration apparatus intended to measure the total gas exchange of man and large animals are probably less advantageous than the air-current types, quite the reverse is the case with corresponding instruments for measuring the pulmonary gas exchange only. On account of the small dimensions to which such an instrument can be reduced it is easy to make it airtight, the more so as the pressure can always be maintained absolutely equal to the atmospheric. Another advantage obtained by the small dimensions is that the variations in the composition of the air can be left out of account and the oxygen absorption can be read off directly on the meter measuring the oxygen admission. Even a continuous graphic record of the absorbed oxygen can easily be obtained. The instruments of this type can give finally a quantitative graphic record of the volumes of air inspired and expired.

Apparatus of this type have been constructed by Ludwig (Sanders-Ezn [1867]), Zuntz and Röhrig [1871], Regnard [1879] and others, but these forms are now obsolete. Two forms are in use at present.

Krogh's apparatus (fig. 15) [1913] which is a modification of an instrument constructed by Haldane and Douglas [1912], is furnished with valves and the air is circulated by the respiratory movements of

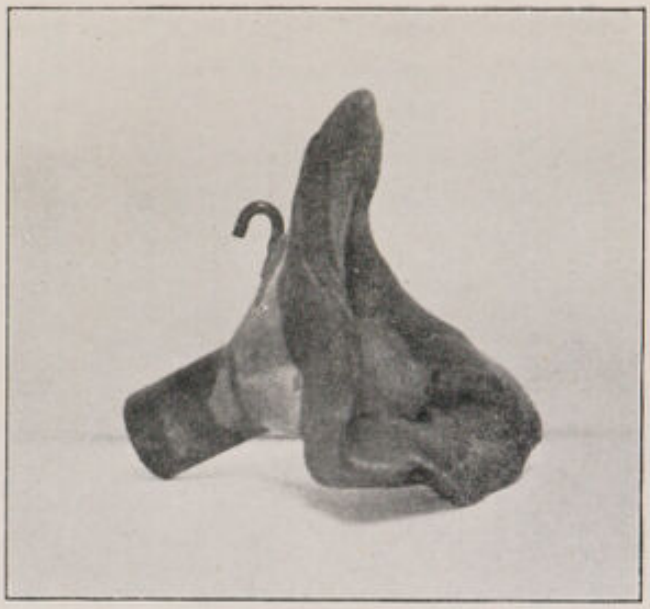


FIG. 13.—Bohr's mask.

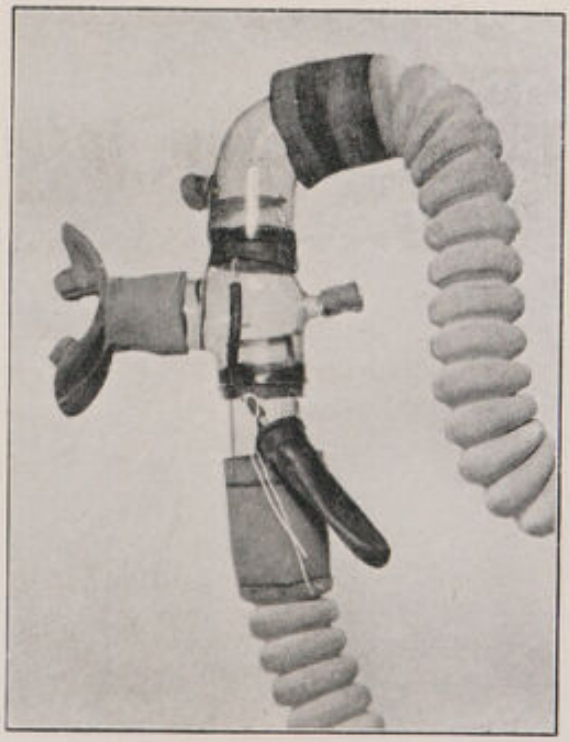


FIG. 14.—Bohr's valves.

the subject. Carbon dioxide is absorbed in a vessel containing a charge of soda lime sufficient to absorb about 1000 litres of carbon di-

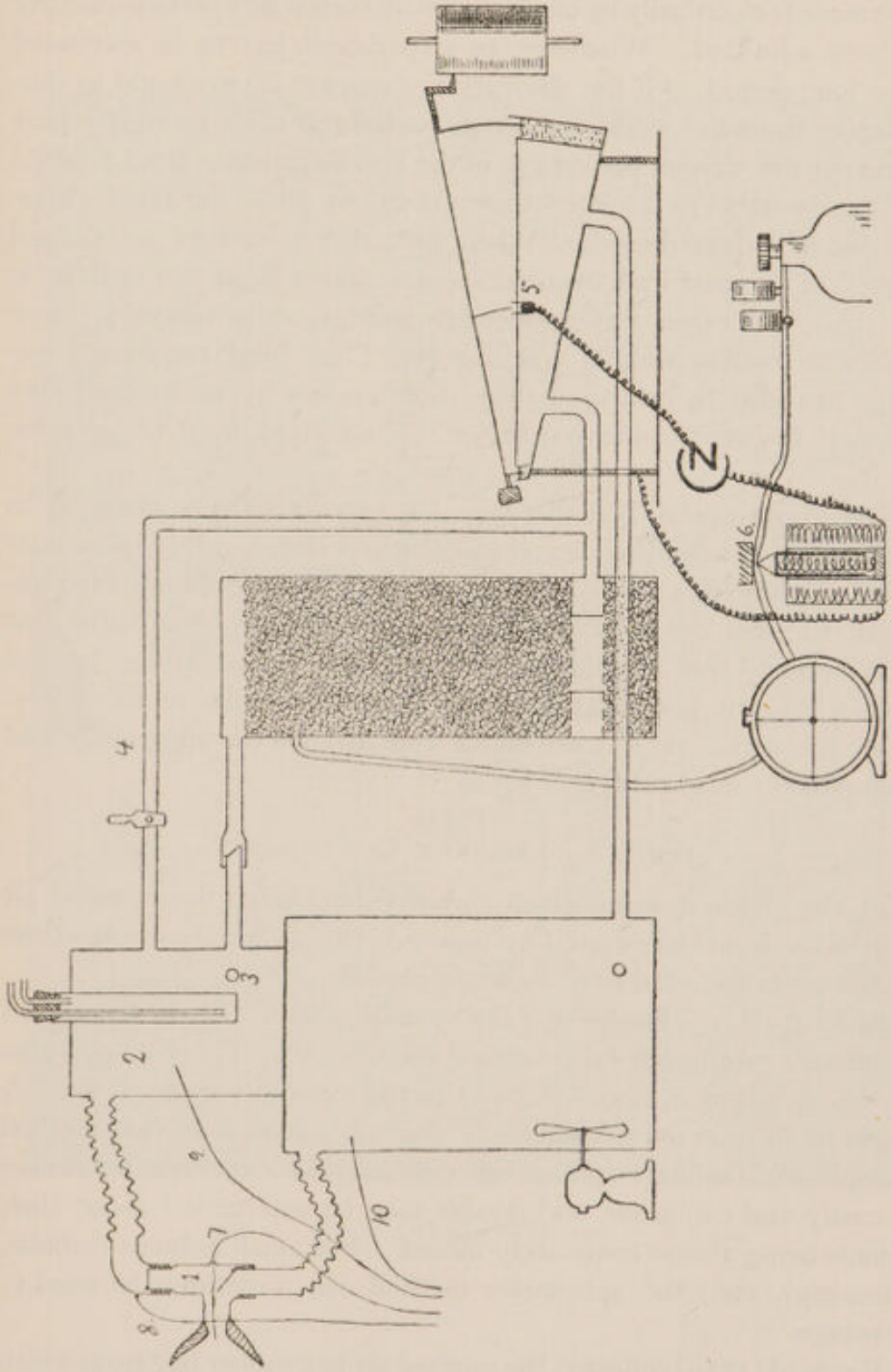


FIG. 15.—Krogh's recording respiration apparatus for men.

oxide, a quantity produced by a man at rest in about seventy hours. The recording spirometer gives a quantitative record of the respiratory

movements, and governs the admission of oxygen by closing an electric circuit at (5). The oxygen from the cylinder is measured by the meter which records electrically by closing a circuit each time a certain quantity has been admitted. Whenever an experiment has to be extended over a long period, or if the absorption of oxygen is very rapid as during heavy muscular work, the oxygen admitted must be nearly pure to prevent the oxygen percentage in the small apparatus from falling.[1]

The apparatus in its present form does not allow the direct determination of carbon dioxide. When such determinations are desired samples of expired and inspired air are drawn from the vessels (2) and (10). The respiratory quotient is determined by analysing these samples for carbon dioxide and oxygen. The total respiratory exchange can also be measured over short periods by multiplying the analytical results by the ventilation as measured from the graphic record.

The apparatus of Benedict (fig. 16) [1909, 1912] is arranged to measure both carbon dioxide and oxygen, and the recording spirometer has an attachment (a " work adder ") which automatically adds the excursions together and so records the rate of ventilation. The instrument has no valves, but a rapid circulation of air is maintained by the blower. This is necessitated by the great resistance in the water-vapour absorbers. If this resistance were avoided the apparatus could be simplified considerably.

1. B. (*b*) Air-Current Instruments.

In the simplest forms of air-current instruments the inspired air is separated from the expired by means of valves, and the whole of the expired air is collected over a certain period.

Speck [1892], Fredericq [1882], and Tissot [1904] have used spirometers equilibrated in various ways, and in Tissot's apparatus they are arranged to record graphically the expired volume of air. A sample of air from the spirometer is afterwards analysed. The method is simple, but the large spirometers necessary for experiments on man are costly and cumbrous, and doubts may be entertained about their contents being always completely mixed. For small animals (rabbits, guinea-pigs, etc.) the spirometer method can sometimes be used to advantage.

Regnard [1879] collected the expired air in a rubber bag from which

[1] When the O_2 admitted shall be an accurate measure of the O_2 used the volume of the apparatus must be reduced as far as possible. The apparatus shown in fig. 15 has for special reasons been enlarged by the addition of an inspiration cylinder.

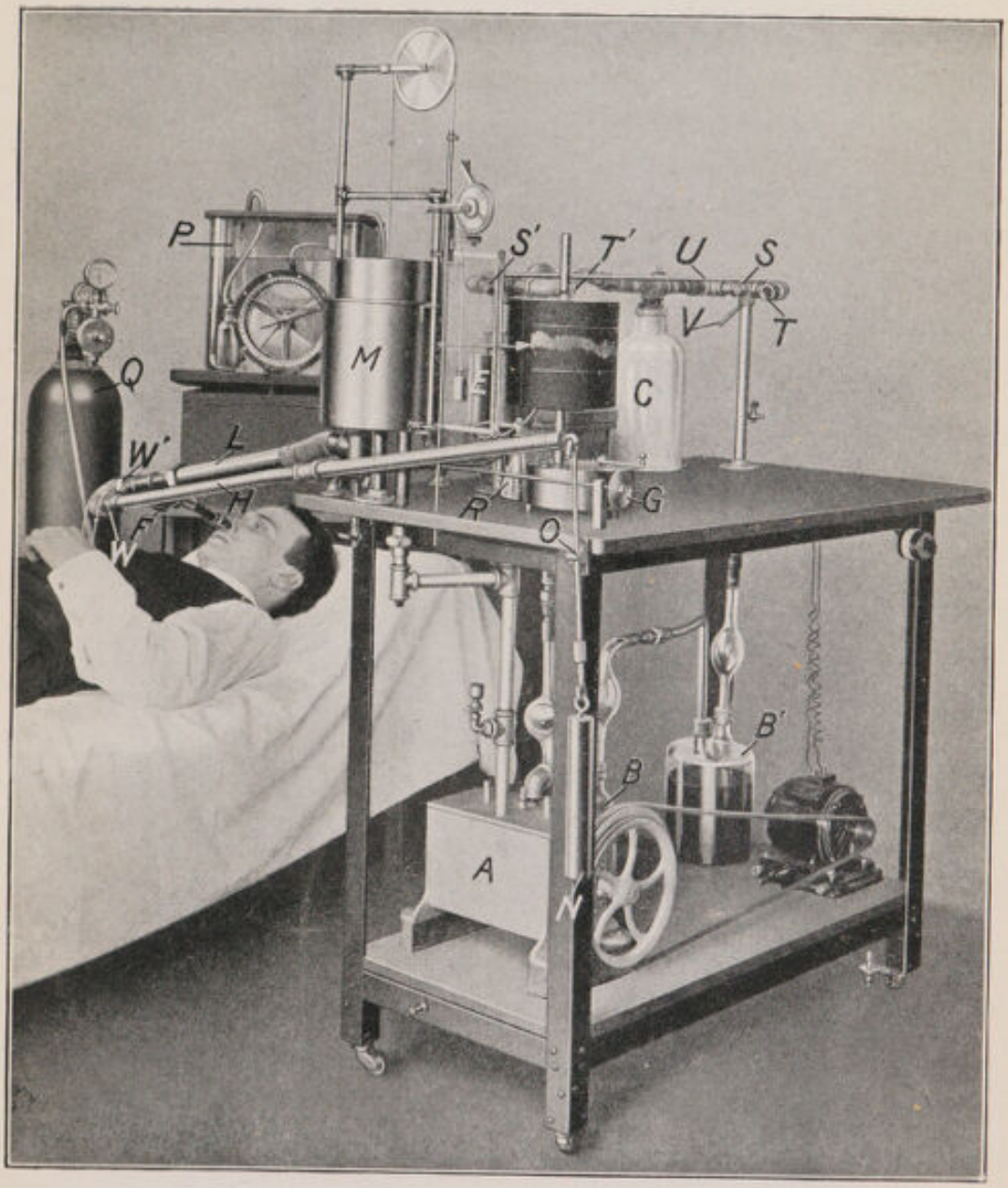


FIG. 16.—Benedict's universal respiration apparatus.

it was afterwards delivered and measured through a meter, but his bags were probably not tight against diffusion and his technique very faulty. The principle, however, is excellent for certain types of experiments, and it has recently been revived by Douglas who has worked out a method which is specially adapted for the study of the respiratory exchange during open-air exercise in circumstances where all other devices would fail, but which will also prove extremely useful in a number of other cases, e.g. on bed-ridden patients (fig. 17). The

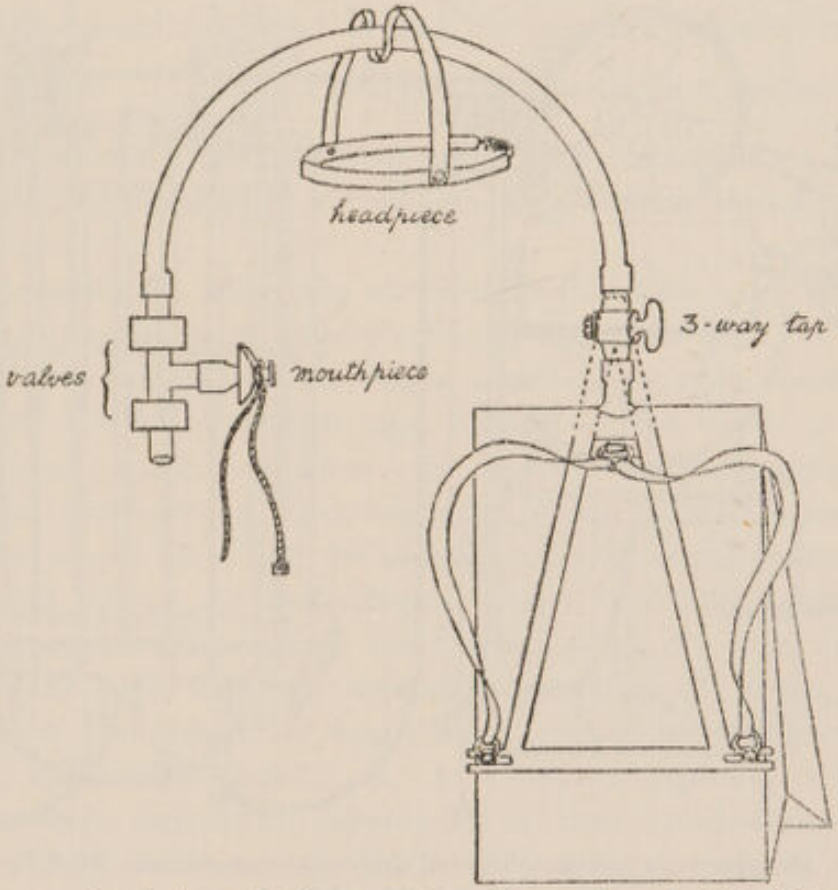


FIG. 17.—Douglas's respiration apparatus. From "Journal of Physiology" (Cambridge University Press).

subject breathes during an introductory period through the mouthpiece and valves. When it is desired to make an experiment the three-way tap is turned so as to connect with the bag and the expired air collected over a certain period. With violent exercise a bag taking 60 litres will not hold the air expired during one minute, but it has been shown (Krogh [1913]) that experiments of even much shorter duration are sufficient to give perfectly reliable results. The air collected in the bag is afterwards analysed and measured by connecting with a gas meter of suitable size and pressing the air slowly out of the bag. When a gas analysis is considered a thing to be avoided, the

contents of the bag can be taken through a Haldane set of vessels for absorbing water vapour and carbon dioxide and the total carbon dioxide determined by weighing.

In the method of Zuntz and his colleagues (Geppert [1887], Magnus-Levy [1894]) the expired air is measured by passing through a gas meter and an average sample taken for analysis (fig. 18). This method has been used in a large number of researches of the highest importance since it was published by Geppert and must therefore be described in

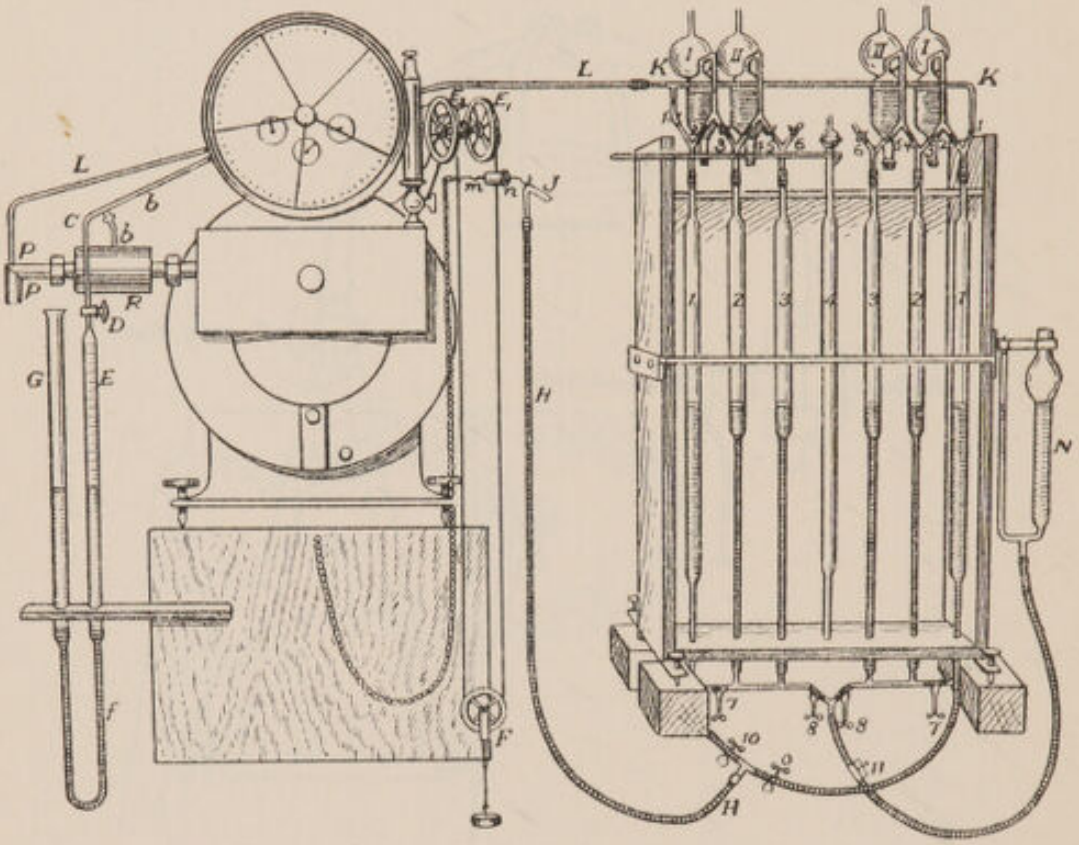


FIG. 18.—Gas meter, air sampling and analysing arrangement. After Zuntz. Tigerstedt's "Handbuch," vol. i.

some detail, though simpler and quite as effective arrangements are now taking its place.

The expired air is measured by passing through a gas meter which it enters through (P). A narrow tube (L) leads from P to the gas sampling tube (part of a Zuntz gas-analysis apparatus) filled with mercury or acidulated water. As the gas meter revolves during each expiration, the weight (F) is lowered correspondingly and with it the tube (H) connected with the gas sampling tube. Some mercury (or water) flows out from (J) and a corresponding quantity of the expired air is drawn into the sampling tube. The apparatus (R, D, G, E) is a so-called thermo-barometer. 100 c.c. dry air at 760 mm. pressure

and 0° have been stored in two metal boxes one of which is inserted into the entrance tube of the gas meter at (P) and the other into the exit tube. The air in these boxes communicates with the burette (E). The enclosed volume of air will be affected by the temperature of the air entering and leaving the meter and by the atmospheric pressure, and the volume changes can be read off on the burette when the water in (G) and (E) has been brought to the same level by moving (G). The burette is so divided that, if a volume of say 107·4 is read off during an experiment, the volume of the air which has passed through the meter can be reduced to normal conditions (0° and 760 mm. dry pressure) by multiplication with $\frac{100}{107{\cdot}4}$. This arrangement is certainly not more accurate and scarcely more convenient than to reduce by means of a table after reading the barometer and a thermometer placed in the exit tube of the gas meter.

In experiments involving exercise in the open a dry gas meter was carried on the back of the person experimented on.

In Bohr's laboratory the Zuntz method has been considerably simplified. In the expiration pipe leading to the meter a mixing vessel (usually placed in a water-bath at room temperature) was provided and samples were drawn from this, either by hand a few c.c. at a time, or simply by letting the mercury run out slowly from a sampling vessel during the experiment. These two improvements are interdependent. The expired air moving along the pipe from the valves to the meter is of very unequal composition, the first part being almost pure atmospheric air from the dead space (mouth, trachea and bronchi) and the last alveolar air. It is very incompletely mixed in a tube, and when samples are taken from the tube it is absolutely necessary that they are drawn only while the current is passing. Otherwise too much alveolar air is sure to get into the sample, since it will in most cases be chiefly alveolar air which is left in the tube after the expiration. In a vessel which will hold at least the volume of two expirations the different portions of expired air are mixed and an average sample can easily be obtained.

Higley and Bowen [1904] have constructed an apparatus by which the carbon dioxide from the expired air is absorbed in a Haldane set of vessels suspended from a balance which will record graphically the rate at which CO_2 is being eliminated. Their method is certainly useful in special conditions involving rapid changes in the activity of the organism.

A very ingenious respiration apparatus has been constructed and used by Hanriot and Richet [1891]. They use three equal gas meters. One measures the inspired air, a second the expired air, and a third the expired air after absorption of the carbon dioxide in a suitable absorber.[1] The difference in reading between the second and third meter shows the amount of carbon dioxide eliminated during a certain time, while the difference between the first and third shows the oxygen absorbed. The experiments made by Hanriot and Richet are not particularly accurate, but in the writer's opinion there is no doubt that the possibilities of this method are great. With modern gas meters of sufficient size placed in one water-bath volumes can be measured accurately to $\frac{1}{10.000}$, and arrangements could easily be made giving a continuous graphic record of ventilation, oxygen absorption and carbon dioxide output.

The use of gas meters for measuring non-continuous air currents requires certain precautions to which due regard has not always been paid. The volume recorded by a meter is independent of the rate only within a certain limit, corresponding roughly to 100 complete revolutions per hour. At higher rates the volumes recorded are smaller than what has actually passed (Benedict [1912]), but with a constant high rate it can still be determined without appreciable error provided the meter is calibrated at the rate desired. With a non-continuous current, as in measuring expirations, the rate varies from 0 to a maximum at the height of expiration. This maximum corresponds roughly to about three times the total ventilation, and when a meter shall measure the expiration accurately the maximum rate should not be above 100 revolutions per hour. The ventilation of a man at rest is something like 400 litres per hour, and the meter employed for measuring the ventilation should not therefore measure less than 12 litres per revolution. During muscular work the ventilation may easily rise to 4000 litres, requiring for its measurement a meter with a drum of 120 litres capacity.

In respiration experiments on animals it is frequently desirable or necessary to suppress all voluntary movement by means of curari. Recourse must then be had to artificial respiration. A number of devices have been described for performing artificial respiration and several of these can be combined with respiration apparatus. A very simple and effective form, which has been used successfully in

[1] H. and R. used potash solution flowing down over glass beads, but soda lime would undoubtedly absorb much better and be easier to use.

numerous respiration experiments, has been described by Tangl [1903] (fig. 19). He uses a three-way tap connected with the trachea and turned at a uniform rate by means of a motor. The inspiration tube of this tap can be connected as in the figure with a pump with one valve driven from the same shaft as the tap, so that it will press a certain volume of air into the lungs each time the tap is opened. An alternative method, which in the opinion of the writer is absolutely preferable, is to connect

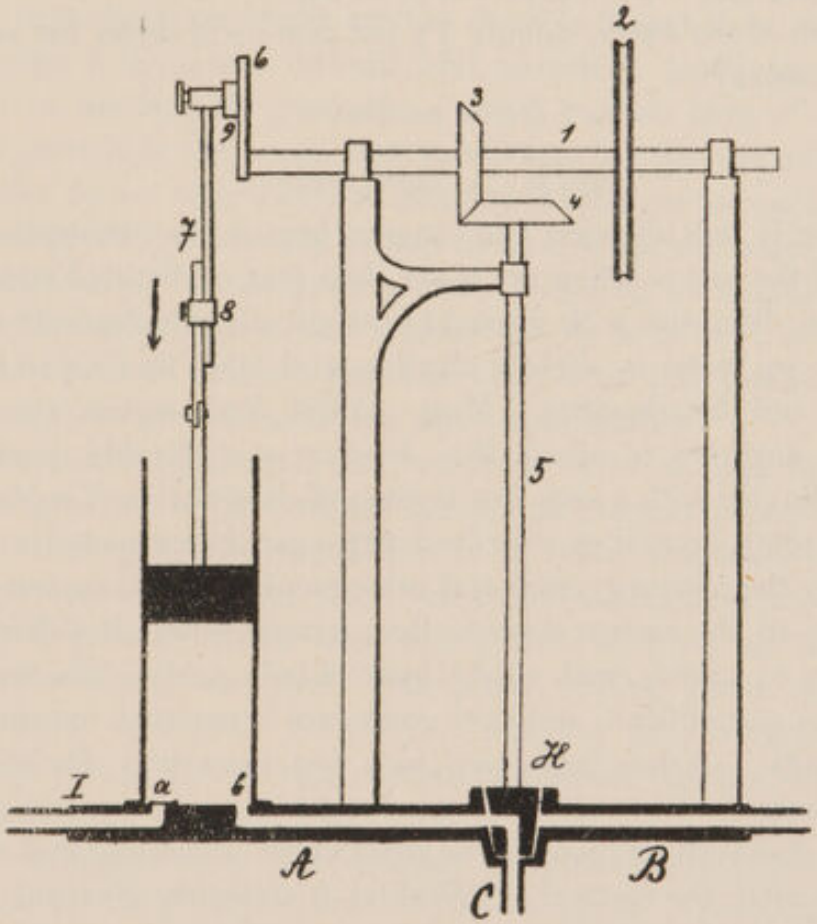


FIG. 19.—From Pflüger's "Archiv".

the inspiration tube with a supply of air at a slight constant pressure (usually 8 to 12 cm. of water). The expiration tube is connected with a gas meter and sampling arrangement.

2. Methods for Studying the Respiratory Exchange of Aquatic Animals.

The technique of respiration experiments on aquatic animals must be based on the properties of the respiratory gases when dissolved in water, properties which differ considerably from those shown by the free gases.

1 litre of distilled water saturated at 15° with atmospheric air (760 mm. dry pressure) (79·04 per cent. N_2, 20·93 per cent. O_2, and 0·03 per cent. CO_2) will contain according to Fox [1907, 1909]

13·68 c.c. nitrogen
7·22 ,, oxygen
0·30 ,, carbon dioxide

corresponding to the absorption coefficients 0·0173 for nitrogen, 0·0346 for oxygen, and 1·002 for carbon dioxide.

1 litre of sea water, salinity 3·5 per cent., will under the same conditions contain

11·1 c.c. nitrogen
5·8 ,, oxygen
about 50 ,, carbon dioxide

There is less nitrogen and oxygen because the absorption coefficients of the salt solution are lower than that of distilled water. The enormous difference with regard to carbon dioxide depends upon the fact that sea water is slightly alkaline, and takes up CO_2 to form carbonates and bicarbonates. Most natural fresh waters also contain variable amounts of alkali, thus binding considerable quantities of carbon dioxide with a very low tension of dissociation (Krogh [1904]).

The total amount of dissolved gases can be extracted and determined by the mercury pump and subsequent gas analysis, but in order to obtain all the carbon dioxide from natural waters in this way, it is necessary to acidify (with dilute hydrochloric acid). The method is cumbrous and difficult, and very great care is required to obtain accurate results. It has been used in a few cases only for respiration experiments.

The dissolved oxygen can be determined accurately and easily by titration after the method of Winkler (Cronheim, Bjerrum, Winterstein [1909]), the principle of which is to add manganese chloride and caustic soda with potassium iodide, thus producing a sediment of manganous hydroxide which almost immediately combines with the oxygen present forming manganic hydroxide. When the liquid is afterwards[1] acidified with hydrochloric acid the hydroxides are dissolved and a quantity of iodine set free, which is equivalent to the quantity of oxygen formerly present and which is determined by titration with a solution of sodium thiosulphate.[2]

[1] The interval can be of any desired length from two hours upwards (Bjerrum).

[2] Various methods are in use for standardizing the thiosulphate solution. The writer has found the best plan to be to titrate distilled water saturated with pure air at 15° which is known to contain 7·22 c.c. oxygen per litre (Fox [1907]).

Another titration method worked out by Schützenberger and Risler is somewhat more complicated, but can be used on water containing organic impurities (see Henze [1910]).

Carbon dioxide is determined by boiling it off from a sample of the water after acidification and in a current of CO_2 free air. The carbon dioxide boiled off is generally taken up in baryta solution and titrated (Warburg [1909]).

The determination of the carbon dioxide liberated in respiration experiments is especially difficult and uncertain, partly because the quantity in question is generally a small fraction only of the total quantity present in the water, and partly also because the animals experimented on are often likely to give off substances (urine, fæces and mucus) which will yield some carbon dioxide when the water is boiled after acidification. It is certainly best, therefore, to acidify slightly only, and to drive the carbon dioxide off by a current of air at a comparatively low temperature, but even with this precaution too high results for carbon dioxide are often unavoidable.

A very serious difficulty and source of error in experiments on aquatic respiration is the action of bacteria as pointed out by Knauthe [1898]. It is generally impracticable to make experiments under aseptic conditions, but when the water employed contains few bacteria only it will take a certain time before they multiply so far as to influence the results seriously. Winterstein [1909] found that when pure sea water is kept in darkness at ordinary temperature without any animals in it, the oxygen content decreases steadily, during the first days about 0·1 c.c. per litre per day.

It has been shown by Winterstein [1908] and Henze [1910, 2] that the respiratory exchange of most aquatic animals is practically unaffected even by considerable variations in the oxygen content of the water. This fact is of importance methodically and facilitates considerably the determination of the oxygen absorption.

While satisfactory respiration experiments cannot be made on air-breathing animals by the simple method of determining the changes in composition of a known volume of air in which the animal experimented on is confined, because the rise in carbon dioxide percentage very soon makes the respiration abnormal and influences the respiratory exchange, the method of enclosing an aquatic animal in a known volume of water, the gases of which have been determined, and analysing the water after a certain time, is as excellent as it is simple. The slight increase in CO_2 tension produced when $\frac{1}{4} - \frac{1}{3}$ of the oxygen is

used up will have no influence whatever on the respiration or gas exchange, and when the oxygen content of the water does not sink below 4 to 5 c.c. per litre the exchange will in almost all cases remain perfectly normal. The principle of this method is very old, since it was employed in the researches of Humboldt and Provençal in 1809, but the technique has, of course, been improved repeatedly.

It is important to guard against the action of bacteria by limiting the duration of the experiment to twelve hours or less (except at very low temperatures), and it must further be borne in mind that when an animal, and especially a fish, is transferred from one vessel to another a considerable time will often elapse before it becomes quiet and the respiratory exchange normal (Lipschütz [1911]).

The technique is extremely simple. A bottle is selected which will hold so much water that the animal can use up about one-third of the oxygen in a suitable time (generally one to six hours). The volume of the bottle is measured and it is filled with water. It is generally desirable to shake the water with air at a temperature just above that at which the experiment is to be performed because that prevents the liberation of air bubbles during the experiment. The animal is put in, and when it has become quiet some more water is run through the bottle and a sample taken for analysis. The bottle is closed and the temperature kept constant during the experimental period. When the animal is sluggish it is necessary to mix the water gently before taking samples.

A number of more or less complicated respiration apparatus for aquatic animals have been constructed by Jolyet and Regnard [1877], Gréhant [1886], Zuntz [1901] and Bounhiol [1905]. They are founded on the Regnault principle, and consist of a water jar introduced in a closed-space apparatus with air which circulates so as to aerate the water in the jar. Analyses of gases both in the water and in the air are necessary when such an arrangement is adopted, and no material advantages are gained to compensate for the complications and the loss of time involved. The only advantage claimed is that the quantity of dissolved oxygen can be maintained nearly constant over a long period and in a comparatively small volume of water, which factors will make for increased accuracy; but since an experiment cannot be extended over a long period on account of the bacteria, and since a decrease of 3 c.c. of oxygen per litre, which can be measured with an accuracy of about 1 per cent., does not affect the respiratory exchange, the advantage is apparent only.

In certain cases, and especially when the natural respiratory movements have been prevented by narcosis, a current of water must be maintained to provide a sort of artificial respiration. Samples of the water are then collected in front of and behind the vessel holding the animal, and the total quantity of water passing during a certain time is measured. Arrangements of this kind have been described by

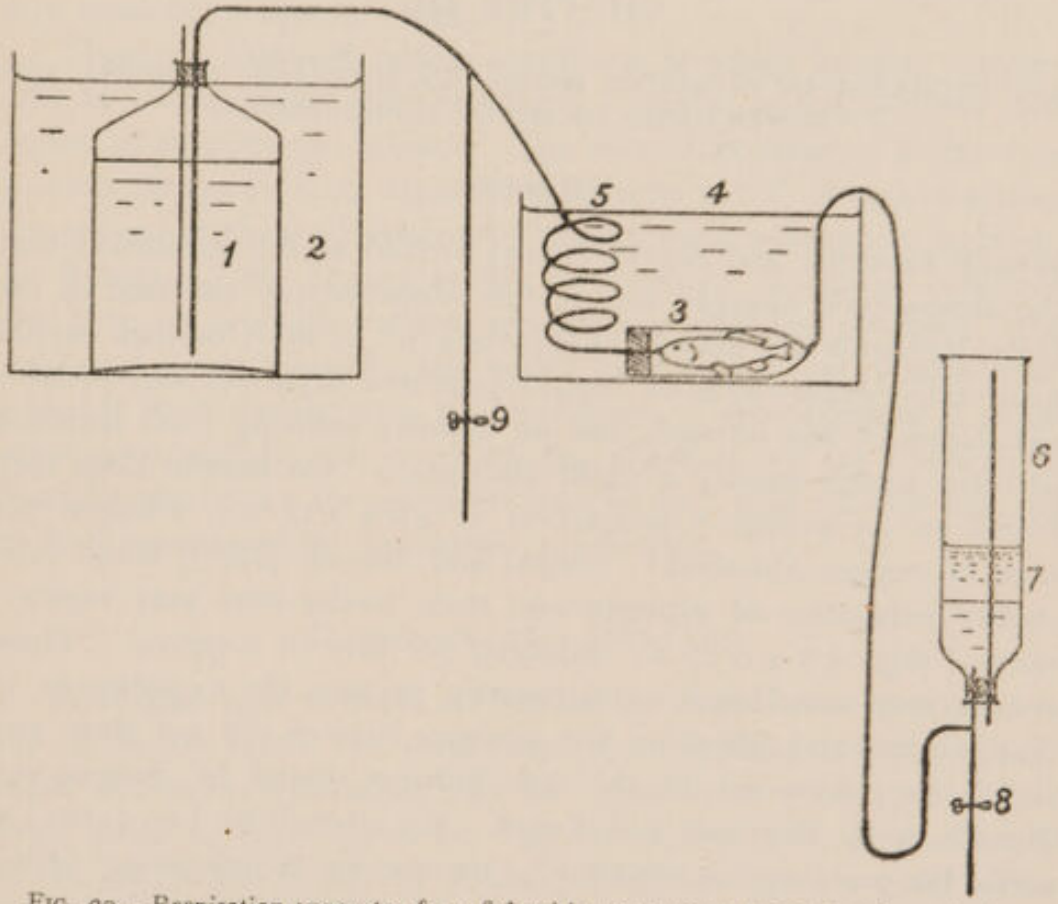


FIG. 20.—Respiration apparatus for a fish with arrangement for artificial ventilation.

Winterstein [1908] who measured the branchial respiration of fishes as separate from the total, and lately by Ege and Krogh [1914] who measured the total oxygen absorption of a narcotized fish. Fig. 20 shows the arrangement adopted by Ege and Krogh. The water is collected and measured in an inverted measuring cylinder (6) and protected against contact with air by means of vaseline oil (7). Samples are drawn at (8) and (9) respectively.

CHAPTER III.

THE EXCHANGE OF NITROGEN, HYDROGEN, METHANE, AMMONIA AND OTHER GASES OF MINOR IMPORTANCE.

NITROGEN.

WHILE Lavoisier and Seguin [1814] arrived at the conclusion that the atmospheric nitrogen was neither absorbed nor excreted by the body, Regnault and Reiset [1849] observed in most of their careful quantitative experiments on healthy animals a slight but very variable exhalation of free nitrogen, and on animals suffering from inanition or other causes usually a slight absorption. On normal dogs they found on an average a production of $4{\cdot}6 \pm 2{\cdot}15$ c.c. nitrogen per litre of oxygen absorbed.[1] Seegen and Nowak [1879] found constantly exhalation of nitrogen and their results were very regular: normal dogs $5{\cdot}5 \pm 0{\cdot}17$ c.c. nitrogen per litre of oxygen.[1] These results were considered untrustworthy because the experiments of Voit, Gruber and others on the nitrogen balance did not show any deficit to correspond to the free nitrogen found by Seegen and Nowak or by Regnault and Reiset. An attempt by Leo [1881] to settle the problem was inconclusive because the technique was faulty, and the question was allowed to remain undecided for a long time. Oppenheimer [1907] found in a series of experiments on dogs that there was almost constantly an absorption of nitrogen (eleven cases out of thirteen) amounting on an average to $2{\cdot}0 \pm 0{\cdot}75$ c.c. per litre of oxygen,[1] but he had no doubt in ascribing the result to experimental errors, and concluded therefore that the gaseous nitrogen did not take any part in the respiratory exchange. About the same time Krogh [1906] working with chrysalides of butterflies, eggs under incubation, and mice, measured excretions of nitrogen amounting to $0{\cdot}39 \pm 0{\cdot}15$ c.c., 0·4 c.c. and $0{\cdot}11 \pm 0{\cdot}07$ c.c. nitrogen respectively per litre of oxygen, and concluded that these insignificant excretions were probably real in so far as they could be ascribed, in the case of the

[1] Averages calculated by Krogh [1908].

eggs and chrysalides, to the liberation of nitrogen which had previously been dissolved in the fats catabolized, and in the case of the mice perhaps to ammonia liberated as such and converted into free nitrogen by combustion in the respiration apparatus. The sources of error of the earlier investigations were inquired into, and it was shown that the figures of Regnault and Reiset, when rightly interpreted, were in accordance with the result that the excretion of gaseous nitrogen, if any, must be extremely slight.

There are, however, certain conditions in which gaseous nitrogen will be excreted and may constitute a serious source of error with regard to the nitrogen balance. The alimentary canal of herbivorous animals always contains denitrifying bacteria and if nitrates or nitrites are present in the food (beetroot) these substances disappear, as shown by Röhmann [1881], more or less completely. Röhmann concludes that they are probably reduced and perhaps yield free nitrogen. Unpublished experiments by the writer have shown that nitrates when added in the mercury pump to the contents of the cæcum of a rabbit are at least partially converted into free nitrogen, but the excretion of free nitrogen from a living animal after feeding with nitrates has still to be demonstrated by respiration experiments.

Hydrogen and Methane.

Hydrogen and methane are formed by fermentation processes in the alimentary canal. In carnivorous animals the quantity is usually small but in herbivorous it may be considerable. The presence of these gases in the expired air was demonstrated by Regnault and Reiset, and it was shown by Tacke [1884], who gave a good bibliography of the earlier literature, that they are chiefly excreted through the lungs and not through the anus. In herbivorous animals they must be taken into account in metabolism experiments, amounting for instance in rabbits to 2 to 8 c.c. per kilogram and hour (Tacke) and in goats to 10 to 30 c.c. (Boycott and Damant [1907]).

Carbon dioxide is formed together with hydrogen and methane in the gut. Boycott and Damant found on goats that the ratio of CO_2 to $H_2 + CH_4$ produced in the intestine was variable, but on an average probably above 2. The intestinal CO_2 must therefore amount to at least 10 per cent. of the total, and as this carbon dioxide is produced by fermentation and not by oxidation the true respiratory quotient is much lower than the apparent. This may have been a

source of error in some of the experiments purporting to demonstrate a formation of fat from carbohydrate.

Oppenheimer [1909] has made experiments to show that free hydrogen cannot be oxidized in the body of the dog.

Carbon Monoxide.

A production of carbon monoxide in the animal body has never been demonstrated or indeed assumed, but experiments have been made by several investigators to see whether it could not be oxidized. It has been found by Haldane [1900] that it cannot be oxidized by mice. This result has been confirmed by Weisz [1906] and found to be the same also in rabbits, pigeons and earth-worms; but Weisz found, contrary to his expectations, that meal-worms, the larvæ of *Tenebrio molitor*, will absorb and probably oxidize notable quantities of carbon monoxide, 7 to 15 c.c. per kg. in twenty-four hours. A renewed investigation of this most extraordinary power of oxidation has recently been undertaken by M. Krogh [1915], using very refined methods of analysis. She was unable to confirm Weisz' result and found that carbon monoxide is not attacked at all by the *Tenebrio* larva or pupa. The respiratory exchange (oxygen and carbon dioxide) is exactly the same in an atmosphere containing 5 per cent. of carbon monoxide as it is in air.

Ammonia.

Several observers have tried in various ways to demonstrate the existence of traces of some highly poisonous organic substance in the expired air of man and mammals. This literature has been critically reviewed by Formanek [1900] who demonstrated the inconclusive nature of the evidence adduced, and found that the substance responsible for the observed effects of injecting water condensed from expired air was nothing but ammonia. This gas had also been found in the expired air of man and animals by several earlier observers. The quantities found in the expired air of man are of the order of 0 to 20 mg. in twenty-four hours. Formanek is of opinion that the ammonia when found does not come from the lungs but is a product of bacterial processes in the respiratory tract. This is borne out by the researches of Magnus [1902] who found that the alveolar wall is impermeable to ammonia.

In certain invertebrate animals ammonia and volatile amines are the chief products of the nitrogen metabolism, and are regularly present

in the expired air, as found for instance by Weinland [1906] in the larvæ of blowflies.

Acetone.

During inanition and also in several pathological conditions, notably diabetes, acetone is normally present in the expired air. The ratio of the acetone excreted through the lungs and that found in the urine is very variable however. Jorns [1903], who gives a review of the literature, found in inanition experiments on himself the quantity of acetone in the expired air to be from 0 up to 12 mg. per hour.

"Kenotoxin."

In experiments on man Weichardt [1908] has bubbled expired air through acidulated water, concentrated the water by boiling *in vacuo* and detected a substance of proteid nature, a "kenotoxin," in the residue. In his latest publication [1911] the "kenotoxin" is shown to originate from drops of fluid carried off mechanically from the wall of the respiratory tract.

CHAPTER IV.

THE STANDARD METABOLISM OF THE ORGANISM. DEFINITION AND DETERMINATION.

THE complex problem concerning the catabolic processes taking place in the animal organism has been attacked on three different lines, one might almost say by three independent armies of investigators. One line of attack is the study of the respiratory exchange of the animal organism as a whole, its variations from internal causes, and the factors by which it may be influenced. Another line is the study of the exchange of single organs, tissues, and cells with the variations observed during activity, under the influence of chemical substances and so forth. A third line again is the study of the catabolism of single substances, of the intermediate stages in the processes, of the enzymes and other agencies which bring about catabolism. Though there can be no doubt that ultimately the three attacking forces will have to join hands, to support each other, and to utilize in common the progress achieved by each, we find that at present they are too far apart for concerted action and the achievements in one field do not materially help the advance in the others.

At present it is legitimate therefore to review them separately, and in this monograph only casual references will be found to the metabolism of single organs or cells and none whatever to the catabolism of definite substances.

In studying the respiratory exchange of an animal we have to do with a quantity which is variable in the extreme. In man the maximum respiratory activity is 10 to 20 times the minimum in one and the same adult individual, and in many lower animals the maximum may be several hundred times the minimum. The problem before us is to define the conditions of these variations, to eliminate them as far as possible, and then to study their influence one by one and quantitatively.

The factor which is of paramount importance in determining the metabolism is the functional activity. In the organism as a whole we cannot have metabolism without some functional activity. In in-

vestigations made upon isolated organs, and especially upon muscles, it has been shown that a certain minimum or "basal" metabolism involving respiratory exchange is inseparable from the life of every organ, and will persist when the organ is doing no work whatever so long as the *ability to do work* remains.

The basal metabolism of an organ is not a constant quantity, but can be modified experimentally by varying the external conditions (e.g. the temperature) and may probably vary also from internal causes.

When an organ is doing work the metabolic processes are invariably increased, and in cases where it has been possible to measure the work a certain proportionality is observed between the work and the increase in metabolism above that basal amount which corresponds to the conditions of the moment.

In the organism as a whole in which the functional activity cannot be brought to a complete standstill we cannot determine basal metabolism in the strictest sense of that term, but we may obtain an approximation to it which can be defined as the metabolism corresponding to a minimum functional activity. This is often termed basal metabolism ("Grundumsatz," Magnus-Levy [v. N.]), or maintenance metabolism ("Erhaltungsumsatz," Loewy [Op.]). I do not consider any of these terms as very appropriate; the first because we can only get an approximation, and not even a close one, to the true basal metabolism, and the second because the metabolism in question has nothing to do with the maintenance of the organism, which certainly cannot be maintained upon it for any length of time. I shall prefer to call the metabolism as defined above the "standard metabolism" (Krogh, 1914, 2), implying simply that all variations in metabolism brought about by functional activity have to be referred to this quantity as a standard.

In practice the minimum functional activity is taken to be attained when voluntary muscular movements are eliminated and no food is being digested or absorbed.

The influence of digestion and absorption of food is in most cases easy to eliminate, though certain herbivorous animals cannot be without food for a sufficient time so as to eliminate it completely, but the muscular movements are often difficult to exclude, and the value of a large number of experiments in which the maintenance of standard conditions was essential has been seriously impaired because muscular movements were not rigorously excluded. In man the muscular movements are excluded by willed muscular inactivity ("vorsätzlicher Muskelruhe," Johansson [1897]) or during sleep. In animals the com-

plete rest is sometimes difficult to obtain and still more difficult to ascertain. Benedict's recording cage (see p. 15, fig. 2) will be extremely serviceable in this respect, but the most reliable results are undoubtedly obtained after immobilization with curari (Zuntz [1876], Frank and F. Voit [1902], Tangl [1911]). The figures obtained by Tangl and his pupils on curarized dogs show a wonderful constancy over long periods as shown by the table quoted on p. 70. In many cases, and especially in lower animals (frogs, fishes, invertebrates), standard conditions with regard to the muscles can be brought about by means of narcosis with urethane (Krogh [1914, 1, 2]) which has, like curari, no specific influence upon the respiratory exchange. Raeder [1915] has recently used urethane with complete success also on mammals (see p. 71).

The standard metabolism is utilized as the basis for the study of the influence of various factors on the metabolic processes and for comparisons between different animals, and before we proceed further it is necessary therefore to examine if and how far it can be considered as constant.

It must always be kept in mind that it is at best only an approximation to the true basal metabolism, the metabolism in the absence of all functional activity. Several important functions, circulation, secretion in kidneys and other glands are never interrupted, and in most experiments on standard metabolism the respiratory movements take place also.

The metabolism of the heart during rest has been estimated by Zuntz and Hagemann [1898] for the horse and by Loewy and v. Schrötter [1902] for man. In both cases it is found to be about 4 per cent. of the total standard metabolism. This figure is based upon an estimate of the work performed (blood pressure × minute volume) and the assumption that the mechanical efficiency of the heart muscle is about the same as that of skeletal muscles (30 per cent. according to Zuntz. According to the work of Evans [1912] (on dogs) the mechanical efficiency is probably much lower (about 10 per cent.) and the metabolism of the heart may easily be as much as 15 per cent. of the total. Variations in the circulation rate or in the blood pressure may therefore easily have quite an appreciable effect upon the standard metabolism.

The metabolism of the kidney appears to be something like 5 per cent. of the total according to experiments by Barcroft and Straub [1911] and by Tangl [1911] on cats and dogs. For other glands

information in such a form that it can be compared with the standard metabolism does not appear to be available.

The metabolism corresponding to the respiratory movements has been determined by Speck [1892] for man as 8 to 10 c.c. of oxygen per litre of air respired, but to his result a correction must be applied (Zuntz and Hagemann) reducing it to 6 c.c. per litre. Loewy [1899] found about 5 c.c. of oxygen per litre ventilation, Bornstein and v. Gartzen [1905] 27 cal. = 5·6 c.c. of oxygen, and Zuntz and Hagemann for the horse about 3·5 c.c. of oxygen per litre ventilation. As the ventilation of a man at rest is something like 7 litres per minute, about 40 c.c. of oxygen or 15 per cent. of the total exchange during complete rest should be required for the mechanical function of respiration. Small variations in ventilation which occur often enough even during rest may have a noticeable effect upon the standard metabolism as measured, and it is obvious that the abolition of the respiratory movements brought about by curari must appreciably reduce the metabolism.

The aggregate influence of the functional activities in the resting body amounts according to the above to at least 25 per cent. of the total standard metabolism. The true basal metabolism is therefore at most 75 per cent. of the standard. It may be and probably usually is still lower. The reason for drawing a sharp distinction between basal and standard metabolism is therefore apparent.

According to the recent work of Mansfeld and his collaborators [1915] the tone of skeletal muscles is brought about by sympathetic innervation and not directly as hitherto assumed. The tone is therefore not abolished by curari except in very large doses, and there can be little doubt that in the standard conditions as at present defined the muscular tone enters as a variable factor of considerable importance. A detailed study of the effect of muscular tone upon metabolism is certainly one of the chief desiderata in the physiology of the respiratory exchange.

The constancy of the standard metabolism has been studied experimentally several times. On man it has been found that the standard metabolism is a constant quantity practically the same during sleep and when the subject is awake and remaining absolutely quiet[1] (Loewy

[1] This statement has recently been controverted by Benedict [1915] who maintains that the metabolism during deep sleep is lower (in the case of a man fasting for thirty-one days by 13 per cent. on an average) than when the subject is awake but quiet. It would seem rather probable that differences in the relaxation of muscular tone during sleep might account for the differences recorded.

[1891]). Differences of a few per cent. are often observed (Johansson [1896, 1897, 1898]), but variations of 1 to 2 litres in the ventilation per minute are sufficient to explain them.

In series of experiments made in short intervals during twenty-four hours Magnus-Levy [1893] and Johansson [1898] observed irregular and slight variations. Johansson found for instance on himself an average CO_2 production per hour of $22{\cdot}2 \pm 0{\cdot}8$ gr. The average deviation is 3·6 per cent. of the total. If the body weight (and composition) remains unaltered the standard metabolism will remain constant over very long periods (Johansson, Magnus-Levy). Magnus-Levy's experiments lasted two years and Johansson's seven months. A series of fifty-one determinations by Benedict and Cathcart [1913] of the standard metabolism of an athlete made almost daily over a period of three months show a variation of $\mu = \pm 4{\cdot}9$ per cent.,[1] which is all that can be desired on a person not specially trained to maintain muscular inactivity.

Experiments on several warm-blooded animals have confirmed these results (Rubner, 1887), and it has been shown further that curari when not given in excessive doses has no influence upon the respiratory exchange which remains the same as during natural complete rest (Frank and Voit [1902], Frank and Gebhard [1902]); when given in very large doses (Zuntz, 1876) it is stated by Mansfeld [1915] to abolish the muscular tone and thereby lower the respiratory exchange considerably.

The remaining chapters of the present monograph will deal with the standard metabolism, its variations under the influence of internal and external factors, its alterations during the life of the individual, and the differences found between different individuals, species, and larger systematic groups. In a great many cases, however, experiments must be considered in which standard conditions have not been maintained, because better material is not available.

The metabolism depending upon functional activity will not be discussed in detail as that will be treated in a special monograph of this series. For present purposes it is necessary only to emphasize the fact that, as in isolated organs, the functional activity of the whole organism causes an increased metabolism which is *added* to the standard. Careful experiments which demonstrate this fact have been made by Johansson [1901]. He found that when he lifted a

[1] Calculated by Lindhard, Pfl. Arch., 1915, **161**, 346.

constant weight to a constant height a variable number (N) of times during a period of constant length (one hour) the metabolism, measured by the output of carbon dioxide, could be accurately expressed by the formula

$$[CO_2] = N\not{p} + q$$

in which q is the standard metabolism and $\not{p}$ a constant, the metabolism corresponding to lifting the weight once.

Johansson and Koraen [1902] found further that when such work was performed after the intake of varied amounts of food both influences produced independent increases in metabolism which were additional in character (see also Johansson [1908]).

CHAPTER V.

THE INFLUENCE OF INTERNAL FACTORS UPON THE STANDARD METABOLISM.

THE fundamental problem which ought to be dealt with in the present chapter is this: Supposing all external factors to remain constant and the supply of oxidative material and oxygen to be sufficient, is the oxidative energy of the resting cells a constant quantity or can the oxidations be increased without any functional activity taking place? This fundamental problem which involves the determination of basal metabolism cannot at present be solved, and we must confine ourselves to the results obtained by the study of the standard metabolism.

The Influence of the Central Nervous System.

There is at present no proof that an increase in metabolism can be induced from the nervous system without a corresponding increase in functional activity, but in certain cases the possibility cannot be excluded and further experimentation is therefore highly desirable.

Rubner [1887] found that when warm-blooded animals (especially dogs) were exposed to low temperatures there was a considerable increase in metabolism. In many cases muscular movements could not be observed, the animals lying absolutely quiet. He introduced the term "chemical heat regulation" for this process, and was of opinion that the metabolic processes in muscles remaining at rest could be increased through nervous stimulation. It has not been proved, however, that the muscles really remained at rest. Slight shivering movements may easily have escaped attention, and there may have been an increased muscular tone apart from actual movements. The graphic records obtained by Benedict and Homans [1911] on a dog show shivering movements at all temperatures below 25° and increasing regularly in intensity with decreasing temperature.

It remains to be demonstrated, however, that there is a quantitative correspondence between the muscular movements recorded during "chemical heat regulation" and the measured increase in metabolism.

The numerous experiments made on man by Speck [1883], Loewy [1890], and Johansson [1897, 1898, 1904] show that in man at least no chemical regulation of heat production exists apart from distinct muscular activity. At low surrounding temperatures the respiratory exchange is never increased unless the subject is unable to suppress shivering or other movements.

Krarup [1902], experimenting on rabbits, found that in these animals the increase in metabolism observed when the surrounding temperature was lowered was in almost all cases accompanied by visible muscular movements, though he records two exceptions. After urethane the movements were generally absent and the respiratory exchange rose and fell directly with the temperature, but *when* they were present the variations were in the opposite direction, as in normal animals. After pithing, all movements ceased and the metabolism varied directly with the temperature. The same is the case also after curari as found by Velten [1880]. Velten's results show that if a chemical heat regulation can be induced from the central nervous system the stimulus must travel along the motor nerves, since these alone are affected by curari. This does not appear likely, and the most probable conclusion seems to be that just as no nervously induced increase in functional activity is possible without a corresponding increase in metabolism so also there is no nervously induced increase in metabolism without an increase in functional activity.

The Thyroid Gland.

Certain glands possessing internal secretion have been shown to influence the standard metabolism in man and mammals, and this is the case especially with regard to the thyroid gland.

Magnus-Levy [1897] found in a long series of experiments on a patient with myxœdema that the standard metabolism was remarkably low (2·9 c.c. oxygen per kilogram and minute) though not lower than it has been found occasionally in perfectly normal men. When the patient was treated with thyroid tablets it rose during three weeks to 5·5 c.c. per kilogram and minute. It then fell off again towards the former figure, being 3·3 after 7 weeks and 3·0 later (7 to 13 weeks). The treatment was repeated twice with the same result. In the intervals between the treatments the myxœdematous symptoms were almost absent at first but they began to appear each time before the treatment was renewed.

In normal people treatment with thyroid preparations sometimes,

but by no means regularly (Anderson and Bergmann [1898]), causes a pronounced increase in standard metabolism (Magnus-Levy [1895]). In patients suffering from exophthalmic goitre the respiratory exchange is increased compared with normal (Magnus-Levy [1895], Undeutsch [1913]) and may reach 8 c.c. of oxygen per kilogram and minute or double the normal (Hirschlaff [1899]).

Magnus-Levy points out that the nature of the effect of the thyroid gland is difficult to ascertain. In exophthalmic goitre muscular shiverings and restlessness are important symptoms which are never absent in severe cases. In Magnus-Levy's experiments no visible movements occurred, but nevertheless the possibility that we have to do with an effect on muscular activity (or tone) cannot at present be excluded. Experiments ought to be made on animals on which curari could be used to suppress any influence upon the muscular activity, but an increase of the true basal metabolism can be demonstrated only if it can be shown that the thyroid has no influence upon the muscular tone.

The Hypophysis.

Benedict and Homans [1912] have studied very carefully the effects of hypophysectomy on dogs. They made use of the recording cage described above (p. 15) and selected for comparison only such periods during which the animal remained quiet. There is no doubt therefore that their comparisons are valid and represent standard conditions. The day to day variations in metabolism are, however, remarkably large. They found that some days after the removal of the hypophysis the metabolism and pulse-rate decreased, in most cases considerably. In young animals the growth stopped and a tendency to deposition of fat developed gradually. The metabolism remained low until, shortly before death, a large drop in metabolism and body temperature took place.

The Sexual Glands.

The effect of the sexual glands upon basal metabolism is even more doubtful than that of the thyroid, though a certain effect upon standard metabolism has been observed both on dogs and on man.

Loewy and Richter [1899] found in experiments on a male dog that castration produced after an interval of eleven days a distinct decrease in the respiratory exchange "when the dog was lying absolutely quiet". Though the weight of the dog decreased, the oxygen per

kilogram and minute went down 14 per cent. In female dogs the effect of castration took a longer time to develop, but the metabolism finally went down from 6·16 c.c. of oxygen per kilogram and minute to 5·05 c.c. (20 per cent.). There was an increase in weight, but a decrease in absolute metabolism amounting to 9 per cent. Ovarial substance, which had no effect on normal dogs, produced in the castrates, both male and female, a very considerable increase in the standard metabolism. Leo Zuntz [1908] observed a decrease in metabolism in some cases of extirpation of the ovaria in women, but the results were not constant. The change took place after a considerable interval of time.

Lüthje [1902], who selected two young male dogs and two females, all from the same litter, and castrated one of each sex, did not observe any distinct difference between the castrates and the controls in the respiratory exchange (carbon dioxide determined in 24-hour periods) though he continued his observation over several years. As shown in the criticism by Loewy and Richter [1902] his method would not be likely to give trustworthy evidence with regard to standard metabolism.

A priori it would appear perfectly natural to expect that certain hormones should be able to stimulate the oxidative energy of the tissues, acting as catalysers, but the experimental evidence in favour of the process must in the writer's opinion be regarded as inconclusive.

Experiments on the influence of internal factors upon standard metabolism have so far been made only on mammals, and while their correct interpretation even for this class of animals is doubtful, it would be hazardous to attempt any conclusion for the whole animal kingdom. In Chapter VIII, section 3, various observations and researches will be mentioned, which suggest that the standard metabolism in certain lower animals may be variable within wide limits independently of all external influences.

CHAPTER VI.

THE INFLUENCE OF CHEMICAL FACTORS UPON THE RESPIRATORY EXCHANGE.

The Influence of Various Drugs.

IN the present section we have to consider the influence of certain drugs which have been shown or are supposed to act on the respiratory exchange. The fundamental problem in this case as in others is to distinguish between such substances which will influence the oxidative energy of the tissues and others which, though they may influence the respiratory exchange, do so by modifying the functional activity of one or more organs. In certain cases a direct influence upon the basal metabolism is easy enough to establish, while in others the nature of the effect is very doubtful.

THE INFLUENCE OF DRUGS UPON OXIDATIONS IN SINGLE CELLS.

In "Ergebnisse der Physiologie," 1914, Warburg has given an extremely valuable account of the investigations undertaken by himself and his collaborators on the influence of a large number of substances upon the oxidations in single cells. Though the greater part of his work is outside the scope of the present monograph, it seems desirable here to summarize some of his results as a basis for comparisons with the effects of the same classes of substances upon entire organisms.

Warburg divides the substances which may influence the oxidations in animal cells into two groups: (1) substances which are soluble in lipoids, and (2) lipoid-insoluble substances.

Substances belonging to the former group will always penetrate into animal cells and become dissolved in the "protoplasm". The effect of any one of these substances upon the oxidations in different cells is qualitatively and quantitatively nearly the same, and substances which are chemically related show analogous effects.

Substances belonging to the second group (salts, sugars, amino acids) do *not* behave uniformly with regard to different cells. Some of them may penetrate into certain cells but remain excluded from others, some may influence the rate of oxidations in certain cases, and leave it intact in others.

1. The lipoid-soluble substances may act in two different ways according to their chemical structure. In some of them the effect depends upon the presence in the molecule of certain chemically active radicles and these are called by Warburg specific (*a*), in others chemically active radicles are absent, they are non-specific (*b*). This latter group comprises the ordinary narcotics.

1. (*a*) Among the specific lipoid-soluble substances Warburg has investigated aldehydes, which inhibit oxidations, ammonia and amines which stimulate oxidations in very small doses, while they inhibit in greater concentrations, and prussic acid which is the most powerful inhibiting substance known, a concentration of $\frac{n}{100000}$ KCN being sufficient to diminish the oxygen consumption of sea urchin eggs about 30 per cent.

1. (*b*) The non-specific narcotics have invariably an inhibiting effect upon oxidations, and for each series of homologous substances the effect increases with the number of carbon atoms in the molecule as shown by the following concentrations of urethanes which have been observed to diminish the oxidations in different cells by 30 to 70 per cent.:—

	Concentration in Red Corpuscles of Birds.		Concentration in Central Nervous System of Frogs.	
Methyl-urethane	1·3	Mol.	1·3	Mol.
Ethyl- ,,	0·33	,,	0·45	,,
Propyl- ,,	0·13	,,	0·13	,,
Butyl- ,, (iso)	0·043	,,	0·06	,,
Phenyl- ,,	0·003	,,	0·006	,,

The effects of each substance on very different cells are nearly the same and the effects on a non-vital enzyme reaction, the alcohol fermentation in yeast juice, are also of about the same magnitude.

2. The lipoid-insoluble substances.

Chloride of sodium.—A solution of pure NaCl, isotonic with sea-water, increases enormously (five times) the respiratory exchange of fertilized eggs of the sea urchin *Strongylocentrotus*. This effect can be abolished by a trace of NaCN or by $CaCl_2$. The pure NaCl solution destroys the eggs very rapidly and in this phase the oxidative energy falls off rapidly. On the respiration of a number of other cells (red corpuscles, muscles) NaCl has no effect whatever.

Ions of heavy metals.—The ions of gold, silver, and copper, in concentrations about 10^{-5} normal, increase the oxidations in fertilized

and unfertilized eggs of sea urchins considerably—20 to 50 per cent. in the case of fertilized, 300 to 800 per cent. in the case of unfertilized eggs.

Hydrogen ion concentration.—Changes in hydrogen ion concentration of the sea water may have a very profound influence upon the oxygen absorption of fertilized eggs of sea urchins. When the water is made more acid the oxidations are inhibited while they are greatly stimulated by alkalis.

H ions.	Relative O_2 Absorption.	
10^{-6} normal	0·36	No segmentation
10^{-8} ,,	1·00	Normal segmentation
10^{-11} ,,	2·1	No segmentation

Loeb and Wasteneys [1913, 3] have confirmed the result of Warburg with regard to bases, but only in so far as they found that a considerable increase in alkalinity, which was very harmful to the eggs, had the effect described, while changes in reaction within physiological limits, which they take to be $H^{\cdot} = 10^{-7}$ to $H^{\cdot} = 10^{-9}$, have no effect whatever.

The Influence of Drugs upon the Respiratory Exchange of Entire Organisms.

The influence of drugs upon the respiratory exchange of entire organisms runs parallel in certain cases to that observed on single cells, but more often a parallelism cannot be established owing very probably to the regulating mechanisms brought into play.

1. (*a*) *Prussic Acid.*—Of lipoid-soluble specific substances prussic acid, HCN, and phosphorus have been studied on higher animals.

The action of prussic acid is very powerful, and it obviously diminishes or destroys the oxidative power of the tissues. Claude Bernard [1857] had made the observation that when an animal was poisoned with prussic acid the venous blood became of a bright red colour which seemed to indicate that the tissues had lost the power of taking up oxygen. A closer study was made by Geppert [1889] who proved that this explanation was correct. After injection of KCN or HCN (1 c.c. of 0·25 per cent. KCN per kilogram) a comparatively slow and usually not lethal intoxication is brought about, which is characterized chiefly by a considerable decrease in the oxygen absorption and also in the carbon dioxide production. The effect on the CO_2 elimination is sometimes obscured, because there is always an increased ventilation of the lungs by which CO_2 is washed out (Geppert). At a certain

stage of the intoxication convulsions are the most prominent symptom, but even during these the oxygen absorption is diminished and may be less than half the exchange during normal rest. When the toxic symptoms begin to disappear the animal is usually paralysed, but at this stage the oxygen absorption is increased as compared with that during the convulsions and may be increased above the normal. Geppert determined the oxygen content of the arterial and venous blood during intoxication with potassium cyanide and found the arterial to be normal while the venous contained, as one would expect from the colour, much more oxygen than usually. Potassium cyanide has no effect on the combination of hæmoglobin with oxygen, and the only possible explanation of the facts observed is that the power of the tissues to utilize oxygen is diminished. The poison appears to affect all tissues in like manner. Loeb and Wasteneys [1913, 1, 2] have observed that hydrogen cyanide inhibits also the oxidations in fish embryos and in medusæ (*Gonionemus*).

A detailed study of the mechanism of the action of prussic acid has not been attempted since Geppert's excellent work was published. It is not known whether it is the oxidation stage alone of the catabolism which is inhibited or if preliminary stages are also or perhaps exclusively affected. The results obtained by Loewy, Wolff and Österberg [1908] concerning the effect of prussic acid on protein metabolism would seem to point towards the latter alternative. It is obvious that a search for intermediate catabolites produced during intoxication with prussic acid ought to be made, and the possible effect of the poison on anoxybiotic organisms should also be studied. Geppert mentions as a chemical analogy to the action of prussic acid on living tissues that traces of prussic acid inhibit the oxidation of formic acid by iodic acid.

Phosphorus.—A similar though much less pronounced effect than that of prussic acid on the metabolism is shown by phosphorus, according to experiments by Bauer [1871] on dogs, Scheider [1895] on rabbits, and Welsch [1905] on dogs and rabbits. The action of phosphorus is chronic and cumulative while that of prussic acid develops and disappears in a very short time.

1. (*b*) Lipoid-soluble non-specific substances or *narcotics* do not appear to have any influence upon the oxidative processes of higher animals in concentrations which are sufficient to bring about narcosis. This result, though seemingly in contradiction to that mentioned above for single cells, is really in good agreement with it, since the concentra-

tions necessary to produce a measurable inhibition of oxidations in cells are several times larger than those necessary to bring about narcosis or to stop the segmentation of sea urchin eggs (Warburg [1910]).

It has been observed repeatedly (Boeck and Bauer [1874], Fubini [1881], Gréhant [1882], Rumpf [1884], Dreser [1898], Impens [1899]) that substances such as morphine, chloral, codeine, etc., had a depressing influence upon the respiratory exchange, but in these experiments the necessary precautions were not observed in so far as standard conditions were not secured before the drugs were administered. Loewy [1891] found on man that the respiratory exchange in the narcotic sleep, after morphine or chloral, was either identical with that during natural sleep (or willed muscular inactivity) or only so much lower as would correspond to the decrease in pulmonary ventilation caused by morphine. Krogh [1914] has observed that the respiratory exchange was the same in frogs narcotized with ethylurethane as in curarized frogs and also in normal frogs at low temperatures, when the animals remain quiet. Ege and Krogh [1914] found that a gold-fish which was very quiet at all temperatures showed the same oxygen absorption when under urethane as in the normal condition. Loeb and Wasteneys [1913, 1, 2] found that chloroform or urethane in narcotic doses had no effect on embryonic fishes and medusæ.

2. Lipoid-insoluble substances.

Chloride of sodium.—Tangl [1911] found in experiments on curarized dogs, the metabolism of which was studied in a long series of short experiments, that the injection of sodium chloride (usually 100 to 150 c.c. of 5 per cent. NaCl) in animals of about 7 kg. produced a considerable rise in the metabolism lasting several hours, and varying in amount between 15 and 39 per cent. of the standard. I quote as an example his exp. XV. on a dog weighing 5800 gr:—

TABLE IV.

Time, hrs.	Per Minute c.c.		
	O_2.	CO_2.	R.Q.
10·46	45·65	35·59	0·780 [1]
11·08	46·76	38·95	0·833
11·27	46·47	37·52	0·808
12·07	52·76	42·31	0·802 [2]
12·27	53·31	40·21	0·755
1·44	52·21	39·81	0·763
4·04	52·32	37·66	0·720

[1] Both kidneys removed before experiment.

[2] From 11·45 to 12·31 injection of 145 c.c. of 5 per cent. NaCl into the jugular vein.

The effect was most pronounced on the oxygen intake, while the CO_2 output was much less affected.[1] Tangl's experiments were performed on animals whose kidneys had been removed and the work of excreting the NaCl cannot therefore be responsible for the increase in metabolism.

The investigation of the influence of NaCl was continued by Verzàr [1911] who found that a similar though slightly greater increase was produced also in curarized dogs with intact kidneys and further that even 1 per cent. or 0·75 per cent. solutions of NaCl produced a distinct increase in metabolism.

Raeder [1915], who worked on urethanized rabbits and whose technique is in several respects an improvement upon Verzàr's, confirmed these results to a certain extent, but the increases in metabolism observed by him were smaller and may, in his opinion, be due simply to the increased functional activity of the heart and kidneys.

Lusk and Riche [1912, 1] found that ingestion of saline solutions (150 c.c. of 4 per cent.) had no influence upon the metabolism of the resting dog.

Hydrogen ion concentration.—Alterations in the hydrogen ion concentration of the organism are possibly responsible for the effects observed in mammals of injections or feeding with alkalis and acids. The inference is by no means certain, however, as it appears doubtful whether the hydrogen ion concentration of the blood or tissues has been at all changed in the experiments in question.

Lehmann [1884] found that alkali produced a slight increase (5 per cent.) and acid a slight fall (5 per cent.) in the metabolism of curarized rabbits. His results have been confirmed by Chwostek [1893] as regards acids and by Loewy [1888, 1903] as regards alkalis. Loewy found that the metabolism of a dog rose 30 per cent. by feeding it for twelve days with 3 gr. of sodium carbonate per day. On man a dose of 5 gr. of sodium carbonate per day was without effect. Raeder found that injections of small doses of acids or alkalis were either without effect or caused a slight increase in the metabolism corresponding to increased functional activity of the heart or kidneys, while larger, toxic, doses invariably produced a decrease in the metabolism. This last effect was observed also by Leimdörfer [1914].

Amino acids.—Graham Lusk [1912, 2] has found that comparatively

[1] In several of the papers here under review rather far-reaching conclusions are drawn from changes observed in the respiratory quotients. As pointed out above (p. 16) these must be regarded with suspicion.

small amounts (20 to 25 gr.) of certain amino acids given per os to dogs brought about an increased heat production lasting several hours. The increase found was very considerable after glycocoll (from 64·8 to 85·7 Cal. in a 4-hour period), less after alanine (64·8 to 77·4), slight only after tyrosine and leucine, and altogether wanting after glutaminic acid. The increase in metabolism fell short in every case of the calorific value of the amount of amino acid given, but was considerably in excess of the amount catabolized as determined by the simultaneous increase in urinary nitrogen. Lusk concludes that the amino acids act by stimulating the catabolic activity of the tissues, but the inference, though very probable, does not appear to the writer as conclusive, especially because the nitrogen of the urine is not in short periods a reliable index of the nitrogen metabolism.

The effects of glycocoll have lately been studied by Wolff and Hele [1914] working on decerebrate dogs. They have administered glycocoll both per os (three experiments) and intravenously in saline (three experiments). By the first method of application they find no effect in two experiments and a slight and doubtful one in the third. After the intravenous administration there is in every case a distinct rise in metabolism which may, however, be due partly and perhaps chiefly to the saline (see above, p. 70).

Urea.—Tangl [1911] found a slight increase in metabolism after injection of urea solutions, but the reality of this appears doubtful, the more so as Lusk and Riche [1912, 1] saw no effect after administration of urea to dogs per os.

Phlorizin.—According to experiments by Belàk [1912] on curarized dogs phlorizin should produce a very slight increase in standard metabolism irrespective of the increased work of the kidneys. The conclusion is not, however, warranted by the numerical results of the experiments.

Adrenaline was found by Hàri [1912] to diminish the respiratory exchange, especially the oxygen consumption, in curarized dogs. Hàri thinks that this may be due to a deficient circulation and consequent oxygen lack.

Baths.—Winternitz [1902] found that saline baths had no influence upon the standard metabolism of men. An increase of 10 to 12 per cent. was produced by carbonic acid baths (1 per cent. saline saturated with CO_2) and a still greater by carbonic acid in 2 to 3 per cent. saline. A mustard bath (200 to 700 gr. mustard in water) of 60 minutes' duration increased the metabolism 25 per cent. and the exchange remained

high for at least an hour afterwards. The mechanism of these effects is unknown, though it is probable that it stands in some relation to the erythema of the skin produced.

The Effects of Variations in the Oxygen Supply upon the Respiratory Exchange.

In 1873 Pflüger expressed the view that the animal cell itself determines its own respiratory exchange, and that the oxidations are independent within wide limits of the oxygen supplied to it. This view was based almost exclusively on speculative considerations of a teleological character and on the assumption that the oxygen supplied to the cells is normally in excess of their requirements. When later the point of view of chemical dynamics was applied by Thunberg [1905] to the problem of oxidations taking place within the living body, he thought it obvious that variations in the oxygen supply must cause variations in the intensity of oxidations.

According to Thunberg we have a reaction between oxygen and certain substances. The velocity of the reaction (consumption of oxygen per unit time) depends upon the number of molecules able to take part in it, and if the molecules of one of the substances (the oxygen) become fewer in number the velocity of the reaction must decline, unless indeed their number is so large that it can be considered as infinite compared with the number of molecules with which it has to react. According to this view, which is fundamentally opposed to that of Pflüger, the oxidative processes must increase with increased oxygen pressure and gradually approach a maximum as shown in fig. 21.

Thunberg, like Pflüger, assumed that the oxygen supply to the tissues in the cases investigated by him was large enough to maintain a positive oxygen tension within the cells.

Thunberg looked upon the catabolism of the nutritive material as a comparatively simple process and above all an oxidation. It must be remembered, however, that according to modern views the breakdown of any substance takes place through a number of definite intermediate stages. The oxygen must take part in the reaction at one of these stages and may conceivably take part in it at more. At each of these stages the reaction proceeds at a certain rate, depending no doubt on the number of molecules taking part in it, but also on the "specific velocity" of the reaction in question, and the reaction velocity of the whole process will be determined at least approximately by the

slowest of the partial reactions. Unless and until the reaction (or one of the reactions) in which the molecular oxygen is involved is or becomes the slowest of the chain the oxygen supply will have very little influence upon the aggregate reaction velocity. It will not be the "limiting factor" in the sense defined by Blackman [1910].

In attempts to determine the concentration at which oxygen becomes the limiting factor in the catabolic process the very serious difficulty is encountered that the oxygen concentration which should be determined is that of the cells in which the oxidations occur. Extremely little is known so far about the oxygen concentration in living tissues under normal conditions, and nothing whatever in cases of oxygen want or with an increased supply of oxygen. In almost all cases all that can be done is to determine the relation between the oxygen pressure outside the organism and the rate of oxidation within, but the information which can be gained in this way is slight only and moreover very uncertain.

It will be convenient to discuss separately the results obtained in experiments on warm-blooded animals which, though far from being satisfactory, are the least fragmentary.

The Influence of a Diminished Oxygen Pressure on the Respiratory Exchange of Warm-blooded Animals.

Experiments on man and on several mammals (by Loewy [1895], A. Loewy, J. Loewy and L. Zuntz [1897], Zuntz, Loewy, Müller and Caspari [1906], Hasselbalch and Lindhard [1914]) made in pneumatic cabinets show that the total pressure can be diminished to about 400 mm. (about 80 mm. oxygen pressure) without any perceptible influence upon the absorption of oxygen. At the lower pressures, generally below 450 mm., the respiration is increased and some carbon dioxide is washed out from the body, as seen from the high respiratory quotients.

In experiments on man, in which gas mixtures with a low percentage of oxygen were breathed (Speck [1892], Loewy [1895], Durig [1903]), the respiratory exchange, or standard metabolism, remained constant until the inspired air contained 12 to 13 per cent. of oxygen (90 mm.). By a further diminution of the oxygen percentage a slight *increase* in oxygen absorption was observed which, however, when corrected for the increased work of the respiratory muscles was converted into a slight decrease. The differences between single ex-

periments are rather large and the necessary corrections somewhat uncertain.[1] Experiments on animals have given similar results. The limit at which the oxygen absorption begins to fall lies somewhere between 12 and 10 per cent. of oxygen in the inspired air (Friedländer and Herter [1879], v. Terray [1896], Durig [1903]).

All these results agree well with the blood gas determinations made by Fraenkel and Geppert [1883] in experiments on dogs. They found that the quantity of oxygen in the arterial blood did not become appreciably diminished (thanks to the regulating mechanisms) before the total pressure was lowered beyond 410 mm. (about 83 mm.) of oxygen. At all higher pressures the average oxygen tension in the capillaries must therefore remain practically constant, and there is no reason why with a constant supply of oxygen the oxygen absorption should not remain constant also.

A diminution of the quantity of oxygen available in the arterial blood will, according to the available experimental evidence, diminish the oxygen absorption in warm-blooded animals, but experiments cannot be carried far in this direction. When the oxygen supply is deficient the qualitative character of the metabolism is changed. Acid substances are liberated in the tissues and carbon dioxide washed out.

The Influence of High Oxygen Pressures on the Respiratory Exchange of Warm-blooded Animals.

The influence of high oxygen pressures on the respiratory exchange of warm-blooded animals was investigated for the first time by Lavoisier and Seguin [1814] who found that the respiratory exchange is independent of the oxygen pressure. This result has been confirmed by all later observers, whether working on man or on animals (Regnault and Reiset [1849], Lukjanow [1883], Fredericq [1884], de Saint Martin [1884], Speck [1892], Loewy [1895], Durig [1903], Schaternikoff [1904], Benedict and Higgins [1911]), and has been called in doubt only by experimenters whose methods were manifestly faulty (Rosenthal [1902]). Paul Bert [1878] found a maximum oxygen absorption in air with about 50 per cent. of oxygen and a slight

[1] In experiments made at high altitudes in mountains (Schumburg and Zuntz [1896]; Zuntz, Loewy, Müller and Caspari [1906]; Jaquet and Stähelin [1900]; v. Schrötter and Zuntz [1902] and others) an increase in standard metabolism is regularly observed at heights above 4000 m. and often also at lower heights, but in the opinion of the writer the physiological conditions during mountain expeditions become too complicated to allow conclusions to be drawn with regard to the influence of the oxygen pressure taken by itself.

decrease with both higher and lower oxygen percentages. His methods were not nearly accurate enough, however, to demonstrate this.

As pointed out by Benedict and Higgins most of the experiments made are not accurate enough to decide whether or not there is a *slight* increase in the oxygen absorption at high oxygen pressures. Loewy [1895] found a slight increase (Table V) when he averaged his figures, but he does not think it real and a calculation of the mean errors shows that it cannot be relied upon.

TABLE V.

Subject.	Oxygen Absorption per Minute.		Increase per cent.
	At Ordinary Pressure c.c.	At 1½-2 Atmos. Pressure c.c.	
Man, W.	226·5	233·5	3·1
,, Os.	293	317	8·2
Dog	209	217	3·8

The most accurate determinations are those made by Benedict and Higgins which show as averages for a large number of experiments on six different subjects the results detailed in Table VI from which

TABLE VI.—Average Absorption of Oxygen in Experiments with Varying Oxygen Tensions (c.c. per minute).

Subject.	20 per cent. Oxygen.	40 per cent. Oxygen.	60 per cent. Oxygen.	90 per cent. Oxygen.
T.M.C.	184	189		183
J.J.C.	228	226	229	220
A.G.E.	219	221	215	214
L.E.E.	244	251		241
H.L.H.	234		233	238
D.J.M.	234	235	222	256
Average	224			225

it is concluded by the authors that the oxygen rich mixtures have no effect whatever on the respiratory exchange. It is extremely probable, however, that there is in these experiments a slight systematic error because the experiments were made with the closed-space apparatus (fig. 16) without any introductory period. When an oxygen rich mixture is breathed some oxygen will therefore simply be used to saturate the blood at the higher oxygen pressure, but on the other hand nitrogen will be washed out from the blood and tissues into the

apparatus. The authors assume that these two effects will counterbalance each other, but this assumption is not warranted, and the nitrogen washed out must be in excess of the oxygen taken up from physical causes, because the oxygen pressure in the organism as a whole is low and remains low even while pure oxygen is breathed, whereas the tissues and fluids are normally saturated with nitrogen at a pressure amounting to $\frac{4}{5}$ of an atmosphere, the whole or almost the whole of which is washed out by breathing oxygen. It seems, therefore, that breathing of oxygen does increase the metabolism to some slight extent, and it must be borne in mind that a large effect is not in any case to be expected, because the oxygen supply to the tissues will only be increased by the extra amount of oxygen physically dissolved in the arterial blood which cannot be more than 10 per cent. of the total quantity carried.

The results obtained on warm-blooded animals point, when considered in their entirety, in the opinion of the writer, towards the conclusion that the oxygen pressure is practically the limiting factor for the oxidations, but that it is so regulated as to be just sufficient. A diminution of the oxygen supply to the tissues, which will take place when the oxygen pressure in the inspired air falls below something like 85 mm., causes a decrease in the rate of oxidation, while an increase in the oxygen pressure appears to produce a slight increase.

That the oxygen tension in the tissues must be the limiting factor for the oxidations would be a self-evident proposition if, as is very generally believed, this tension were practically nil. It should be pointed out, however, that the direct evidence in favour of such a view is extremely defective and uncertain. It is now generally admitted that the method invented by Ehrlich [1885] to determine the presence or absence of free oxygen is untrustworthy, as the stains employed may very well become reduced even if free molecular oxygen is present. The determinations of oxygen quantities (Pflüger [1868, 1870], Hammarsten [1871]) or tensions (Strassburg [1872], Fredericq [1911]) in secretions, which have in most cases (though not always) shown that oxygen was practically absent, are untrustworthy, because oxygen is used up in the fluids in question. This was shown by Pflüger [1870] for milk and bile and has been observed by the writer for urine (unpublished experiments). The oxygen tension of freshly voided urine amounted in one experiment to about 20 mm., but the oxygen disappeared completely in less than half an hour. In very dilute urine a tension of about 35 mm. was determined, and as it was

maintained in the sample for over an hour it probably represents the actual tension in the kidney at the time.

The experiments of Verzàr [1912] show conclusively that in the salivary glands the oxygen tension is comparatively high, while it appears to be low (less than 20 mm.) in the muscles. In the latter organs the oxygen tension is clearly the limiting factor for the oxidations, but it is obvious that a great deal of exceptionally difficult work will have to be done before we can say anything quantitatively about the relation between oxygen tension and rate of oxidations in the warm-blooded organism.

The Toxic Effect of very High Oxygen Pressures.

At pressures above 1500 mm. (O_2 in the inspired air) oxygen has a toxic effect upon warm-blooded animals. The temperature falls and the respiratory exchange becomes diminished according to the experiments of Paul Bert [1878]. The technique of these determinations does not, however, inspire much confidence. The mechanism of the poisonous action of oxygen is unknown. The symptoms bear some resemblance to the symptoms of prussic acid poisoning and it has been argued that oxygen under high pressure might inhibit oxidations. Pflüger [1873] points to the analogy with phosphorus, which does not absorb oxygen from an atmosphere of the pure gas but burns readily at lower partial pressures.

The Effects of Varied Oxygen Tensions on Cold-blooded Animals.

Henze has made a number of experiments which show very clearly the effects of varied oxygen pressures and the manner in which they act. In experiments on eggs of sea urchins the same respiratory exchange was observed when the oxygen quantity of the water varied from about double the normal (35 per cent. tension) to about half the normal amount, when the water was agitated. When the eggs were lying quietly on the bottom of a bottle in a layer ½ cm. high the respiratory exchange was much diminished compared with experiments in which the water was gently agitated (4·9 against 11·2), and when comparative experiments with oxygen-rich and oxygen-impoverished water were made without agitation the eggs in the oxygen-rich water showed the larger oxygen absorption (3·7 against 2). In animals with a good circulation and branchial respiration (e.g. the crustaceans *Carcinus mœnas* and *Scyllarus latus*, the molluscs *Aplysia limacina*,

Eledone moschata and the fishes *Coris* and *Sargus annularis*) the oxygen consumption is within wide limits practically independent of the oxygen tension of the water. With very low oxygen pressures symptoms of asphyxiation were observed. It must be assumed that normally the tissues of these animals contain free oxygen.

TABLE VII.—EXAMPLE—*CARCINUS MŒNAS*.

Oxygen in the Water.[1]	Oxygen Consumption.[1]
13	3·0
19·5	3·6
28·5	3·15
52·6	3·5
60	3·4

In hyaline pelagic animals with a very small proportion of dry substance (*Pelagia*, *Carmarina*, with less than 1 per cent. of dry substance, according to Vernon [1876]) (see below, p. 144) the oxygen consumption is also independent of the oxygen pressure, and it is reasonable to assume that a positive pressure of oxygen is found in all the tissues. Finally, in forms which have a comparatively high proportion of dry substance and very imperfect respiratory and circulatory arrangements, the oxygen consumption is clearly dependent on the oxygen pressure of the water, and approaches a maximum, which is attained only when the oxygen pressure is higher than the normal.

TABLE VIII.—EXAMPLE—*ANEMONIA SULCATA*.

Oxygen in the Water.[1]	Oxygen Consumption.[1]
10	1·1-1·3
12	1·7
17	2·3-2·6
21	2·8
26	3·7-4·6
40	5·1

In this latter case Henze assumes that the oxygen pressure in the tissues or in some of them at least is normally 0, but that a positive pressure may be produced when there is a sufficiently high oxygen pressure in the water. It was directly observed on *Sipunculus* that

[1] Henze's figures are in arbitrary units. The oxygen quantity, 28·5, corresponds to water saturated with atmospheric air.

the hæmerythrin of its blood changed colour to oxyhæmerythrin when the animal was brought into oxygen-rich water.

On fresh-water fishes Winterstein [1908] has made a number of determinations showing that the oxygen consumption is practically independent of the oxygen pressure down to about 2 per cent. pressure (0·7 c.c. O_2 per litre).[1]

Thunberg [1905] has made a number of very careful experiments on certain air-breathing animals: *Lumbricus*, *Limax*, *Tenebrio* larvæ. The results are summarized in the following table of averages. The gas exchange of the animals in air is taken as 100. The single experiments agree on the whole extremely well with one another.

TABLE IX.

Tenebrio.		Limax.		Lumbricus.	
O_2 per cent.	O_2 Absorbed.	O_2 per cent.	O_2 Absorbed.	O_2 per cent.	O_2 Absorbed.
0·52	23	—	—	—	—
1·05	46	—	—	—	—
2·62	76·5	—	—	—	—
5·25	82·6	5·25	45·7	—	—
10·5	93·1	10·5	73·1	—	—
—	—	15·75	86·5	—	—
21	100	21	100	21	100
—	—	50	116·6	—	—
—	—	96	121·8	96	144·3

The results obtained on the meal-worm (*Tenebrio*) and on *Limax* are shown graphically in fig. 21.

Thunberg assumed that the oxygen tensions in the tissues were proportional to and only slightly lower than in the surrounding air, and considered the results as showing the mass action of the oxygen in the oxidative reaction. As the respiration mechanisms of these animals are rather imperfect,[2] however, it is perhaps more probable to assume that the oxygen tension in large parts of the tissues has in all cases been very nearly zero. This assumption will at all events bring Thunberg's results into line with those of Henze and Winterstein, and it would seem to be a more or less general rule for cold-blooded

[1] It should be borne in mind in this connection that at low temperatures and with a low CO_2 pressure the dissociation curve of oxyhæmoglobin rises very rapidly and that practically complete saturation may be reached at a very low pressure.

[2] The meal-worm is a tracheate insect but has not been observed to make respiratory movements. The earth-worm has no special respiratory organ.

animals that the oxygen consumption is independent of the oxygen pressure of the surrounding medium when there is a positive tension of the gas in the tissues of the organism, and that the oxygen pressure becomes the limiting factor only when the oxygen supply fails and

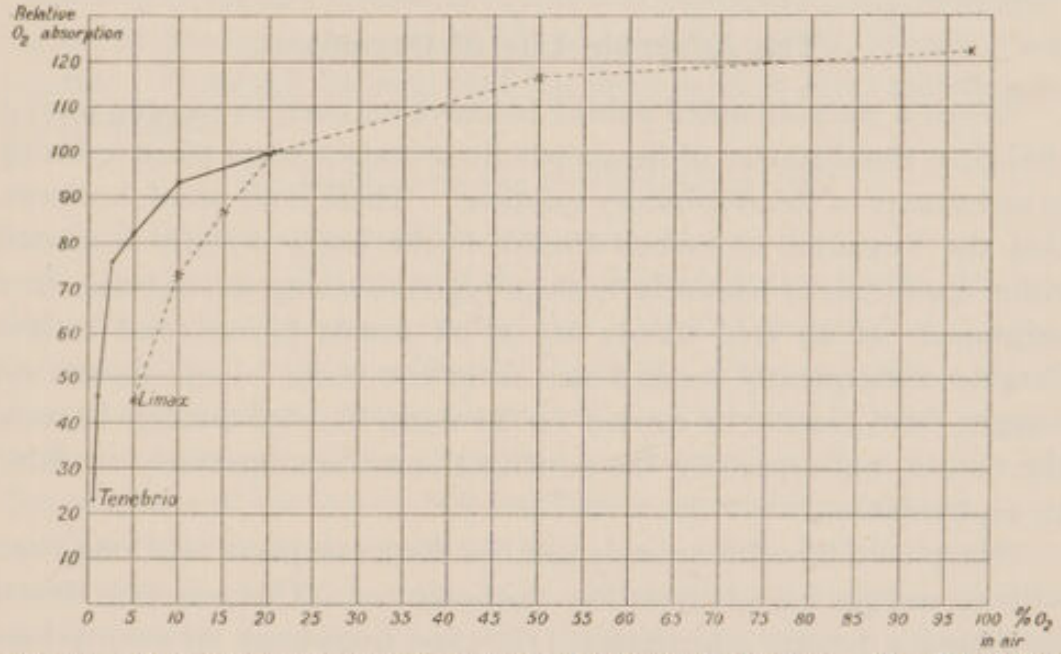


FIG. 21.—Relation between oxygen pressure and oxygen consumption. After Thunberg.

the oxygen tension in some of the tissues becomes zero. This conclusion is obviously hypothetical, however, and experiments will have to be made in which the oxygen consumption is directly compared with the oxygen tension in the tissues themselves.

TOXIC EFFECTS OF HIGH OXYGEN PRESSURES.

High oxygen pressures appear to have the same effect on cold-blooded animals as on warm-blooded. Lehmann [1883, 1884] has made a number of experiments on frogs and on organs of frogs and snails. He found that oxygen compressed to 10 to 14 atmospheres kills these animals with symptoms which are similar to asphyxiation. At low temperatures a considerable power of resistance is shown against high oxygen pressures. The animals become paralysed but may recover even after thirty hours' exposure. When the animals are rapidly decompressed gas bubbles are liberated in the tissues as well as in the blood, which shows that the oxygen tension must become very high everywhere within the organism.

Pütter [1904] has found that the action of oxygen on certain protozoa becomes harmful at quite low pressures. *Spirostomum ambiguum*, for instance, shows negative chemotaxis against air, and

water saturated with air has a rapidly deleterious effect on the protoplasm. Water with an oxygen tension of 7 per cent. is about normal for the animal. With 4 per cent. oxygen tension oxygen want begins to appear and in oxygen-free water death ensues rapidly.

The Anærobic Life of Organisms.

When a warm-blooded animal becomes exposed to oxygen want a change in the character of the metabolic processes takes place resulting in an increase in the respiratory quotient. There is no proof, however, that the formation of carbon dioxide in the body is really increased either absolutely or relatively to the oxygen consumption because other substances of an acid nature are at all events formed and carbon dioxide consequently washed out from the body. Experiments on oxygen want cannot be carried far on warm-blooded animals because the tissues, and especially the nervous tissues, are extremely sensitive to asphyxiation.

Many cold-blooded animals can live for a comparatively long time without oxygen especially at low temperatures. This was well shown in Pflüger's famous experiments [1875] on frogs kept for twenty-four hours or more in pure nitrogen, and a large number of later observations on diverse invertebrate animals have shown the same (Paul Bert [1878]). In such experiments a considerable quantity of carbon dioxide is liberated. Pflüger [1875] and later Aubert [1881] have compared the quantity of carbon dioxide liberated by frogs in pure nitrogen with that produced in air and found that the differences were not considerable. As Lesser [1908] has pointed out, the experiments are not conclusive, because the muscular activity of the frogs was greater in nitrogen than in air, and there can be no doubt, moreover, that a certain quantity of the carbon dioxide liberated in the nitrogen experiments was preformed in the tissues. On the other hand the quantities liberated were so large that carbon dioxide must have been produced in the oxygen-free atmosphere, and we have to do with anoxybiotic catabolism which may or may not be a phase in the normal oxidative breakdown of the nutritive substances.

The anoxybiotic processes have been studied on certain animals which normally live without oxygen. Bunge [1885, 1890] found that the parasitic worms (*Ascaris*) living in the intestinal canal of higher animals, where the oxygen tension is practically always nil, will remain lively for many days in oxygen-free saline and produce

considerable quantities of carbon dioxide. When oxygen is offered to them they are unable to utilize it. The processes taking place in this case were studied by E. Weinland [1901] who found that carbohydrates were the substances chiefly and perhaps exclusively catabolized by *Ascaris* ($\frac{1}{3}$ of the dry substance of which is glycogen), the process leading to the production of carbon dioxide and fatty acids, valerianic and caproic. Weinland believes that the process takes place according to the formula:—

$$4C_6H_{12}O_6 = 9CO_2 + 3C_5H_{10}O_2 + 9H_2$$

but the hydrogen stipulated has never been observed.

Lesser [1909-10] has found that analogous processes take place in the earth-worm (*Lumbricus*) when that animal is deprived of oxygen. Carbon dioxide and fatty acids are produced. When air is administered to earth-worms after an anoxybiotic period an abnormally high oxygen intake is observed with a very low respiratory quotient [1910, 3]. The products of the incomplete breakdown are rapidly oxidized.

Experiments on anoxybiosis have been made further by Pütter on infusoria [1905] and on the leech (*Hirudo*) [1906-7], but a detailed account seems unnecessary as the methods employed are unreliable and the conclusions arrived at unwarranted, as shown by Lesser.

On the tissues of chrysalides of flies (*Calliphora*), which were ground to a paste, Weinland [1906] has observed that a catabolism of fat could take place in the absence of oxygen, resulting in the formation of carbon dioxide and free hydrogen.

Pütter [1905] has expressed the opinion that the anoxybiotic metabolism is to be considered as the more general or "primitive" scheme of animal metabolism and the oxidative process as the secondary. This singular proposition probably contains an element of truth, in so far as the initial stage in the breakdown of the foodstuffs is probably not oxidative. Certain animals (endoparasitic worms) are capable only of performing this stage. They are able to excrete the products which are not harmful to them in the concentrations reached. They are absolutely anærobic. Others (like earth-worms) are able to endure want of oxygen for a considerable time. The products of anoxybiosis are not very harmful to them, though their vitality is generally impaired when they remain without oxygen for a long time. In a number of cases the catabolic reactions are probably inhibited by the accumulation of their products and the harmful effects thereby counteracted.

CHAPTER VII.

THE INFLUENCE OF PHYSICAL FACTORS UPON THE RESPIRATORY EXCHANGE.

The Influence of Temperature.

A VERY large number of experiments have been made on the influence of temperature upon metabolism both in cold-blooded and in warm-blooded animals, but comparatively few of them have been made under standard conditions. In most, the animals have been free to move about and even in cases where they have been tied, muscular movements have not been prevented or muscular tone abolished. In these conditions a fundamental difference has been observed between the effects of temperature upon cold-blooded and upon warm-blooded animals.

COLD-BLOODED ANIMALS.

In cold-blooded animals the respiratory exchange almost always rises with increasing temperature, but generally irregularly and to a very different degree in different animals. Experiments have been made among others by Regnault and Reiset [1849] on *Lacerta*, by Jolyet and Regnard [1877] on fishes, by Schulz [1877] on frogs, by Vernon on a large number of terrestrial [1895, 1897] and marine [1896] animals, by Konopacki [1907] on the earth-worm, by Martin [1902] on the reptile *Cyclodes gigas*, by Slowtzoff [1909] on insects, by Battelli and Stern [1913] on insects, by Knauthe [1898] on fishes, by Montuori [1913] and by Lindstedt [1914] on different aquatic animals, by Marie Parhon [1909] on bees.

Vernon's experiments [1897], which are probably the most complete, consisted in series of determinations made on the same animal or group of animals both at increasing and decreasing temperatures between 30° and 2°. Each temperature at which a determination was made was maintained constant for fifteen to thirty minutes. The Haldane air-current apparatus was employed. As seen from the table in which the results are given in mg. CO_2 per kilogram and hour and in which averages of several such series with each species are given, differences were observed between the gas exchange with rising and falling temperature. The results obtained with rising temperature are in each case given first.

TABLE X.—Mg. CO_2 per Kilogram and Hour.

Animal.	2° C.	6°	10°	12·5°	15°	17·5°	20°	22·5°	25°	27·5°	30°
Rana temporaria first series	89	99	97	97	97	98	113	138	169	256	408
	59	67	78	101	116	123	159	199	238	271	301
Rana temporaria second series	44	57	77	96	93	107	130	139	154	261	651
	52	55	67	91	96	110	155	183	220	326	616
Rana esculenta	25	41	61	74	92	96	97	121	135	154	186
	25	59	74	95	107	95	122	146	168	150	186
Bufo vulgaris	89	72	178	172	152	149	196	192	271	477	719
	63	65	83	82	124	115	152	213	313	769	719
Amblystoma tigrinum	90	86	113	111	123	142	142	202	247	246	313
	54	84	98	132	135	151	158	201	236	252	313
Molge vulgaris	143	136	217	182	179	184	182	182	285	448	462
	73	115	144	174	164	240	203	265	250	326	462
Anguis fragilis	21	28	53	31	56	70	69	136	141	178	210
	12		29	26	46	55	57	95	132	151	186
Helix pomatia	44	57	84	117	135	159	173	146	155	164	188
	30	48	66	81	97	99	156	205	223	243	188
Lumbricus terrestris	23	24	43	48	46	48	56	53	76	136	228
	17	22	42	42	45	55	55	76	111	107	228

The results have been summarized by Tigerstedt [W.] in the curves, fig. 22. Vernon himself concluded from the observations that the respiratory exchange might remain practically constant over a considerable range of temperatures (in the earth-worm for instance between 10° and 20°), and that the cold-blooded animals possessed some nervous mechanism by which their heat production could be regulated. There is no reason to believe, however, that the deviations from a regular increase with the temperature are anything but accidental and due to the imperfect control over the conditions other than temperature in Vernon's experiments. This is shown by the discrepancy between Vernon's two series on Rana temporaria and by the fact that Konopacki failed to find in the earth-worm any indication of a constant metabolism between 10° and 20°.

Martin's observations on *Cyclodes gigas* are summarized as follows :—

TABLE XI.

Temp. of Air.	Temp. of Animal.	CO_2 per Kg. and Hour. mg.
5·0	5·5	13
9	9·2	42
15	15·2	53
20·5	20·4	55
25	24·5	64
30	29·3	78
35	34·8	97
39	38·5	292

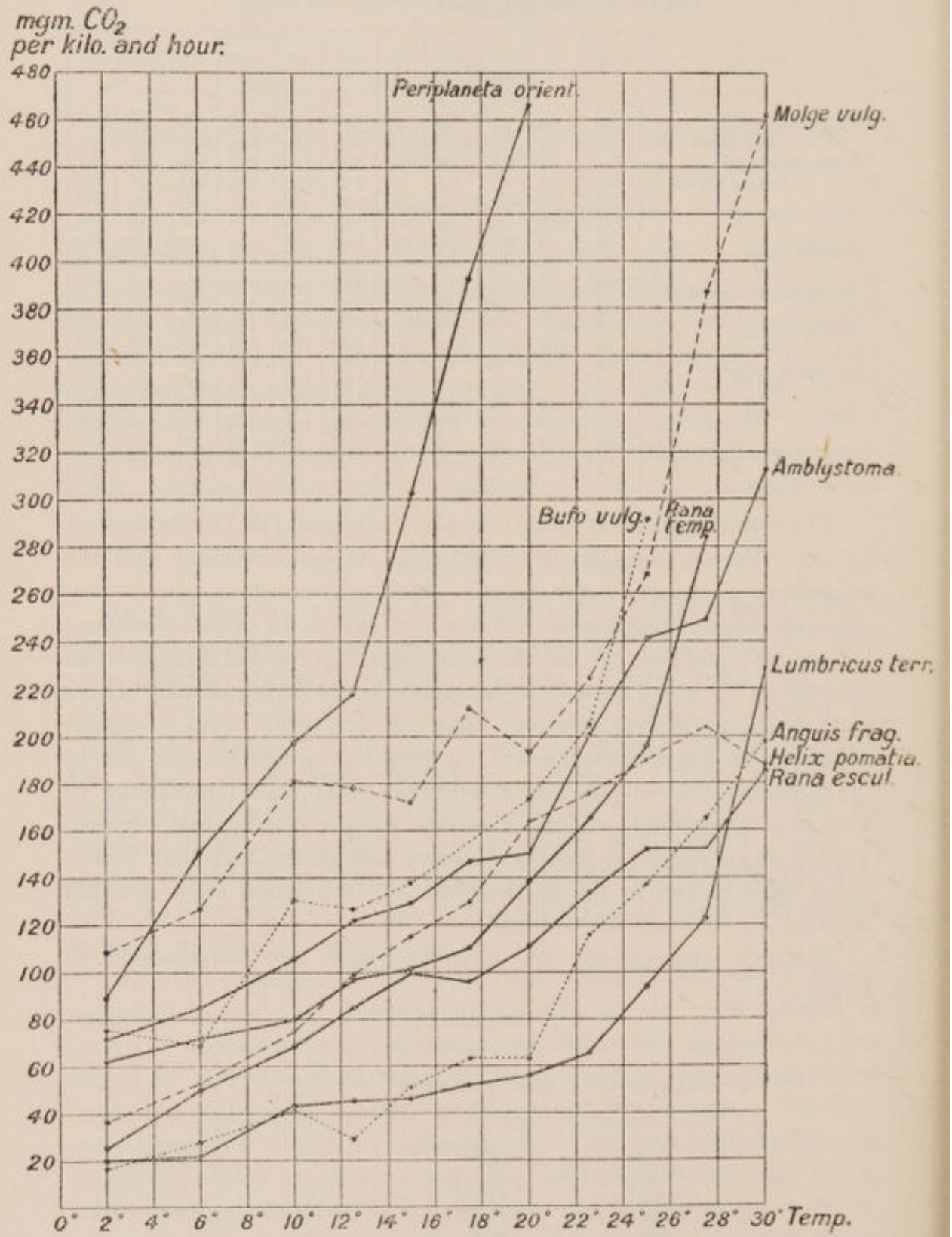


FIG. 22.—The variation of the respiratory exchange with temperature. After Vernon.

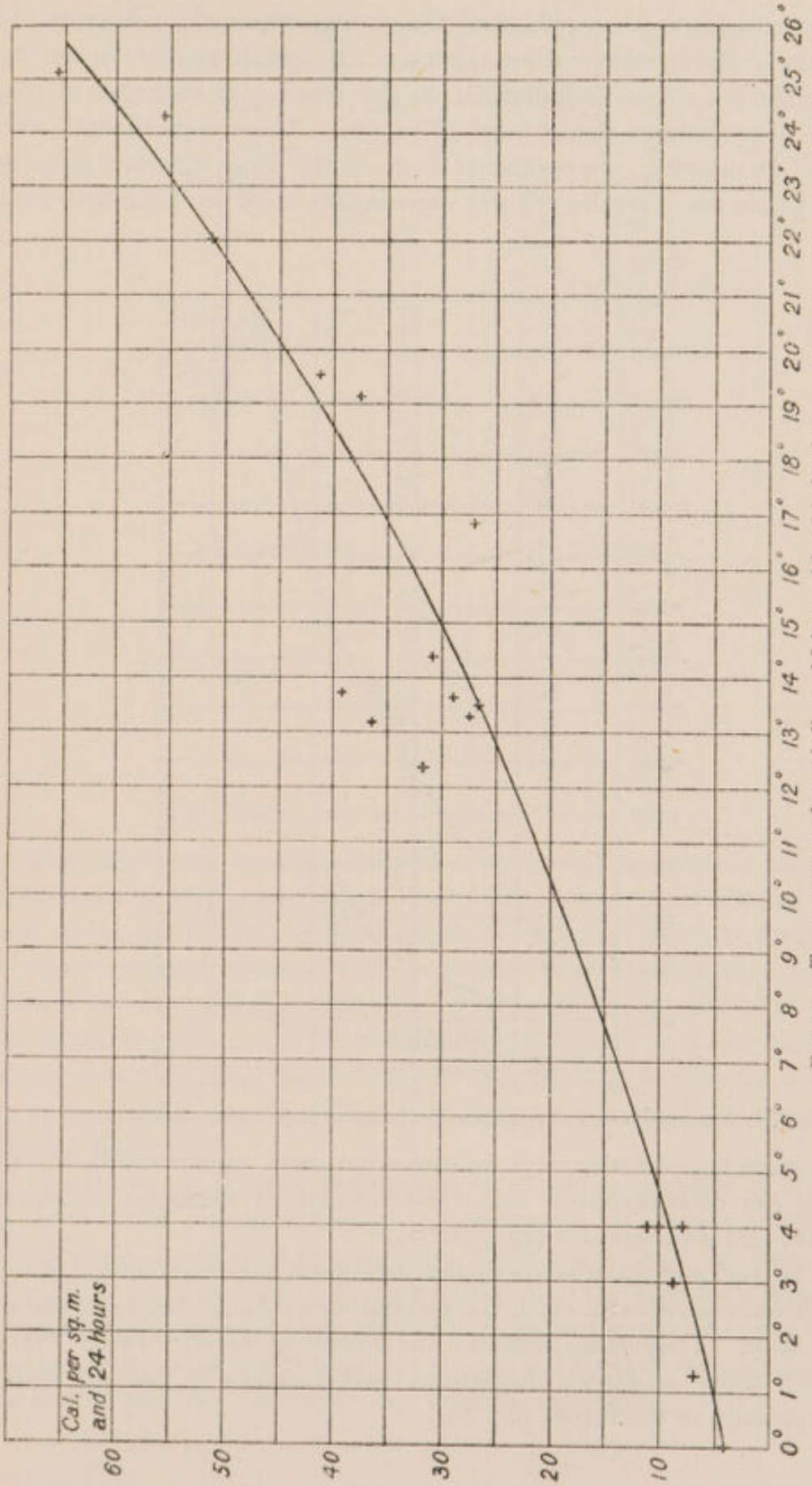


FIG. 23.—Temperature and metabolism of fishes. After Lindstedt.

Cronheim [1911] has published the results obtained by Knauthe by means of Zuntz's respiration apparatus for aquatic animals in curves; they show a rather irregular rise in the respiratory exchange of carp with temperatures rising from 7° to 25°. These experiments were made in summer. Experiments made on the fishes in winter gave on the whole lower results. Later experiments made by Lindstedt using

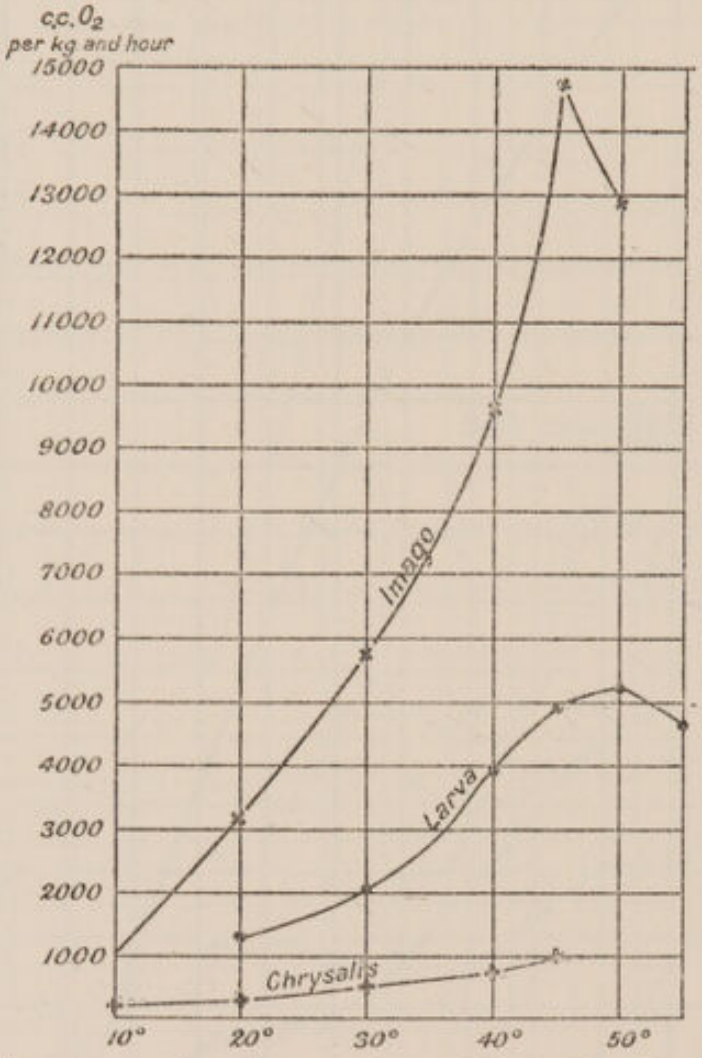


FIG. 24.—Temperature and respiratory exchange of flies. After Battelli and Stern.

the same apparatus have given somewhat more regular results for the influence of temperature upon the respiratory exchange of various fishes and invertebrates (fig. 23).

Battelli and Stern's experiments on insects have been carried to very high temperatures at which the respiratory exchange begins to show a decrease. They have obtained the following results (Table XII) of which those on larvæ, chrysalides, and imagines of flies are shown graphically in the curves (fig. 24).

TABLE XII.—Respiratory Exchange per Kilogram and Hour.

Species.	Temp. ° C.	O_2 per Kg. and Hour, c.c.	R.Q.
Cockchafer .	20	930	0·65
	30	1620	69
	40	3030	72
	45	4400	73
	50	4250	82
Silkworm chrysalides	20	130	0·65
	30	260	67
	40	360	66
Flies—			
Larvæ . .	20	1300	0·81
	30	2040	81
	40	3900	84
	45	4900	85
	50	5200	87
	55	4600	88
Chrysalides .	10	170	0·52
	20	260	65
	30	480	67
	40	710	72
	45	990	75
Imagines . .	10	960	0·61
	20	3100	74
	30	3800	76
	40	9600	78
	45	14700	76
	50	12900	75

The individual results obtained by Vernon on various marine animals are in most cases rather discordant. Vernon has summarized them in the table in which the respiratory exchange of each form at 16° has been taken as unity. Vernon denotes as the temperature increment the ratio between the respiratory exchange at 24° and at 10°. This figure is given in the last column. It is high (5 to 3) for hyaline pelagic animals such as *Beroë*, *Cestus* or the Salps, while animals, which are not pelagic and opaque or only slightly transparent, have low temperature increments.

Montuori [1913] made determinations of ½-hour duration at about 22° on various marine animals, and thereafter on each a series of ½-hour experiments with 20 min. intervals at about 32°. He found in all cases an increase during the first half hour at the high temperature, but the respiratory exchange then fell off gradually and after twenty-four to twenty-eight hours regained its normal level or became lower. His results are, like Vernon's, very irregular individually.

TABLE XIII.—Relative O_2 Absorption of Marine Animals.

Name of Animal.	10°	12°	14°	16°	18°	20°	22°	24°	Temperature Increment.
Salpa tilesii . . .	·44	·60	·78	1	1·24	1·45	1·71	2·00	4·5
Cestus veneris . .	·45	·61	·80	1	1·20	1·43	1·68	1·97	4·4
Beroë ovata . . .	·40	·58	·78	1	1·23	1·47	1·75	2·04	5·1
Carmarina hastata .	·66	·77	·89	1	1·11	1·23	1·34	1·46	2·2
Rhizostoma pulmo .	·52	·67	·83	1	1·20	1·43	1·67	1·93	3·7
Pterotrachea coronata .	·63	·73	·85	1	1·19	1·42	1·71	2·03	3·2
Salpa pinnata . .	·46	·62	·80	1	1·22	1·46	1·72	1·99	4·3
Tethys leporina . .	·79	·85	·92	1	1·11	1·25	1·43	1·61	2·0
Amphioxus lanceolatus	·58	·72	·86	1	1·14	1·28	1·42	1·56	2·7
Octopus vulgaris . .	·74	·81	·92	1	1·14	1·31	1·56	1·87	2·5
Heliasis chromis . .	·82	·87	·92	1	1·10	1·21	1·35	1·53	1·9
Serranus scriba . .	·65	·74	·86	1	1·14	1·30	1·47	1·67	2·6
Mean . . .	·61	·72	·85	1	1·17	1·35	1·56	1·80	3·3

Very remarkable results have been obtained on bees by Marie Parhon. She made experiments on large numbers of bees in a small Regnault apparatus. The results of a series of experiments made in summer at different temperatures are summarized in the curve,

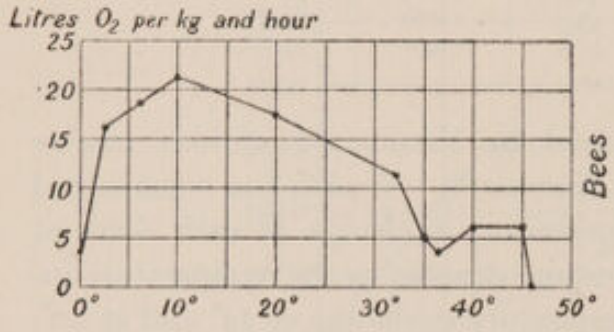


Fig. 25.

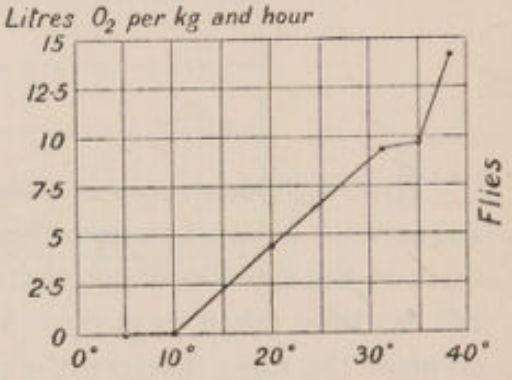


Fig. 26.

Respiratory exchange and temperature. After M. Parhon.

fig. 25, which is to be compared with fig. 26, showing the results obtained on flies. While the curve for the flies is about normal [1] for a cold-blooded animal, and does not differ very much from that obtained by Battelli and Stern, that for the bees shows a maximum exchange at 10° [2] and a more or less regular decrease at higher temperatures. This

[1] That the oxygen absorption is found to be o up to a temperature of 10° is undoubtedly abnormal and due to experimental errors.

[2] This temperature is that of the water-bath surrounding the Regnault apparatus. The temperature in the respiration chamber was always higher (15·1° against 10° in the water) and of course the temperature of the bees must have been higher still.

curve resembles closely that of a small warm-blooded animal. Marie Parhon finds further that the temperature in the cluster of bees inside the hive shows a very striking constancy throughout the year. The average value for each month varies only between 34·1° (July) and 31·8 (October). During the winter (December, January, and February) it remains at 32·4. The temperature regulation of the bee cluster (but by no means of a single isolated bee) must, according to this author, be considered as just as perfect as that of a mammal or bird.

That the cluster of bees in winter generates a large amount of heat has been shown also by Phillips and Demuth [1914] who did not observe, however, the absolute constancy claimed by Mlle. Parhon.[1] According to Phillips and Demuth the temperature in the hive fluctuates with the outside temperature until it falls to 57° F. (14° C.) when the bees form into a compact cluster in which heat is generated and a higher temperature maintained. "The nearly spherical cluster of bees . . . consists of an outer shell of bees close together with their heads towards the centre. This ring may be several layers thick. The bees in this outer shell are quiet except for an occasional shifting of position. Inside this rather definite shell the bees between the combs are not so close together nor are they headed in any one way. Considerable movement, such as walking, moving the abdomen from side to side, and rapid fanning of the wings takes place inside the sphere, and when a bee becomes unusually active the adjoining bees move away leaving an open space in which it can move freely." The temperature in the centre of the cluster was in one case recorded as being 75° F. (40° C.) higher than outside it at a distance of $4\frac{1}{4}$ inches.

Warm-blooded Animals.

In intact warm-blooded animals a fall in the surrounding temperature regularly causes not a decrease but an increase in the respiratory exchange thanks to the mechanism of "chemical heat regulation". This has been shown over and over again by Zuntz and Röhrig [1871], Pflüger [1876, 1878], Colasanti [1877], Voit [1878], Carl Theodor [1878], and several others. The most elaborate study of the chemical

[1] They lay stress upon the importance of not in the least disturbing the bees. As Mlle. Parhon went on putting thermometers into the hive until she found the highest temperature the bees must have been greatly disturbed, and her figures probably indicate the maximum temperature which the bees can be induced to set up.

heat regulation has been made by Rubner [1887, 1902], who found for instance [1887] in a guinea-pig during a period of inanition the following figures (Table XIV):—

TABLE XIV.

Temperature of Air, °C.	CO_2 per Kg. and Hour, Grm.
0°	2·91
11°	2·15
21°	1·77
26°	1·54
30°	1·32
35°	1·27
40°	1·45

At very high temperatures (above 35°) the regulation breaks down and the respiratory exchange rises with increasing temperature of the body, as seen in the last experiment of the above series. A break-down may occur also at low temperatures when the rectal temperature falls considerably below the normal. This is well shown in a series of experiments by Pflüger [1878] on a rabbit which was during the determinations immersed in a water-bath.

Rectal Temperature, °C.	O_2 per Kg. and Hour, c.c.
39·2° – 38·3°	738
38·3° – 37·8°	763
37·8° – 37·3°	839
37·3° – 37·6°	888
37·6° – 28·6°	859
28·6° – 24·0°	608
24·0° – 20·0°	457

The Influence of Temperature upon the Standard Metabolism of Animals.

In all the experiments so far mentioned both on cold-blooded and warm-blooded animals we have to do with two distinct effects of the temperature, viz. one upon the central nervous system causing variations in the innervation of different organs and especially of the muscles, and one upon the tissues themselves influencing the reaction velocity of the metabolic processes. In the warm-blooded animals the action of low temperatures on the skin produces reflexly innervation of the muscles resulting either in movements or in increase of tone. In the cold-blooded animals the processes in the central nervous system

itself are probably acted upon, and increased muscular activity is produced by increasing temperature except as we have seen in the cluster of bees which in the aggregate reacts against the temperature somewhat after the fashion of a warm-blooded animal.

When the influence of the temperature on the metabolic processes themselves is to be studied the nervous influences must of course be excluded and the experiments made under absolutely standard conditions. Comparatively few experiments conform to this obvious requirement.

Experiments on man made by Loewy [1890], Johansson [1896], Rubner and Lewaschew [1897] have shown that a low surrounding temperature does not produce any increase in the metabolic processes unless voluntary or involuntary muscular movements are brought about, but the standard metabolism of man has not been measured over any range of body temperatures.

It has been found repeatedly both on man and on animals (Rubner) that even a slight increase in body temperature over the normal produces an increase in the standard metabolism.

The influence of low temperatures upon warm-blooded animals in which the muscles were put out of action in various ways has been studied by Velten [1880], Pflüger [1878], Zuntz and Röhrig [1871], Krarup [1902], Krogh [1914, 3], and others.

Velten found on a curarized rabbit the following figures for the respiratory exchange in the order given (Table XV):—

TABLE XV.

Rectal Temperature, °C.	O_2 per Kg. and Hour, c.c.
38·3°	581
37·4°	557
31·4°	386
26·2°	219
23·1°	181
30·4°	211
36·4°	455

It is obvious from the low results, obtained when the temperature was again rising, that the lowest temperatures must have had some harmful effect on the animal.

Similar but shorter series of experiments have been made on curarized rabbits by Pflüger and by Zuntz and Röhrig. Krarup made some experiments on rabbits after pithing. The animals were allowed

to cool very gradually and experiments of short duration were made from time to time during the process. The results of one of his experiments, in which the temperature of 26° was reached before the

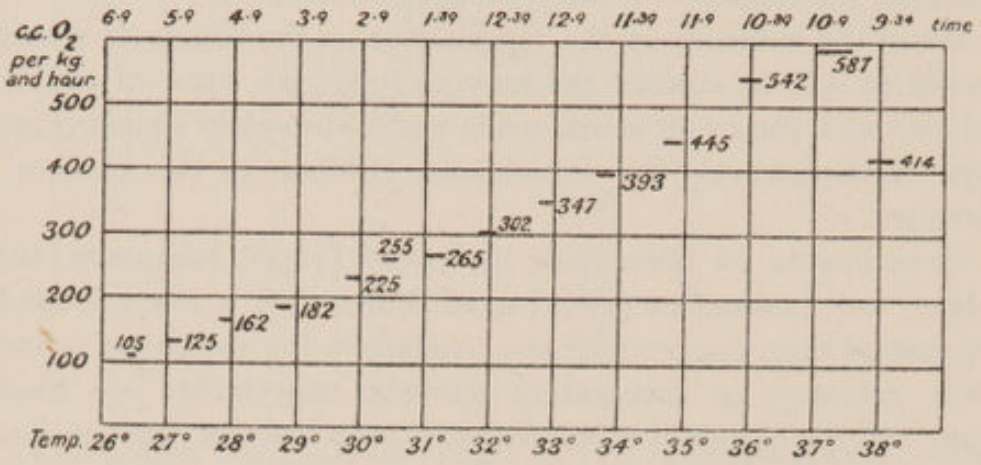


FIG. 27.

animal died, are given graphically in fig. 27. The whole series of determinations lasted from 9 in the morning to 7 in the afternoon.

Krogh experimented on a young dog under curari (weight about 950 gr.) and obtained the following set of figures :—

Time.	Rectal Tp.	O_2 per Minute c.c.
12·09-12·16	28·7	6·8
1·16-1·22	32·2	9·8
1·44-1·48	37·2	13·0
2·47-2·58	22·7	4·8
3·25-3·35	14·1	2·15
4·00-4·06	28·1	7·5
4·22-4·28	28·0	7·8
4·57-5·02	36·8	11·0
5·08-5·13	36·8	11·4
5·36-5·40	39·9	11·2

of which some are shown in fig. 28 (H).

Cold-blooded animals.—Ege and Krogh [1914] have made experiments on a gold-fish (*Cyprinus auratus*) immobilized by narcotization with urethane. The influence of the temperature upon the oxygen consumption was found to be the same as in the normal fish which was at all temperatures exceptionally quiet, and a very regular curve was obtained showing the quantitative relation between the temperature and the metabolism (see fig. 30).

Krogh [1914, 3] made a number of comparative experiments by means of a small Regnault apparatus (described p. 26) on the influence of temperature upon the metabolism of

1. A toad which had been decerebrated a year before (fig. 28 ×).

2. A frog (*Rana temporaria*) completely narcotized with ethyl-urethane (fig. 28 +).

3. A frog of the same species immobilized with curari (fig. 28 O).

4. Frogs incompletely narcotized with urethane.

5. Normal frogs.

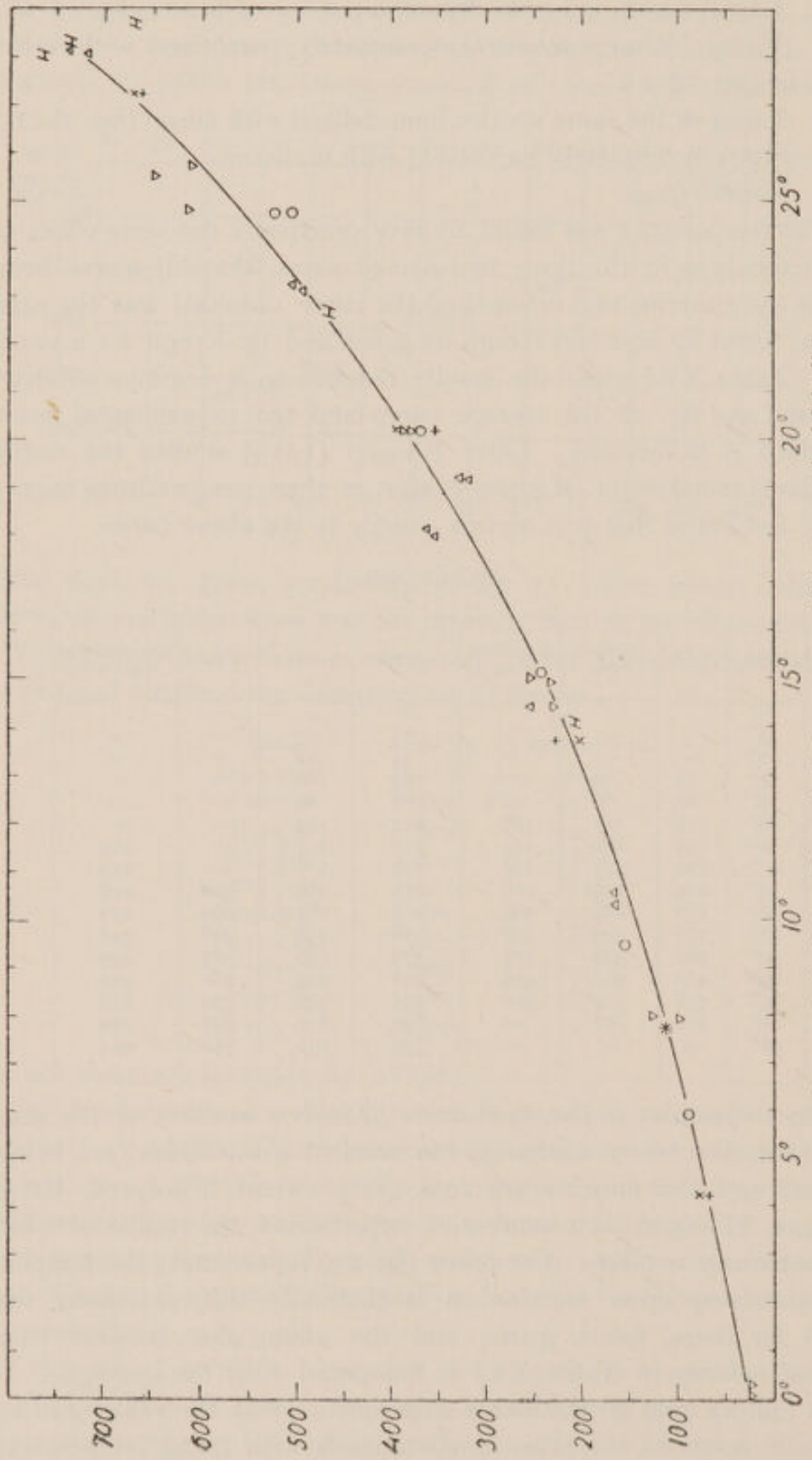
The temperature was found to have practically the same effect on the metabolism in the three first-named cases, the differences being within the experimental errors, and the curve obtained was the same as that found by Ege and Krogh for a fish and by Krogh for a young dog. Table XVI gives the results reduced to a common arbitrary standard and fig. 28 the average curve and the experimental results on which it is founded. Later Ellinger [1915] studied the resting (standard) metabolism of gnats (*Culex*) at three temperatures from 3° to 20° and found that it conforms exactly to the above curve.

TABLE XVI.

Temp.	Toad.	Urethane Frog.	Curarized Frog.	Gold-fish.	Average.	Dog.	Chrysalides of Tenebrio.
0°	—	—	—	23	23	—	—
2°	—	—	—	44	44	—	—
4°	68	69	—	67	68	—	—
6°	89	88	92·5	86	89	—	—
8°	113	111	116	111	113	—	—
10°	141	140	144	142	141·5	—	103
12°	172	174	178	178	175·5	—	152
14°	209	215	218	218	215	206	206
16°	258	266	264	266	263·5	260	272
18°	317	322	316	318	318	318	346
20°	386	383	373	379	380	387	439
22°	460	452	435	448	449	460	545
24°	536	527	502	534	525	539	656
26°	618	608	—	630	619	622	770
28°	—	—	—	730	730	716	924

On chrysalides of the meal-worm (*Tenebrio molitor*), at the stage when the respiratory exchange has reached a minimum (see below, p. 111) and the muscles are to a great extent histolyzed, Krogh [1914, 1, 2] has made a number of experiments, the results of which are extremely regular. The curve (fig. 29) representing the temperature influence upon metabolism is distinctly different from that found for frogs, fishes, gnats, and the young dog, as seen when the last column in Table XVI is compared with the average.

It follows from all the above experiments that the velocity of the catabolic reactions increases in all animals with rising temperatures



× toad, + urethanized frog, ○ curarized frog, ▽ normal fish, △ narcotized fish, *H* dog.

FIG. 28.—Temperature and standard metabolism. From "Zeitschr. f. phys. chem. Biol."

up to a maximum at and above which the temperature has a deleterious effect upon the organism. The maximum temperature probably differs considerably for different animals, but very few determinations have been made so far.

The more rigorously standard conditions are maintained the more regular is the influence of temperature observed. Attempts have been made by Kanitz [1907], Snyder [1908], Pütter [1914], and others to represent the temperature influence on the respiratory exchange as governed by the rule of van't Hoff, which has been found to express satisfactorily the temperature influence on the velocity of a number of chemical reactions, especially such which take place

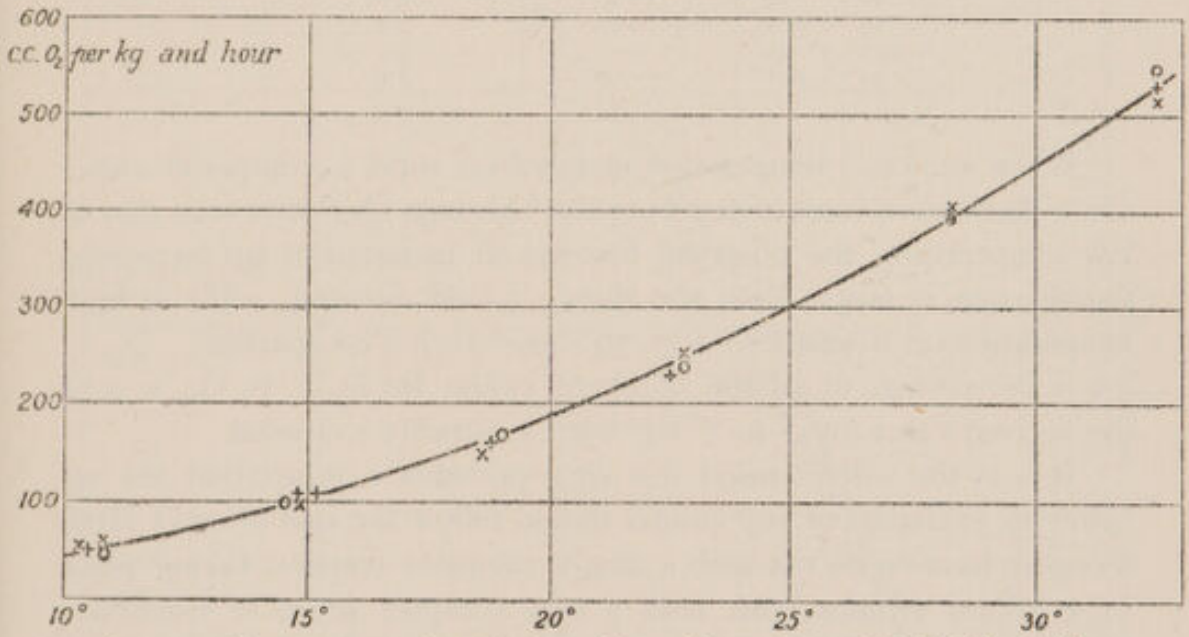


FIG. 29.—Temperature and metabolism of chrysalides. From "Bioch. Zeitschr."

in dilute solutions. When the velocity of a reaction at a certain temperature is v_t it will, according to van't Hoff's rule, at a temperature 10° higher be $v_{t+10} = v_t\ Q_{10}$ where Q_{10} is a constant[1] for the reaction in question. For most of the chemical reactions studied Q_{10} lies between 2 and 3, that is the velocity is doubled or even trebled when the temperature rises 10°.

When it is attempted to express the temperature variation of the respiratory exchange by means of the rule of van't Hoff, Q_{10} is found

[1] A slight decrease in Q_{10} is regularly found for chemical reactions when the temperatures are much increased, e.g. $Q_{0\text{-}10} = 3{\cdot}0$, $Q_{70\text{-}50} = 2{\cdot}3$. The formula of Arrhenius $v_t = v_o e^{q\frac{Tt - To}{Tt\,To}}$ in which q is a constant and T_t, T_o the absolute temperatures ($T_t = t + 273°$) generally expresses the facts observed in chemical experiments better than the simple rule of van't Hoff.

to vary greatly, and in the experiments which have given the most uniform results Q_{10} shows a steady and very large decrease with increasing temperature. For the curves shown in figs. 28 and 29 we have :—

TABLE XVII.

	Q_{10} for Frogs, Fishes, etc.	Q_{10} for Chrysalides of Tenebrio.
0° – 5°	10·9	—
5° – 10°	3·5	—
10° – 15°	2·9	5·7
15° – 20°	2·5	3·3
20° – 25°	2·2	2·6
25° – 27·5°	2·2	2·3
27·5° – 30°	—	2·1
30° – 32·5°	—	2·0

When an actual temperature-metabolism curve is compared with a van't Hoff curve constructed from the "average Q_{10}" it is seen that at low temperatures the observed increase in metabolism by increasing temperature is larger than the theory would demand, while at high temperatures it is smaller. Fig. 30 shows such a comparison. $Q_{10} = 3·9$ is the average of all the observed values for Q_{10}. In $Q_{10} = 2·74$ the highest value for 0° to 5° has been arbitrarily excluded.

It is to the writer's mind not very probable a priori that the respiratory exchange of any animal should follow the rule of van't Hoff, since we have to do not with a single chemical reaction taking place in a dilute solution, but with a very complex series of reactions[1] which perhaps cannot even be regarded as taking place in a homogeneous medium or between substances in dilute solution. If, however, the differences between the conditions in the cells and those in homogeneous dilute solutions should be negligible, and if further all the reactions involved should be influenced by the temperature in accordance with the rule of van't Hoff, the result must nevertheless show a considerable divergence if a limiting factor comes into play. Reasons have been given above for assuming that the oxygen pressure in the tissues is probably in many cases a limiting factor for the oxidative phase of the

[1] Several inorganic complex reactions have been observed in which the rule of van't Hoff does not hold, and one has been found in which the reaction velocity *decreases* with increasing temperature (Miss Benson, "Journ. of Phys. Chem.," 1904, **8**, 116). A critical summary of the applicability of the rule of van't Hoff both to chemical and to a number of physiological processes has been given by Jeanne van Amstel, "De Temperatursinvloed op physiologische processen der alcoholgist". Proefschrift, Amsterdam, 1912 (Dutch).

catabolic reaction. This must mean that at increasing temperature

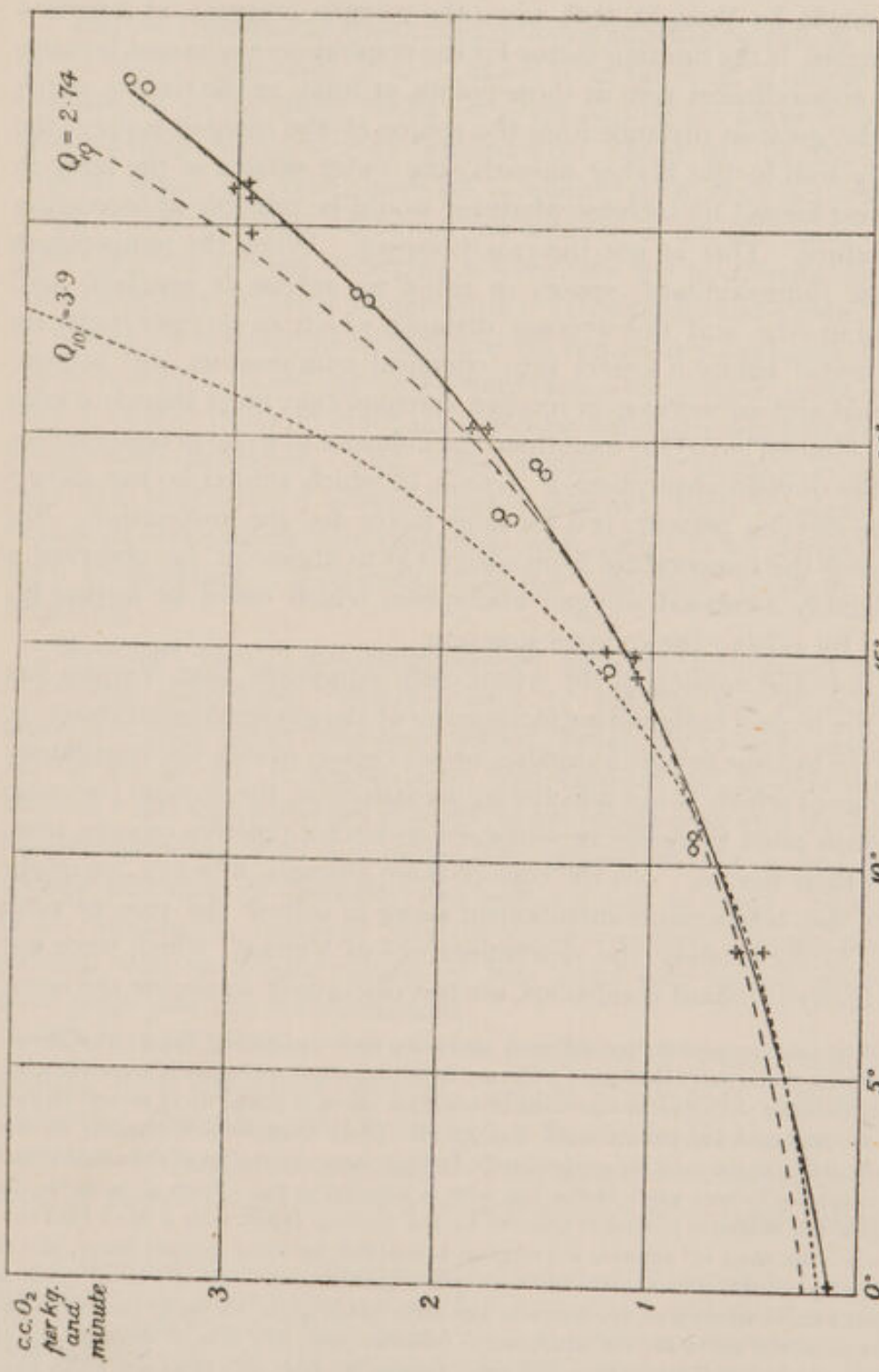


FIG. 30.—The temperature metabolism curve of a fish compared with van't Hoff curves. From "Internat. Revue f. Hydrobiologie".

the respiratory exchange cannot increase as rapidly as would otherwise be the case, and it is possible that this may be the explanation or

part of the explanation of the divergence between the observed facts and the "theory".[1]

It might be thought that when the oxygen pressure, at a certain temperature, is the limiting factor for the respiratory exchange, because it is or approximates zero at those points, at least, in the tissues which are at the greatest distance from the source of the oxygen supply (the capillary wall in the higher animals, the outer surface of the body in the lowest forms), no increase whatever would be possible at increasing temperature. This is not the case however. When the temperature rises the (intercapillary) spaces *in which no oxygen is available* will increase in size, and the average distance which an oxygen molecule has to travel before it enters into chemical combination will become shortened and an increase in oxygen consumption must therefore take place. Henze [1910] has examined the influence of a rise in temperature upon the oxygen absorption of *Actinia*, in which animal he has shown that the oxygen pressure is a limiting factor for the respiration. By increasing the temperature from about 14° to about 22° he observed a considerably increased oxygen absorption which could be further increased by raising the oxygen pressure.

It is in the opinion of the writer very significant that Vernon has found the largest temperature increments of the gas exchange (above, p. 89) in the hyaline pelagic animals (*Salpa*, *Cestus*, *Beroë*), the respiratory exchange of which is not affected by variations in the oxygen pressure, and which must therefore be supposed to have a positive oxygen pressure in their tissues.[2] In the case of these animals, if in any, we might expect the temperature-metabolism curve to follow the rule of van't Hoff. Unfortunately the determinations of Vernon, which were not made under standard conditions, are too discordant to decide the issue.

[1] Pütter [1914] considers that different processes may be limiting factors at different temperatures, that a van't Hoff curve with one definite constant corresponds to each process, and that therefore the actual temperature-metabolism curve is made up of several distinct parts, of which each is a perfect van't Hoff curve. In an example (constructed) he lets the permeability of the cells for oxygen be the limiting factor from 0° to 5° and assumes that this permeability follows van't Hoff's law with a constant = 8·0. From 5° upwards the velocity of the oxidative process is taken to be the limiting factor with a van't Hoff constant = 2·0, but from 15° upwards the reaction is modified by some noxious factor, also of course acting according to the rule but with a constant = 16·0. The combined result of all this is a curve which does not resemble any metabolism curve known to the writer, but it is not unlike the curve for the temperature influence upon the rate of development of certain embryos. Pütter's reasoning is possible because he deals with processes which have been very inadequately studied.

[2] Their oxygen consumption per unit body weight is very low at all temperatures because their dry organic substance amounts only to about $\frac{1}{2}$ per cent. of the weight.

The Possibility of Acclimatization in Cold-blooded Animals.

The temperatures at which cold-blooded animals are able to live and to be active range from 2° to 3° below 0° in the case of arctic marine animals, of which many living at great depths are never exposed to temperatures above 0°,[1] to temperatures about 40° in the case of tropical forms, and even above 40° (probably up to 60°) in a few forms living in hot springs. Instances are known in which nearly related forms or even animals belonging to the same species inhabit localities with extremely different temperatures[2] (Davenport and Castle, 1895). It would be interesting to compare the respiratory exchange in such cases, because it would appear unlikely from a teleological point of view that it should differ so much as would be ordinarily implied from the temperature difference. One would expect that animals living at a very low temperature should show a relatively high standard metabolism at that temperature compared with others living normally at a high temperature. Extremely little has been done, however, in this direction.

Montuori [1907] has attempted to acclimatize different animals (*Carcinus*, *Amphioxus*, several fishes) by heating the water in the aquaria in which they were kept slowly (during six to seven days) from 11°-13° to 27°-30° at which latter temperature the animals then remained. He compared the respiratory exchange after two days at the high temperature with that at the low, and found that it had not increased but actually decreased to about one half or less! This result is so improbable, however, that it appears almost certain that the animals were no longer normal or that some very serious error must have crept into the determinations.

Krehl and Soetbeer [1899] have compared the heat production of animals from temperate climates (*Lacerta*, *Rana*) with tropical forms (*Alligator*, *Uromastix*) and found higher figures for the former than for the latter at identical temperatures. Their results are complicated, however, by the two facts that their tropical animals were much larger and

[1] According to Ad. Jensen, The Selachians of Greenland, Mindeskrift for J. Steenstrup, Copenhagen, 1914, a certain species of ray (*Raja hyperborea*) is never found outside those areas in the Davis Strait and North Atlantic where the temperature of the bottom water in which it lives is below 0°. The boundary line between these areas and those in which the water is warmer (+1° to +3°) is in several places very sharp and *Raja hyperborea* has been caught just up to that line.

[2] A species of *Ephydra* (a fly) lives as larva both in brackish water at certain points on the Danish coast and in a hot spring in Iceland at a temperature of about 50°.

TABLE XVIII.

	Weight, gr.	Cal. per Kg. and Hour at 25·3°.	Cal. per Kg. and Hour at 37·0°.
Lacerta	110	0·8	1·5
Rana	600	0·5	0·95
Alligator	1380	0·3	0·47
Uromastix	1250	0·26	0·4

not very nearly related systematically to the temperate ones. Moreover standard conditions were not maintained, and most species of the two first-named genera are more active than those of the two last.

A systematic study of the possible acclimatization of animals with regard to standard metabolism is highly desirable.

The Influence of Light.

A number of observers, notably Moleschott and his pupils [1855], Selmi and Piacentini [1870], Pott [1875], have found that the respiratory exchange of animals is higher in the light than in darkness.

Moleschott and his pupils working on frogs found an increase of 8 to 25 per cent. in the light; Selmi and Piacentini found on the dog and Pott on the mouse that the different spectral lights had very different effects, the respiratory exchange being highest in yellow light and lowest in violet. Moleschott and Fubini [1881] found on frogs that the effect of light was diminished but not abolished when the animals were blinded. In all these experiments muscular movements were not excluded, and the results are probably to be ascribed to an influence on the functional activity of the muscles through the central nervous system and the organs of sense.

In experiments in which standard conditions have been maintained no effect of light has been noticed. Experiments have been made by Loeb [1888] on chrysalides of butterflies and by C. A. Ewald [1892] on curarized frogs. Loeb's results are very irregular individually, but on the whole unfavourable to the assumption of an augmenting effect of light upon the metabolism. In Ewald's careful experiments no measurable effect of light could be detected.

With regard to the fundamental problem the latter experiments are just as inconclusive as the former, because the light never reached the cells in which the metabolic processes take place. Experiments will have to be made on hyaline aquatic animals suitably narcotized to ensure standard conditions.

The Influence of Electric Currents.

d'Arsonval [1891] found that high frequency alternating electric currents, d'Arsonval or Tesla currents, without producing any form of muscular activity had a very distinct influence upon the respiratory exchange of man and animals, increasing it sometimes 100 per cent. His methods were unreliable, however, and the experiments of Loewy and Cohn [1900] on man and of Spasski [1900] on rabbits show, in the opinion of the writer, conclusively that there exists no real effect of these currents on the standard metabolism.

CHAPTER VIII.

THE VARIATIONS IN STANDARD METABOLISM DURING THE LIFE CYCLE OF THE INDIVIDUAL.

WE have now to consider a group of phenomena to which in the present state of our knowledge no definite cause of a physical or chemical nature can be assigned, but which are nevertheless of the utmost importance from a biological point of view. During the life of the individual, from the fertilization of the egg until the natural death of the organism from old age, an immense number of morphological changes take place, and these are regularly accompanied by corresponding changes in the metabolic activity. We have to consider especially the variations in metabolism taking place during development and growth, during maturity and during senile decay.

In the vertebrate animals and in most of the invertebrates we have only one more or less continuous period of growth lasting sometimes until sexual maturity is reached, sometimes much longer, but in the holometabolic insect we find intercalated between the larval and the imago stages the pupal stage in which no growth in the ordinarily accepted sense of that term takes place, but in which the morphological structure is remodelled more or less completely.

It will be convenient to deal first with the results obtained in experiments on eggs and embryos of different animals, then with pupal metabolism, and finally with the changes in metabolism taking place during the remaining parts of the normal life cycle: postembryonic growth, maturity and old age.

Beyond these regular changes, which are more or less common to all forms, we will also have to study in the present chapter certain changes in metabolism which take place less regularly and in certain forms only: the latent life of many invertebrates, the changes in metabolism during breeding periods, etc., and the hibernation of mammals. Our information with regard to these problems is certainly very imperfect, and will serve less to elucidate them than to indicate fields which appear fruitful for future research.

Metabolism During Embryonic Development.

We have in the egg of an animal a single cell or perhaps rather a single nucleus provided generally with an infinitesimal amount of

"protoplasm" and a large store of unorganized nutritive material. During development organization of this material takes place. The amount of nuclear substances and living protoplasm is increased and often enormously increased. At the same time some of the nutritive material becomes catabolized, and in all eggs which are not nourished from outside during development (all known eggs except those of Mammals and Selachians) the total potential energy present is steadily diminished.

The old view of Pflüger [1868] that the respiratory exchange of the embryo of a warm-blooded animal must be very small can now be dismissed without comment, the more so as it never had any experimental foundation. The principles which must be guiding in the study of embryonic metabolism were first enunciated by Bohr [1900].

We have during the development of the embryo a rapid formation of organized tissues. This formation may probably require the expenditure of energy, but at the same time the tissues when formed must have a certain metabolism, and the fundamental problem before us is to distinguish as far as possible between these two components of the embryonic metabolism, and to determine the "cost of production," if any, of living "protoplasm" from unorganized chemical substances.[1] Bohr saw further that a certain amount of energy might possibly be transferred to the newly formed tissues whose energy content might be higher because they were living, than that of the "dead" material from which they were formed. If this latter possibility were realized the direct and indirect methods of calorimetry must give different results, the expenditure of energy as calculated from the respiratory exchange being higher than that found by direct biocalorimetric determination on embryos during development. In their classical paper, "Ueber die Wärmeproduktion und den Stoffwechsel des Embryos," Bohr and Hasselbalch put this theoretical possibility to the test of experiment, and found, as mentioned in detail on p. 12, that there was a complete agreement between the metabolism as determined by direct and by indirect calorimetry. Determinations of embryonic metabolism by

[1] The term "Entwickelungsarbeit" has been introduced and used by Tangl [1903] in the important series of "Beiträge zur Energetik der Ontogenese". By "Entwickelungsarbeit" Tangl denotes the total energy expended during embryonic life. The determinations of the work of development have been made in most cases by comparisons of analyses (chemical and calorimetric) at the beginning and end of the incubation period.

respiratory exchange methods must therefore be regarded as valid and we may proceed to discuss the results of such investigations.

Warburg [1908, 1909] measured the respiratory exchange (oxygen absorption) of the eggs of sea urchins (*Arbacia*). He found that a very large increase in metabolism took place as the result of fertilization. One hundred and seventeen million eggs, containing 1 gr. of nitrogen, consumed per hour before fertilization 2·0 mg. of oxygen, after fertilization 13·6 mg. It would be natural to assume that this increase depends upon the functional activity, the process of mitosis and segmentation which is induced by the fertilization. Warburg's experiments show very clearly, however, that such a dependence does not exist. A corresponding or even greater increase in metabolism can be brought about in the unfertilized eggs by a number of substances (see p. 67), and after fertilization the segmentation can be inhibited, e.g. by phenylurethane, while the oxygen absorption is not affected at all. On the other hand we cannot have segmentation except when the respiratory exchange is increased either by fertilization or as the effect of some chemical agency. In his latest publication [1914] Warburg has shown that the increase in oxygen absorption following immediately upon fertilization is due to the alteration of the surface layer ("Grenzschicht") of the protoplasm.

When the eggs develop in normal sea water after normal fertilization the amount of oxygen absorption necessary to reach a certain stage is constant (at least at a constant temperature[1]), but if the eggs have each been fertilized by more than one spermatozoon, the velocity of segmentation is increased without a corresponding increase in metabolism, and the stage of 4 cells may be reached with about one-half the normal oxygen absorption.

As segmentation progresses the respiratory exchange is increased. In one experiment Warburg found for instance an oxygen absorption of 13·2 mg. per gr. nitrogen per hour at the stage of 8 cells and in the stage of 32 cells 20·5 mg.

Meyerhof [1911] determined directly the heat production in the different stages and found at 19° the data in Table XIX.

Meyerhof's figures for oxygen absorption agree on the whole with those obtained by Warburg.

Meyerhof determined also the heat production of the spermatozoa and found per gr. nitrogen, when the spermatozoa were quite fresh, 880 calories per hour. The heat production decreased rapidly.

[1] All Warburg's experiments were made at a temperature of 20·2° to 20·5° C.

TABLE XIX.

		Number of Cells.	Cal. per gr. N per Hour.
Before segmentation		1	6·5
After segmentation	0-1 hour	1	28·5-30
	1-2 ,,	2	32-36
	2-3 ,,	4	38-42
	3-4 ,,	8	43-47
	4-5 ,,	16-32	56-68
	5-6 ,,	32-64	70

Bohr and Hasselbalch [1900] have studied the carbon dioxide production of the embryo of the common fowl. Later Hasselbalch [1900] determined also the oxygen absorption, and finally Bohr and Hasselbalch [1903] measured the heat production together with the total respiratory exchange. The special merit of these investigations lies in the careful determinations of the weight of the embryo at all stages. Table XX and fig. 31 show the CO_2 production and the corresponding weight for each stage.

TABLE XX.

Day of Incubation.	Weight of Embryo. gr. (*a*)	gr. (*b*)	CO_2 in 24 Hours, c.c.
1			11·4 [1]
2			2·6
3	0·02	0·004	1·5
4	0·06	0·054	6·1 [2]
5	0·11	0·155	10·6
6	0·35	0·373	17·9
7	0·63	0·615	20·2
8	0·80	1·200	29·6
9	1·47	2·04	37·1
10	2·30	2·89	47·3
11	2·67	4·37	61·1
12	4·25	5·67	104·6
13	6·45	7·54	147
14	8·84	10·00	183
15		12·29	238
16	13·76	15·21	293
17	15·88	17·50	365
18		21·55	364 [2]
19			363
20			354
21			376

In series *a* eggs from different hens belonging to the same race were incubated. In series *b* eggs from the same hen were used throughout. The determinations of CO_2 production were made on one single egg.

[1] During the first days CO_2 is given off from the shell.

[2] The figures for the fourth and eighteenth day have been obtained by interpolation.

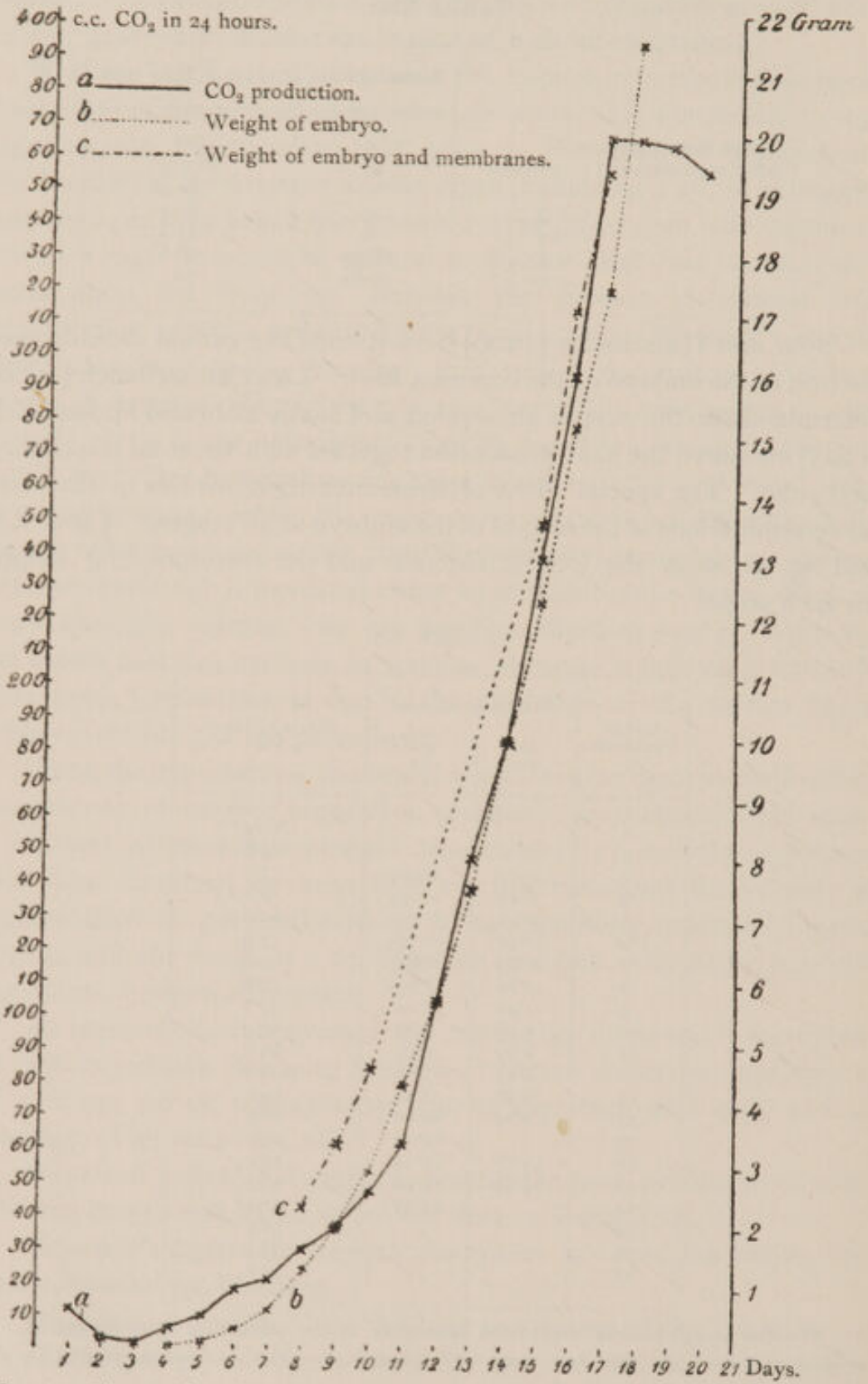


FIG. 31.—Changes in weight and respiratory exchange during embryonic development. From "Skand. Arch. Physiol."

When Bohr and Hasselbalch calculated the respiratory exchange per kg. and hour for the later stages of the development (from the fifth to the eighteenth day) they found that it is not very variable (590 to 830 c.c.), while the average, 718 c.c., is about the same as that found for the grown hen in Regnault and Reiset's experiments. It must be borne in mind, however, that the embryo is very quiet, while the experiments on hens were not made under standard conditions. For the earlier stages a much higher respiratory exchange per kg. and hour is calculated, but here the determination of the amount of living tissue which takes part in the metabolic processes is very uncertain and in all cases too low, because the "yolk sac" could not be included.

Material has not been furnished by these experiments which will allow a definite distinction to be made between the true basal metabolism of the embryo and that required for the activity of tissue formation. In the opinion of the writer the experiments do show, however, that the tissue-forming activity can (during the later stages of development at least) be responsible for at most a small fraction of the total respiratory exchange, since the formation of new tissues takes place with decreasing velocity, while the respiratory exchange is during the whole period from the ninth to the eighteenth day practically proportional to the weight of the embryo.

Hasselbalch [1902] has attempted to show that during the first hours of incubation free oxygen is not only not absorbed but actually produced by the eggs. His results are due, however, to the large amounts of gas (nitrogen and oxygen) which at ordinary temperatures are absorbed by the fatty substances in the yolk and partially liberated when the eggs are incubated at 38°.

Bohr [1900] has studied the respiratory exchange of mammal embryos by the following elegant method. Pregnant guinea-pigs or rabbits were narcotized with urethane, a tracheal cannula was introduced, and the pulmonary gas exchange measured in 10-minute periods. The uterus was laid open by bloodless operation, and the respiratory exchange of the embryos could now be suspended either for a time or permanently by compressing or ligating the umbilical cords. Comparisons were made between normal periods in which the circulation of the embryos was not interfered with and such in which it was suspended. The results of five series of experiments on guinea-pigs were as follows:—

TABLE XXI.

Weight of an Embryo, gr.	c.c. CO_2 per Kg. and Hour.	
	Mother.	Embryo.
16	490	756
24	483	250
36	452	586
39	408	462
62	478	488

The averages are for the adult animal 462 ± 15 c.c. per kg. and hour.
and for the embryo 509 ± 68 ,, ,,

Within the limits of error the respiratory exchange is therefore the same, and these experiments are especially valuable because standard conditions were secured by the urethane. The respiratory quotient of the embryos was in all cases very nearly 1, and it was concluded therefore that the metabolism of the mammal embryo is chiefly a catabolism of carbohydrate.

In experiments on the eggs of a snake (*Coluber natrix*) Bohr [1903] found that the respiratory exchange calculated per kilogram of embryo decreased during the period of incubation (Table XXII).

TABLE XXII.

Weight of Embryo, gr.	CO_2 per Hour, c.c.	CO_2 per Kg. and Hour, c.c.	Temperature.
0·38	0·275	724	27·8
0·54	·295	548	28·0
0·56	·370	659	28·0
0·81	·380	467	27·2
1·40	·510	362	27·4
Young animal 3·8	·950	250	27

The comparison between the embryos and the young snake is not of much value as standard conditions were not observed, while on the other hand the animal had been without food for a very long time.

By comparing experiments made at 15° with others made at 27° to 28° Bohr found that at the higher temperature the development is about thrice as rapid and the production of carbon dioxide about thrice as large. The figures are very uncertain, however, and the conclusion drawn from the experiments, that the greater part of the energy expended is utilized for the growth of the tissues, is certainly unwarranted as the standard metabolism is greatly increased by the increase in temperature.

Metabolism During the Pupal Life of Insects.

When the metamorphosis from larva to chrysalis begins, an insect is a completely organized animal provided usually with a considerable reserve of fat and ceasing to take food and make muscular movements. In this animal a histolysis takes place which, though very different in extent and rapidity in different forms, will in extreme cases (flies, butterflies) reduce the organism to few and small heaps of single cells and a yolk of nutritive material. From the cells the organism of the imago is developed by a process which bears a very close resemblance to embryonic development.

Sosnowski [1902], Weinland [1906], and Tangl [1909, 1] have made investigations on the chrysalides of flies (*Musca vomitoria*, *Lucilia cæsar*, *Ophyra cadaverina*). They have found that the respiratory exchange (CO_2 production) is high at first, then falls for some days, and finally rises again. I give (Table XXIII) as the best example the figures obtained in one of Weinland's series of experiments on 305 chrysalides of blow-flies weighing 22·6 gr. at temperatures varying irregularly between 16° and 20°.

TABLE XXIII.

Day.	Loss of Weight, mg.	CO_2 in 24 Hours, mg.
1	220	195
2	530	140
3	510	100
4	240	83
5	130	81
6	220	90
7	140	96
8	150	112
9	180	146
10	140	169
11	190	238
12	310	331
13	280	334
	Total 3150	2090

Towards the end of the pupal period muscular movements take place leading up to the opening of the cocoon and the appearance of the fly. The metabolism measured during the last days is therefore not purely standard metabolism.

Tangl also ascribes the large metabolism in the initial period of the pupal life to muscular movements. Weinland [Op.] denies that such movements take place, and thinks that the histolytic pro-

cess itself must be responsible for the large metabolism during the first stage. The facts as known are not sufficient to warrant either conclusion, and it is just as possible that the metabolism is proportional at each stage to the amount of organized "living" tissue present.

Krogh [1914] has made similar determinations on the chrysalides

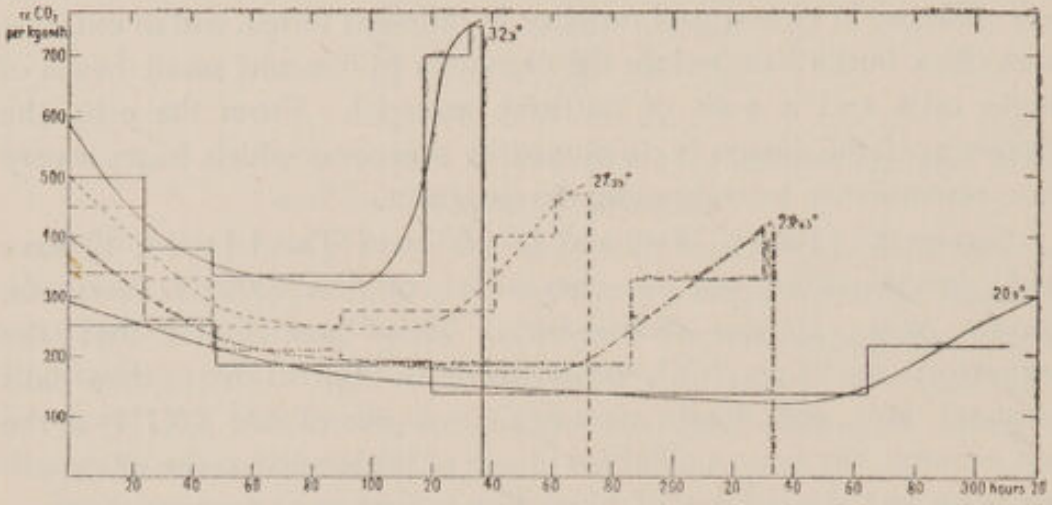


FIG. 32.—From "Zeit. f. allgem. Physiol."

of a beetle (*Tenebrio*, the meal-worm) and obtained curves of the same general form (fig. 32). These chrysalides are able to make movements of the abdomen during the first stage but practically never do it except when stimulated. Krogh determined the total metabolism (production of carbon dioxide) together with the duration of the pupal life at different temperatures. The results are given in Table XXIV.

TABLE XXIV.

Temperature.	Duration of Pupal Life, hours.	CO_2 Produced During Pupal Life by 1 Kg. Chrysalides, litres.	Average CO_2 Production per Hour, c.c.
32·7°	137·9	59·3	427
27·25°	172·5	58·0	336
23·65°	234·1	59·1	252
20·9°	320	59·6	186

At the four temperatures investigated the incubation time varies from 138 to 320 hours, but the total production of carbon dioxide is practically the same in all cases. The cost of production of the imago or the "work of development" in the sense of Tangl is independent of the temperature. If it had been lower at a certain temperature than at others, as was expected when the investigation was undertaken, that temperature would have been an optimum temperature for

the pupal development. The result means, therefore, that no such optimum exists. According to unpublished experiments by the writer this appears to hold also for the embryonic development of the eggs of an insect (*Acilius sulcatus*).

The review of the field of embryonic and pupal development shows that so far the data for distinguishing between the energy required for tissue building (or tissue disintegration) and the simple basal metabolism of the tissues existing at any given moment are insufficient. The available evidence points rather to the conclusion that the expenditure of energy required for tissue formation is quite small.

The Respiratory Exchange During Growth and Senile Decay.

Comparative experiments on the standard metabolism at different ages have been made on man by Magnus-Levy and Falk [1899]. The older experiments of Tigerstedt and Sondén [1895] were also made on man, but standard conditions were not rigorously observed. The general results of Tigerstedt-Sondén's experiments were very similar to those of Magnus-Levy and Falk.

Calculated per unit weight (kilogram) the metabolism of growing individuals is much larger than of adults, and in old age there is a distinct decrease. As will be shown in detail in the next chapter adult individuals belonging to the same species, but of different size, have a larger gas exchange per kilogram the smaller their size, while it has been shown that when the metabolism is calculated per unit surface (square metre) about the same figure is obtained for all sizes. A comparison between young and adult human beings must, therefore, be instituted on the basis of surface instead of weight, as there are large differences in size. When this is done Magnus-Levy and Falk find that the differences, though of course diminished, are not abolished as the following table (XXV) shows:—

TABLE XXV.—Standard Metabolism of Males of Different Age.

Age, Years.	Weight, Kg.	Surface, Sq. M.	Per Square Metre and Minute.	
			Oxygen, c.c.	CO_2, c.c.
2·5-11	11·5-26·5	0·627-1·094	175-154	150-122
10-16	30·6-57·5	1·205-1·834	159-132	133-109
22-56	43·2-88·3	1·516-2·441	129-111	105-82
64-78	47·8-69·3	1·622-2·077	103-87	86-63

Magnus-Levy and Falk have also made experiments on three sub-

jects of approximately the same weight and height (and consequently the same surface) but very different age. They obtained the results

TABLE XXVI.

Age, Years.	Weight, Kg.	O_2 per Minute, c.c.	O_2 per Kg. Relative Figures.
15	43·7	217	110
24	43·2	196	100
71	47·8	163	75

given in Table XXVI, but as individuals of the same age and stature may also have very different standard metabolisms, these experiments are inconclusive.

Magnus-Levy and Falk believe that their results show that the oxidative energy of the "protoplasm," as distinct from reserve material and connective tissue, is greater in the growing organism than in the adult and decreases with old age, but they are careful to point out the possible sources of fallacy arising from the fact that in old age the relative amount of inactive tissue increases. That the view of Magnus-Levy and Falk is fallacious can be shown very clearly when their results are compared with those obtained on younger children. In such the metabolism per square metre is distinctly lower though the rate of growth is certainly more rapid. Thus Scherer [1896] found per square metre and minute for children up to 18 days an oxygen absorption of 65 to 96 c.c. Forster [1882] for a child of 60 days 107 c.c., and Schlossmann and Murschhauser [1909] for one and the same child when 144 days old (weight 5790 gr.) 128 c.c., when 284 days old (weight 8450 gr.) 129 c.c., and when 380 days old (weight 8930 gr.) 133 c.c., while Magnus-Levy and Falk's average figures are 150 c.c. for a boy of 2½ years, 131 for a boy of 6 years, and 91 for a man between 27 and 43 years.

The results of Scherer are not very accurate, and the very low respiratory quotients found by him on new-born children are certainly erroneous, but some quite reliable determinations have been made by Hasselbalch [1904] on such children, and published in Danish. Hasselbalch's results show that the standard metabolism of young children, though higher per kilogram than the standard metabolism of adults, is distinctly lower when calculated per square metre.

TABLE XXVII.—Respiratory Exchange of New-Born Children.

Sex.	Age.	Weight, gr.	Length, cm.	Per Kg. and Hour, c.c. O_2	Per Kg. and Hour, c.c. CO_2	R.Q.	Per Kg. and Hour, Calories.	Per sq. m.[1] and 24 Hours, Calories.	
♀	¾ h.	3750	51	344	333	0·970	1·73	542	Very quiet, sleeping during last half of experiment.
♀	1½ h.	3950	54	313	270	0·862	1·54	491	Very quiet.
♂	1¾ h.	4500	53	371	300	0·808	1·81	601	Sleeping.
♂	1 h.	2550	47	443	339	0·766	2·14	590	Sleeping, sometimes sucking.
♀	2 h.	1825	44	313	273	0·871	1·55[2]	382[2]	Sleeping, Respiration irregular. *Born one month too early.* Died next day.
♂	2½ h.	3600	54	360	306	0·849	1·77	546	Sleepy and sometimes sleeping. Cries for one minute.
♂	1¾ h.	3400	52	321	275	0·854	1·58	480	Hungry and sleeping at intervals.
							Average 1·76	541	

[1] According to Meeh's formula $S = 11{\cdot}9\ W^{\frac{2}{3}}$.

[2] Excluded from average.

Recently a very important paper on infant metabolism has been published by Benedict and Talbot [1914]. They have determined the standard metabolism of 60 children aged between 15 hours and 17 months, and calculated the results on the basis both of weight and of surface (using three different formulæ). Their results are seemingly very irregular as shown by the charts, figs. 33 and 34,[1] but when the

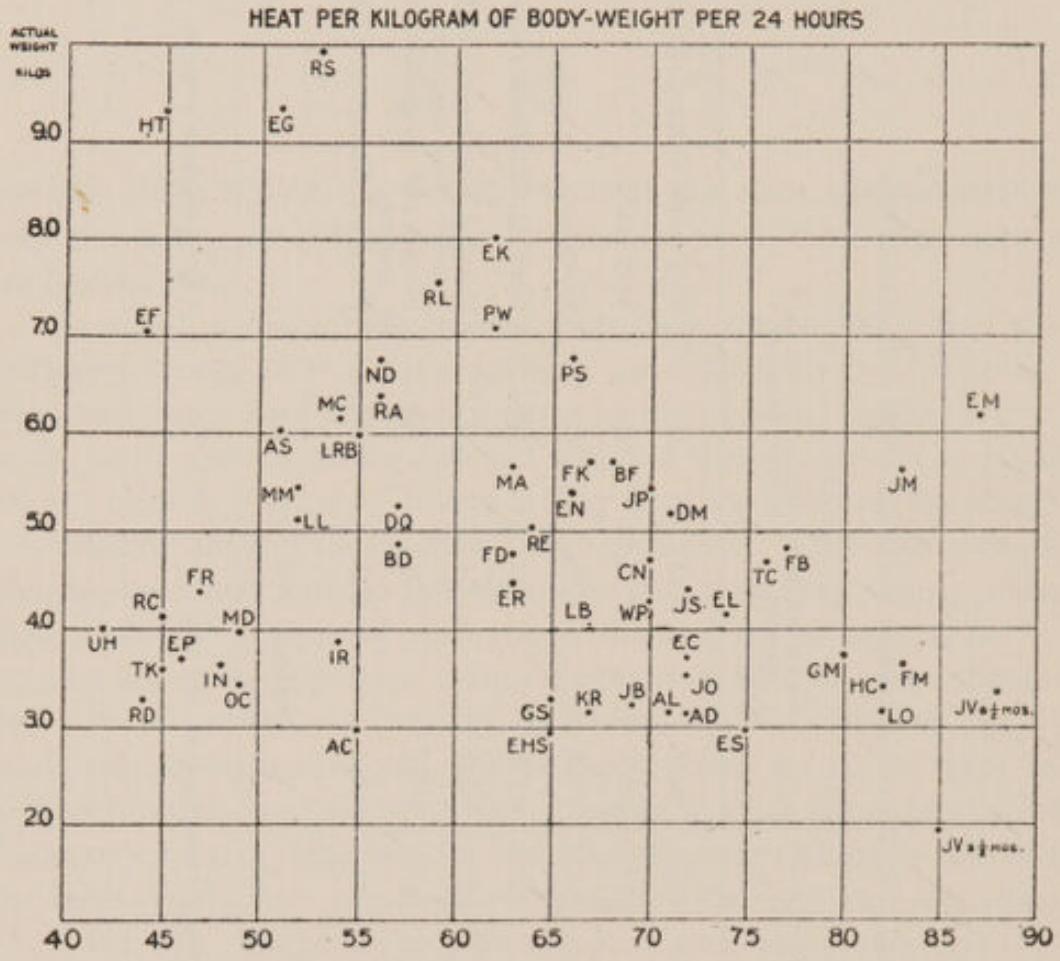


FIG. 33.—From "Amer. Journ. Diseases of Children," 1914, 8, 42 (Benedict and Talbot).

ages of the infants are taken into account correlations of some interest can be established. In Table XXVII*b* the material available in Hasselbalch's, Benedict and Talbot's, and Magnus-Levy and Falk's investigations has been utilized to calculate the average standard metabolism (production of heat per square metre per minute) for individuals

[1] Benedict and Talbot calculate standard metabolism per 24 hours. In the opinion of the writer the 24-hour basis ought to be reserved for determinations of "normal" metabolism for comparisons with food requirements, etc., while 1-hour or 1-minute units are better suited for standard conditions, which are seldom maintained or studied over periods of greater length.

varying in age from minus 1 month (an infant born 1 month too early) to 35 years.

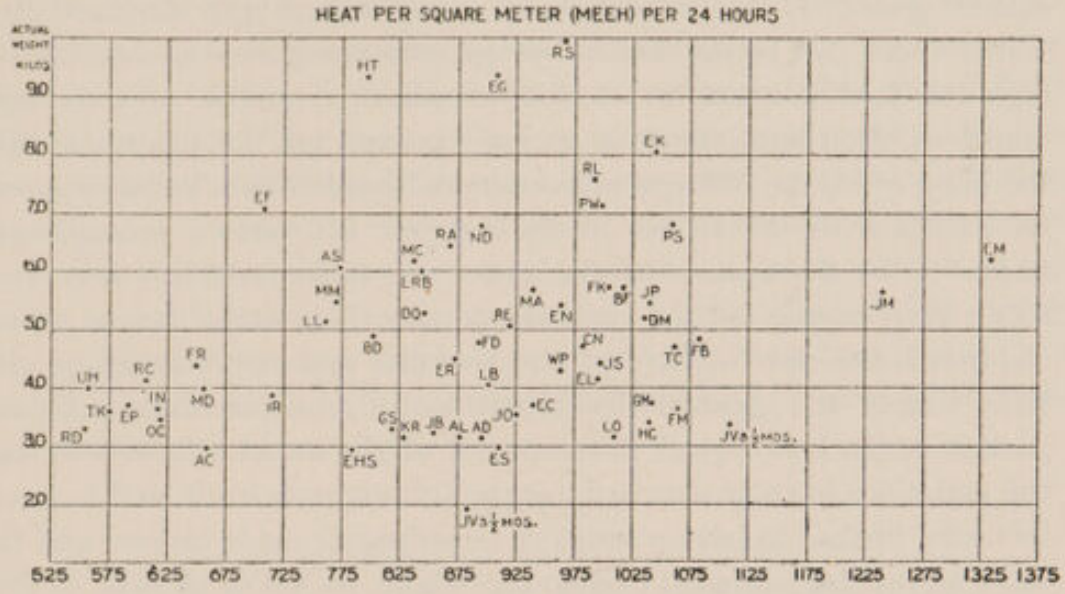


FIG. 34.—From "Amer. Journ. Diseases of Children," 1914, **8**, 45 (Benedict and Talbot).

TABLE XXVII*b*.—THE VARIATION OF STANDARD METABOLISM WITH AGE. EXPERIMENTS ON MAN.

Age Average.	Body Weight Average Kg.	Metabolism Calories per sq. m. per Minute.	No. of Subjects.	Author.
– 1 month .	1·83	0·27	1	Hasselbalch
1½ hour .	3·63	0·38	6	,,
1·8 days .	3·69	0·41	6	Benedict and Talbot[1]
10·5 ,, .	4·00	0·45	4	,, ,,
2·5 months	4·72	0·56	22	,, ,,
4·5 ,, .	4·32	0·63	9	,, ,,
8·5 ,, .	6·1	0·72	20	,, ,,
2·5 years .	—	0·74	—	Magnus-Levy and Falk[2]
6 ,, .	—	0·64	—	,, ,, ,,
35 ,, .	—	0·44	—	,, ,, ,,

It is obvious from this table that the standard metabolism increases in infants with increasing age, and the increase is so large during the

[1] The averages are calculated from the average figures given by B. and T. for each subject, and no account has been taken of the varying number of determinations, on which these averages are based, and the resulting very different "weights" of the figures here averaged. For this reason a detailed calculation of deviations has been omitted, and it has only been roughly ascertained that the standard deviation in the different series is about 10 per cent. or less (see p. 133), and the averages given therefore reliable to within 5 to 2 per cent. A full statistical treatment of the splendid material brought together by B. and T. would almost certainly yield results of very great interest.

[2] M.-L. and F.'s determinations have been calculated on the basis of a R.Q. = 0·82 which at all events comes very near the truth.

earlier stages that it is quite pronounced also when the material is calculated on the basis of body weight instead of surface. As the rate of growth is undoubtedly most rapid at first and declines afterwards, there can be no doubt that growth is not responsible for the high standard metabolism of children above 1 month. As the very young children certainly on an average possess less adipose tissue than the older ones, the differences cannot, as Benedict and Talbot suggest, be ascribed to differences in the amount of "active protoplasmic tissue". In the opinion of the writer the factor which is most probably responsible for the regular increase in metabolism of young children is the development of the muscular system *as such*, and perhaps simply the gradual development of a muscular tone. A comparison of the histological development of the muscles in infants with the variations in their standard metabolism suggests itself, and it would be useful further to have a series of experiments made on one and the same animal (or animals) during the whole period of growth in conditions in which muscular movements and if possible also the muscular tone could be abolished.

Variations in Standard Metabolism in the Full-Grown Organism.

The phenomena to be dealt with in the present section are for the most part very obscure in character, not only with regard to possible causes, but also, unfortunately, with regard to the very facts which have in several cases been ascertained only in a vague and general sort of way. The outcome of a discussion of the heterogeneous and scanty material existing is, therefore, less a statement of results than a caution against results, and some suggestions for further research.

1. *Periodic variations.*—Hanriot and Richet [1891] found diurnal variations in the respiratory exchange of man corresponding to the variations in body temperature, but as standard conditions were not maintained their observations are inconclusive. Johannson [1898] experimenting on himself, and maintaining standard conditions as rigorously as possible, found that in the period from 12 at night to 8 in the morning the carbon dioxide production was 3·7 per cent. lower than the average for 24 hours, while in the period from 8 a.m. to 4 p.m. it was 3·5 per cent. higher, and from 4 p.m. to midnight 0·1 per cent. higher. Johannson himself ascribes the results to unavoidable differences in activity. Magnus-Levy [1894] has obtained similar results on man and also on a dog. Recently Benedict [1915], however, has

observed regular diurnal variations in the resting metabolism of a man fasting for 31 days.

Lindhard [1910, 1912] has observed very pronounced seasonal variations. He made determinations of the carbon dioxide output in half-hour periods on himself during an arctic expedition (North-East Greenland, 76° 46′ N. Lat.). The experiments were made under approximately standard conditions each morning fasting and in a kneeling position.[1] Consecutive series of about ten experiments were made and such series repeated every 2 to 3 months. The agreement of the experiments in each series is remarkable. Lindhard found that during the arctic summer day, which lasts in that latitude from the end of April until September, the standard metabolism is increased as compared with the winter night.

TABLE XXVIII.

	c.c. CO_2 per Kg. and Hour.	Ventilation of Lungs Lit. per m.
April	214 ± 0·7	8·1
June	238 ± 1·5	8·25
August . . .	241 ± 0·6	8·7
November . . .	237[2] ± 2·0	8·7
January . . .	208 ± 0·9	7·9

Along with the increase in metabolism an increase in pulmonary ventilation and a decrease in alveolar CO_2 tension were also observed. The increase in ventilation will account for part of the increase in metabolism through the increased work of the respiratory muscles (see p. 59), but the general effect is ascribed by Lindhard to the light acting indirectly as a climatic factor. Similar but much less pronounced variations were observed by Lindhard in a series of experiments made in Copenhagen upon two other subjects. The difference in light between summer and winter is of course much less at 56° northern latitude than at 76°.

2. *The influence of muscular training.* — It has been shown by Zuntz and Schumburg [1901] for man and by Zuntz [1903] for the dog that the standard metabolism is increased after a prolonged period of severe muscular work. This increase may be due partly to an increase in the amount of muscular tissue, but in some cases at least an

[1] The space available in the laboratory did not allow any other.

[2] Muscular training was probably to a certain extent responsible for the high figure for November. See below.

increased oxidative energy of the muscle cell must be assumed. Recent observations by Lindhard [1915] confirm this result.

3. *The influence of feeding and fasting.* — Magnus-Levy [1894] found that the standard metabolism, measured 12-24 hours after the last meal, became higher when the animal (dog) had been fed for some time on protein. Schreuer [1905] has shown, however, that the influence disappears in the next 24 hours and that we have to do in this case with a direct effect of food, which has not been completely catabolized or excreted in the usual period, and not with any increase in the oxidative energy of the cells.

E. Voit [1901] found that the 24-hour metabolism of fasting warm-blooded animals (man, dogs, rabbits, hens) fell off steadily during a prolonged fast when it was calculated per unit of the surface as determined by the formula $s = k\, w^{\frac{2}{3}}$, and also when calculated per kg. of the weight. Voit figured out by a somewhat complicated calculation the amount of "nitrogen in active organs," one might perhaps say of "protoplasm" in his fasting animals, and found that after an initial fall the metabolism per unit of active nitrogen remained practically constant throughout the fast.

I reproduce one of his Tables calculated from an experiment by Rubner (Table XXIX).

TABLE XXIX.—Fasting Metabolism of a Dog.

Day of Fast.	Weight, gr.	Calories in 24 Hours.			Per 100 gr. N.
		Absolute.	Per kg.	Per sq. m.	
3	2185	155	71·0	730	310
5	2093	117	55·9	556	243
7	2007	102	50·8	499	220
9	1923	97	50·5	488	221
$\frac{11+12}{2}$	1841	95	51·6	494	227
$\frac{13+14}{2}$	1735	88	50·7	467	222
$\frac{15+16}{2}$	1646	81	49·2	452	218
$\frac{17+18}{2}$	1507	72	47·8	428	219

It must be remembered that in these experiments standard conditions were not maintained, and that the animals in all probability made more muscular movements during the first days of the fast than later. It has been shown on man, notably by Zuntz and his collaborators

(Lehmann, Müller, Munk, Senator and Zuntz [1893]), that the standard gas exchange per kg. remains constant even during a prolonged fast.[1] This result has on the whole been confirmed by Benedict's recent investigation [1915] of a prolonged fast in man. It has been extended also to other mammals and can probably safely be accepted as approximately valid for all warm-blooded animals, but whether it can be extended to cold-blooded also is uncertain and unlikely.

A. V. Hill [1911] found in calorimetric experiments on frogs kept in darkness in a Dewar flask—conditions in which they usually remain very quiet, so that the metabolism probably approaches the standard—that the production of heat fell off during the first two weeks of inanition from 0·55 cal. per c.c. of frog per hour to 0·26 cal., but afterwards remained remarkably constant as shown by fig. 35. This indicates, ac-

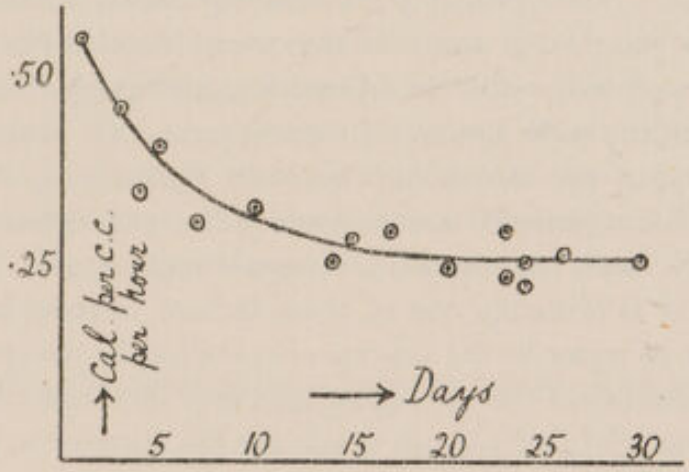


FIG. 35.—From "Journal of Physiology" (Cambridge University Press).

cording to Hill, that the amount of reserve material stored in the tissues determines to a certain degree the intensity of the metabolic processes. The experiments are not sufficient, however, to prove this contention, because it is possible that a decrease in muscular tone may be primarily responsible for the decrease in metabolism, but it appears to be supported by casual observations made by the writer and others, and a comprehensive investigation of this problem, in which standard conditions were rigorously maintained and both oxygen, carbon dioxide

[1] In a recent investigation Zuntz [1913] found on a dog which was for a long time given an insufficient amount of food that the metabolism calculated per square metre decreased considerably during 10 months from 931 cal. in 24 hours, when the dog weighed 10 kg., to 631 when the weight had gone down to 4·98 kg. Then it rose again, however, and reached 921 cal. (weight 4·1 kg.) before the animal died.

A similar experiment was made simultaneously by Morgulis [1913] who obtained a rather different result.

and perhaps the heat produced were measured, would be sure to give results of considerable value.

4. *Environmental factors.*—In warm-blooded animals the "environment" of the cells is maintained practically constant with regard to temperature, concentration of hydrogen ions, salts, oxygen, sugar, and probably other sources of energy. The cells have lost consequently their power of adaptation to changes in all these respects, and if one of the regulating mechanisms breaks down the death of the organism results. It is only natural, therefore, that in these animals the standard metabolism is a constant which is independent of changes in the outside world, because these changes are always toned down to insignificance by the regulating mechanisms before reaching the cells.

In cold-blooded animals we have an extremely wide diversity of conditions. Some probably possess regulating mechanisms which are not very inferior to those of the warm-blooded (the temperature regulation excepted), while in others any and every condition of life may vary within wide limits. In such forms we must expect that the intensity of the metabolic processes is distinctly influenced by numerous environmental factors besides the well-defined ones which have already been mentioned: temperature, oxygen pressure, etc. Want of food is probably one of these factors in most lower animals. The amount of water in the tissues—depending in many cases simply upon the humidity of the air—must be a very important factor, notably in many terrestrial molluscs, in which the life appears to become latent and the metabolism to drop to a minimum when they are deprived of water.

Certain animals have periods of suspended activity, the determining causes of which are unknown, but during which the standard metabolism must certainly be reduced. Thus several small flies, the larvæ of which live in fungi, have a number of generations during the summer, but in the autumn chrysalides appear in which development cannot be induced by any temperature, however high, before the spring (February), and the writer has found that the metabolism remains low until this occurs.[1]

The same appears to be true also with regard to many other chrysalides and some insect eggs. In the case of the silk-worm eggs a beginning has been made by Luciani and Piutti [1888] to

[1] We have here a close analogy to the resting period of numerous plant seeds and buds. The determining causes are unknown in both cases.

study the latent period from the metabolic point of view, but unfortunately the determinations during the latent period were made at decreasing temperatures, so that the temperature effect cannot be separated from a "spontaneous" fall in metabolism which may have occurred.

5. *Possible breeding variations in standard metabolism.*—Krogh [1904] has described variations in the respiratory exchange of the frog corresponding to the seasons and especially to the state of the reproductory organs, showing a very large increase during the breeding season. Later experiments (Krogh [1914]) have shown, however, that in this case we have to do only with changes in muscular activity, as the differences disappear completely when the animals are narcotized. There is, however, a case on record in which a large "spontaneous" increase in standard metabolism is still an eventuality which must be taken into consideration.

Valenciennes [1841] has described how the female *Python*, when the eggs are laid, curls up around them covering them completely with her body. The temperature measured between the coils then becomes extremely high, though the animal does not make any movements beyond respiring deeply and frequently. The following temperature observations have been extracted from the paper of Valenciennes:—

TABLE XXX.—Temperature of a Brooding Python—Eggs Laid May 6. Incubation 56 Days.

	Temp. of Air.	Temp. of Python.	Difference.
May 8	28·23	41	16
,, 17	22·5	37	14·5
,, 31	23	34	11
June 11	21	33	12
,, 28	21·7	32	10
July 2	24	28	4

On July 2 the eggs were hatched. The mother left them, and her temperature fell to 24° though she took food for the first time since February 2. The writer has had occasion to observe that a *Python* is especially quiet during the first period of the incubation when the temperature is highest, and it appears unlikely that muscular movements should be at all responsible for the large increase in temperature. Respiration experiments on a brooding *Python* are certainly desirable but not easy to obtain.

Hibernation in Mammals.

A small number of mammals (but not a single bird) show the peculiarity that their temperature regulation at times ceases to function, with the result that the temperature of the body falls and the animals get into a state of torpor. By stimulations of different kinds a process of awakening can be induced which is characterized by a rapid increase in body temperature and a resumption of the normal functions. The hibernation problem has been studied repeatedly from the point of view of the metabolic processes, but the results are far from satisfactory which is perhaps only natural when the very great difficulties inherent in the investigation are duly considered.

The transition from the ordinary to the hibernating state has been studied by Pembrey and White [1896, 1, 2] on dormice and bats. They found that the muscular activity is the chief factor determining the temperature and metabolism of these animals, while the physical regulation of the loss of heat from the body is unimportant. An active animal will maintain and even increase its temperature (by increased activity) when the surrounding temperature falls, but as soon as it becomes quiet the metabolism and the body temperature drop very rapidly as seen from the examples quoted.

TABLE XXXI.

Temp. of Air.	Rectal Temp. of Dormouse.	Time.	Remarks on Dormouse.
21·25	33·5	12.15	Wide awake, running about.
At 12.15 brought into a cold room.			
9·5	34·5	12.30	Wide awake, running about.
9·25	30·5	1.43	,, ,, ,, ,,
9·25	18	2.30	Coiled up and going to sleep.
9·25	14·5	3.00	Coiled up, asleep.
9·25	11	7.00	Very fast asleep and motionless when temperature taken.
9·25	13·5	8.00	Slightly more awake.
9·5	35·75	9.00	Wide awake, running about.

In an experiment on the metabolism made by means of the Haldane apparatus the sleepy dormouse was in the ventilated chamber in a water-bath of 25° for 30 minutes before the first period of determination and thereupon consecutive periods of 15 minutes each were taken.

TABLE XXXII.

Temp. of Bath.	CO_2 Discharged Deci-mg.	Remarks on Dormouse.
25°	113	Coiled up.
24·75°	112	,,
15°	220	Active at first, then coiled up.
15°	68	Coiled up.
15°	21	,,
25°	17	,,
25°	14	,,
25°	20	,,
24·5°	25	,,
24·75°	20	,,

The dormouse was coiled up and fast asleep at the end of the experiment.

Observations and determinations have been made also by Hári [1909, 1] on the bat. At fairly high temperatures bats show the usual "chemical" heat regulation, but when the temperature falls below a certain point, differing according to the animal's state of nutrition from 19° to about 12°, the movements cease, and a state of torpor develops resulting in a rapid fall of the body temperature.

It is known (Merzbacher [1904]) that hibernating animals have normally a labile temperature, which usually falls considerably during ordinary sleep. The temperature of bats especially will fall during their sleep in the daytime to a few degrees above that of their surroundings.

It appears to follow from the data given that in hibernating animals low temperatures do not necessarily produce muscular movements through the heat regulating mechanism of the central nervous system, and that the immediate cause of the fall in body temperature is simply that the standard metabolism of these animals at a comparatively high surrounding temperature becomes insufficient to cover the loss of heat and therefore to maintain the temperature. Further experiments on the gas exchange of animals going into hibernation made by means of Benedict's recording cage, and also on such animals under curari, are very desirable.

It is known that during the hibernation, when the sleep is deep, the respiratory exchange rises and falls with the temperature just as in a cold-blooded animal. The most reliable figures have been given by Nagai [1909] for the marmot, but an extended investigation is required.

TABLE XXXIII.

Temp. of Marmot.	Per Kg. and Hour.		R.Q.
	O_2.	CO_2.	
10°	30·5	18·7	0·61
13·5°	77·3	50·0	0·64
24·4°	258·0	199·8	0·77
36·5°	605·5	486·9	0·804 (Awake)

During the sleep the respiratory quotient is low and probably even generally below that corresponding to a complete catabolism of fat (0·71). Some experimenters (Pembrey, Valentin, Voit [1878], Regnault and Reiset [1849]) have observed extremely low respiratory quotients even down to 0·1 (Valentin) or 0·26 (Pembrey), but according to Nagai, to whose criticism the writer can on the whole subscribe, the very low values are unreliable, and the average quotient during hibernation is probably about 0·6 or a little over. Hári [1909, 2], like Nagai, found fairly high respiratory quotients (about 0·68) in hibernating bats. In one animal, however, the quotient was during the whole period of observation from February 9 to March 7 considerably lower —on an average 0·53.

It should be borne in mind that respiratory quotients representing faithfully the catabolic processes going on in the body can be obtained only when the store of carbon dioxide either remains unaltered or can be considered as insignificant compared with the quantities exhaled during the determination. Changes in body temperature will almost certainly affect the carbon dioxide absorbed in the tissues, and even slight changes in the pulmonary ventilation, which are apt to occur when the sleeping animal is disturbed by the manipulations involved in the experiment, will do the same, and may therefore have a disastrous effect upon the determination in experiments of short duration.

Various hypotheses have been put forward to explain the low quotients observed during hibernation. Regnault and Reiset, who first observed the low quotient in a sleeping marmot, were of opinion that oxygen might in some form be stored within the organism for later use especially during the process of awakening. This hypothesis has been supported by the observation made repeatedly that the body weight of a hibernating animal may increase, and further by the fact that these animals during their sleep will endure oxygen want for a considerable period (up to 4 hours, Spallanzani). Valentin, Voit, and

Nagai have shown, however, that the increases in body weight, which are only occasionally observed in the sleeping animals during periods of comparatively short duration, must in all probability be ascribed to condensation of water vapour. Nagai makes the following calculation of the quantity of oxygen stored according to Regnault and Reiset's hypothesis in one of their experiments. They found an oxygen absorption of 28 c.c. per kg. and hour and an elimination of carbon dioxide of 11·1 c.c. (R.Q. = 0·4). As about 16 c.c. oxygen would be used up in catabolizing the quantity of fat corresponding to 11·1 c.c. CO_2, 12 c.c. oxygen should have been stored per kg. and hour. In 30 days, which is a common duration for a period of sleep, this would have amounted to 8640 c.c. and the animal should be able to live on for 3 weeks more in an oxygen-free atmosphere. It can live at most for 4 hours, and this power of enduring oxygen want does not therefore afford any real support to the hypothesis of oxygen storage. It should be added that no mechanism is known in any animal by which it is possible to store oxygen, beyond the quantity taken up by the respiratory pigments.

Dubois [1896], Pembrey and Weinland and Riehl [1907], believe that during the hibernation a conversion of fat into glycogen takes place and that the glycogen is used up as combustion material during the process of awakening. Weinland and Riehl have supported this hypothesis by finding during the process of awakening a high respiratory exchange with a quotient of about 1·0 indicating, in their opinion, an exclusive combustion of carbohydrate, and they have determined further [1908] the total amount of glycogen present in marmots during sleep and just after awakening. They found from 3 to 4 gr. per kg. in three sleeping animals and 1·9 in a fourth just after awakening. The glycogen determinations of Weinland and Riehl are too few in number to inspire confidence. Similar determinations have been made by Hári on bats, but the rather discordant results do not show any increase in glycogen during the hibernation. There is, therefore, no satisfactory evidence to demonstrate any formation of glycogen during the hibernation, but on the other hand the possibility that such a formation takes place cannot be denied.

Nagai points out that the amount of glycogen which must be stored in order to explain such low quotients as found by Pembrey or even by Regnault and Reiset would be far in excess of the quantities which can be found in the animal body, but as these quotients are untrustworthy the demonstration is superfluous. The respiratory

exchange determined by Nagai himself would correspond to a formation of 13 mg. glycogen per kg. and hour or 4 gr. in 13 days. A marmot will wake up at intervals varying between 14 and about 30 days and use, according to Weinland and Riehl, about 2 gr. glycogen per kg. each time. The figure deduced from Nagai's respiration experiments is therefore still considerably in excess of the requirements and would lead, if a formation of glycogen from fat were alone responsible for the low quotients, to a very great accumulation of glycogen in the body. As will be shown presently it is not at all certain that glycogen is used exclusively or at all as combustion material during the process of awakening.

Nagai expresses the opinion that abnormal metabolic processes and especially incomplete oxidations, are in the main responsible for the low respiratory quotient during hibernation. He has shown that lactic acid appears in the urine in large quantities (from 25 to 120 mg. per kg. and day), that the nitrogen metabolism is only slightly diminished as compared with the total metabolism and that the catabolism of proteins becomes very incomplete. The urinary nitrogen falls to $\frac{1}{8}$ while the oxygen absorption is only $\frac{1}{20}$, and the CO_2 output $\frac{1}{38}$ of the corresponding quantities when the animal is awake but starving. During the sleep amino acids and urea make up respectively 65·6 and 17·6 per cent. of the total nitrogen, while during ordinary inanition the figures are 22 per cent. amino acids and 66 per cent. urea. It has not been proved by Nagai that the incomplete oxidations, which undoubtedly occur, are quantitatively sufficient to explain the low respiratory quotients.

It is obvious that it would not be possible to calculate the heat production of hibernating animals from their respiratory exchange, and a comparison between direct calorimetric experiments and respiration experiments would be likely to furnish a clue to the nature of the processes taking place.

The respiratory exchange of hibernating mammals during the process of awakening has been studied by Marés [1892], Dubois [1899], Pembrey, Weinland and Riehl and Henriques [1911]. The awakening is initiated by some stimulus which may be a sudden increase or decrease in the temperature of the surrounding medium, and perhaps any kind of stimulus acting on the central nervous system through the cutaneous senses. All observers agree that the awakening is accompanied by an enormous increase in the respiratory exchange. It is believed by some (Dubois) that the liver is the seat of the increased metabolism, and that it is brought about by the direct influence of

the nervous system upon the catabolism. It is a fact, however, that during the awakening violent shivering takes place, and most observers have thought it natural to ascribe the increased exchange and the production of heat to these muscular movements. The movements begin usually in the masseter muscles and spread gradually and comparatively slowly towards the hinder part of the body. The temperature rises much more rapidly in the mouth than in the rectum.

I reproduce as an example a series of determinations by Henriques on the hedgehog.

TABLE XXXIV.—Hedgehog. Weight, 660 Gr. Temperature of Room, 13°. Tracheotomy Finished, 11.30. Temperature in Rectum and in Mouth 3·6° just after Tying Down. 11.35: Temperature in Mouth 6·7°, in Rectum, 6·2°.

	Temp. in Mouth.	Temp. in Rectum.	Per Kg. and Hour.		R.Q.
			CO_2.	O_2.	
11.45-12.15	7·7-10·0	6·5- 7·5	233	375	0·62
12.20-12.50	10·2-11·8	7·8- 9·0	233	334	0·70
12.55-1.25	12·3-17·1	9·1-10·7	614	851	0·72
1.30-2.00	17·5-27·0	10·8-14·1	1411	1983	0·71
2.05-2.35	27·8-31·7	15·2-26·6	1465	2082	0·70

The experiment to see whether awakening could be brought about in an animal poisoned with curari has, so far as I am aware, never been made.

With regard to the respiratory quotient during the process of awakening the different observers disagree profoundly. Dubois and Weinland and Riehl [1907] have found quotients (on the marmot) approaching unity and indicating an almost exclusive catabolism of carbohydrate. Marés and also Henriques, on the other hand, have invariably observed quotients both on the marmot and on the hedgehog about 0·7 and indicating therefore a combustion of fat. In point of technique Henriques' experiments are certainly the best and most reliable, but, as pointed out above, it is extremely doubtful whether the observed respiratory quotients correspond to the real metabolic quotients when the temperature of the animal is changing rapidly. All the quotients published should therefore be considered with profound distrust, and it appears to be impossible to determine the nature of the catabolic processes in question by means of respiration experiments alone. Henriques [1911] has made an experiment which, though not in itself conclusive because incomplete, indicates the way

in which the problem can perhaps be solved. He calculated from the average temperature and the specific heat of the animal body the amount of heat present in a hibernating hedeghog at the beginning of the series of respiration experiments. Just after the series, when the animal was fully awake, it was killed and the quantity of heat present determined in an ice calorimeter. The increase in heat was found to be 13412 cal. – 3561 cal. = 9851 cal. From the oxygen absorbed during the series of experiments, and assuming a combustion of fat, the heat produced worked out as 10335 cal. The heat lost during the experiment was assumed to account for the difference, but a determination was not undertaken. It is obvious that the process of awakening ought to be studied by means of a respiration calorimeter.

CHAPTER IX.

THE RESPIRATORY EXCHANGE IN DIFFERENT ANIMALS.

THE task of instituting a valid comparison between the oxidative energy of the tissues of different animals is extremely difficult, and, when types belonging to different zoological classes or even larger systematic groups are concerned, at present almost hopeless. It is not surprising, therefore, that so far very few conclusions of a general character have been reached and that opinions are divided even with regard to fundamental problems.

Though the number of determinations of respiratory exchange made is very large, and representatives of all larger groups have been studied, the material available for comparison is scanty, because comparable experimental conditions have only rarely been maintained.

It is necessary to approach the problem with great caution by comparing first the standard metabolism in individuals belonging to the same species and of approximately the same size (weight), next in individuals belonging to the same species but of different weight. These comparisons will furnish the necessary, though insufficient, basis for the further comparison between different species, genera and wider systematic groups.

Comparison between Individuals belonging to the Same Species and of (nearly) the Same Size.

A sufficient material for this comparison exists only in the case of man, and even with man the results have to be reduced to a common standard by division with the body weight. It is obvious that even if the metabolism should not be proportional to the weight the errors introduced cannot be large, when the individuals to be compared differ only slightly.

Numerous experiments by Magnus-Levy and Falk [1899], Loewy [1889, Op.], and especially Benedict and his collaborators [1914, 1915], have shown that men of the same size and weight may differ considerably with regard to their standard metabolism. This follows also

from what has been said above on the variation of the metabolism in one and the same individual. The results obtained range from 2·8 c.c. oxygen absorbed per kg. and minute (Jaquet [1902]) to 5·5 (Caspari [1905]), or from about 0·8 Cal. per kg. and hour to 1·6 Cal. The differences are to be ascribed in many cases to differences in the proportion of fat in the body, as the fatty tissues appear to have a very slight metabolism only. Fat persons have also been directly observed to have a smaller respiratory exchange than lean ones (Geppert [1887], Magnus-Levy and Falk [1899] and Schattenfroh [1900]). In other cases differences in the development of the muscles and differences in muscular training are responsible for differences in metabolism (see above, p. 119). The value 5·5 c.c. O per kg. and minute (= 1·6 Cal. per kg. and hour), which is very unusual, was observed by Caspari on a trained athlete, and recently Benedict and Smith [1915] have shown by comparing a number of athletes with "normal" subjects of similar height and weight that the metabolism of athletes is on an average distinctly greater than that of non-athletes (1·083 Cal. per kg. and hour as against 1·017).

By the earlier writers no systematic difference was detected between the sexes (Magnus-Levy and Falk), but a comparison instituted by Benedict and Emmes [1915] on a large material (determinations of standard metabolism on eighty-nine men and sixty-eight women) appears to show that the metabolism of men is slightly greater than of women. The data have not been treated statistically and are, therefore, difficult to judge.

In individual cases it is often difficult or impossible to account for the deviation of the metabolism from the average, and there can be little doubt that "standard metabolism" as defined at present does not mean quite the same thing in different individuals. In the writer's opinion differences in muscular tone are probably at the bottom of the metabolic differences, and when it becomes necessary to obtain a greater uniformity of results a more strict definition of standard conditions will have to be adopted, and it will probably be the safest plan to compare the metabolic activities of different individuals during deep sleep, as suggested by Benedict.

On the other hand the uniformity obtainable with the present definition should not be underestimated as it has been recently by Benedict and his collaborators.

Tigerstedt (Op.) has averaged the results of long series of determinations of the standard metabolism of man, and found that all the

different series show practically the same average, 1·04 Cal. per kg. and hour with an average individual deviation, μ = 0·1 Cal. or 10 per cent.[1] As mentioned above (p. 60) the standard deviation in a series of determinations on a single subject, studied by Benedict and Cathcart, amounts to μ = 5 per cent. It is rather surprising, therefore, to find that the individual differences are not on the whole larger.

Comparison between Animals of the Same Species but of Different Size. The "Surface Law".

While it had often been observed before that smaller animals had per unit weight a greater respiratory exchange than larger ones, a quantitative study of the influence of size upon metabolism was first made by Rubner [1883] on grown dogs, weighing from 30·4 to 3·1 kg. Standard conditions were not rigorously maintained, but the animals were resting and the surrounding temperature kept at such a height that "chemical" temperature regulations could not come into play. Rubner found that, calculated per kg., the metabolism increased regularly with decreasing size. When, however, the surface of the animals was taken into account a practically constant metabolism per square metre of surface was found for all.[2]

TABLE XXXV.—METABOLISM OF DOGS. CALORIES PER SQ. M. IN TWENTY-FOUR HOURS.

Weight, kg.	Metabolism per kg. Cal.	Metabolism, per sq. m. Cal.
31·20	35·7	1036
24·00	40·9	1112
19·80	45·9	1207
18·20	46·2	1097
9·61	65·2	1183
6·50	66·1	1153
3·19	88·1	1212

[1] Tigerstedt writes the average of a series of 15 determinations in the form 1·046 ± 0·100 cal., which would imply that the mean error on the average figure 1·046 was 0·100 cal. A recalculation of some of his material has shown me, however, that what is meant is that the standard deviation of a single determination is 0·100 cal. The mean error of the average works out in this case as $\frac{0{\cdot}100}{\sqrt{15}} = 0{\cdot}026$, and the result should have been given as 1·046 ± 0·026.

[2] The surface (S) of an animal is approximately proportional to the square of a linear dimension (e.g. length of body) while the weight (W) is similarly proportional to the third power of a linear dimension. We have, therefore, $S = c\, W^{\frac{2}{3}}$. The constant c has been worked out for a number of species. It does not vary very much even in forms of very different shape. For man and also for the dog we have c = 12·3, for the rabbit 12·9, the horse 9·0, the rat 9·1, and the guinea-pig 8·9 (Loewy [Op.]).

The average per unit surface works out as 1143 ± 25 Cal., μ = 65 Cal. or 5·7 per cent. The agreement is therefore better than in most series of experiments on men of approximately identical size. Similar results have been obtained by Slowtzoff [1903] in experiments on dogs in which standard conditions were carefully maintained, and by Kettner [1909] in respiration experiments on guinea-pigs of different age and weighing from 140 to 800 gr. Kettner finds that the metabolism per kg. and hour decreases fairly regularly with increasing weight, the difference between the highest and the lowest figure being 135 per cent. of the latter, while the differences between the results per square metre are independent of the size and amount to at most 30 per cent.

Frank and Voit [1901] have made experiments on dogs which had fasted for several days previously and were under curari during the determinations. They found :—

TABLE XXXVI.

Weight, kg.	CO_2 per kg. and h., gr.	CO_2 per sq. m. and h., gr.
28·7	0·61	16·6
24·1	0·60	15·4
(22·4	0·46[1]	11·6)[1]
22·2	0·54	13·7
19·3	0·68	16·4
18·5	0·74	17·4
14·4	0·76	16·3
12·4	0·84	17·4
10·9	0·77	15·3
8·7	0·78	14·2
8·1	0·74	13·4
6·1	0·84	14·9
5·35	0·88	15·4
Average	0·73	15·5
Standard deviation	$\mu = \pm 0{\cdot}105 = \pm 14{\cdot}4$ %	$\mu = \pm 1{\cdot}4 = \pm 9{\cdot}3$ %

The agreement is not quite as good as in Rubner's series, and there appears to be a tendency for the figure per square metre to decrease with decreasing size.

Recently Benedict [1915] has discussed at some length the relationship between body weight and metabolism, body surface and metabolism, and the " amount of active protoplasmic tissue " and metabolism. While admitting that large individuals have on the whole a larger metabolism than small ones of the same species (man) he denies that there is any close relationship between size and meta-

[1] This figure has been left out of account because the condition of the animal, as pointed out by Frank and Voit, was extremely abnormal.

bolism, and deprecates especially the use of the surface as a basis for comparisons. His own figures and charts show very clearly, however, that such relationships exist, that the metabolism per kilogram of body-weight decreases fairly regularly with increasing size (weight), while the figures per square metre (as computed) do not show any marked tendency but are fairly evenly distributed. Benedict has concentrated his attention on the other factors which influence undoubtedly the standard metabolism: the "amount of active protoplasmic tissue" and the varying "stimulus to cellular activity" and this has led to an under-estimation of the size relationship.

It is quite possible of course that the surface as at present defined $cW^{\frac{2}{3}}$ does not give the very best agreement in comparisons of different individuals. The main point is that metabolism in warm-blooded animals is not proportional to the weight (W) but to W^n (Dreyer [1912]) where n is certainly not far from $\frac{2}{3}$. When the "best n" has been determined by mathematical analysis of the material, and the size factor excluded by reducing all the observations to this standard, it would certainly be possible by dividing the subjects into groups according to a number of points of view (sex, age, height, indices of build, etc.), and treating the observations statistically, to obtain numerical results of great reliability and value.

From a calculation by the writer of some of Benedict and Talbot's material mentioned above (p. 116) it appears probable that the surface relationship holds also when young warm-blooded animals are compared with adults of the same species, though a very important age factor must be superimposed. In the embryo on the other hand the determinations of Bohr and Hasselbalch [1900] show that the respiratory exchange is simply proportional to the weight.

The results obtained on cold-blooded animals are conflicting and uncertain. Experiments made by Jolyet and Regnard [1877] and Knauthe (published by Cronheim [1911]) on fish and other marine animals have been utilized by Hoesslin [1888] and Zuntz [1906] to establish the "surface law," but the observations are too few, and while some of them undoubtedly indicate that smaller animals have the larger respiratory exchange per kg., the results per unit surface being more or less constant,[1] other experiments by the same authors show quite the reverse. Standard conditions were in no case maintained.

Buytendijk [1909] made a few determinations on different cold-

[1] In Knauthe's experiments on carps the respiratory exchange of fish of 12 gr. weight is much higher per kg. than of any other size, but for fish from 100 gr. to 700 gr. the differences are irregular and within the limits of error. The high result obtained for the very small and young fish may very well be due exclusively to their livelier movements.

blooded marine animals with the object of studying the relation between size and oxygen absorption. He found in most cases, but not in all, that the smaller individuals had a relatively larger metabolism, but ascribes this to their greater activity and to the fact that they were generally immature and growing. Vernon [1896] made experiments on several pelagic animals. His main object was to study the influence of temperature, and in order to utilize his material for determining the influence of size he had to reduce all the observations to a definite temperature (16°). The factors used for the reduction are admittedly "very uncertain" and the results cannot be accepted as conclusive, the more so as standard conditions could not be maintained. The following table shows the chief results obtained by Vernon. The figures for the oxygen absorption per unit surface[1] have been added by the writer :—

TABLE XXXVII.

	Number of observations.	Weight, W., gr.	O_2 absorbed, per kg. and h., mg.	$O_2 \sqrt[3]{W}$.[1]
Rhizostoma pulmo	6	62·2	16·7	66
	2	69·6	15·4	63·5
	4	87·1	8·3	37
	7	93·0	10·6	48
	8	107·0	6·0	28·5
Carmarina hastata	2	15·2	8·8	21·8
	3	27·6	6·5	19·7
	5	30·2	10·0	31·1
	1	30·7	12·9	40·4
	2	34·5	8·5	27·6
	4	44·8	8·8	31·2
	5	54·7	7·8	29·6
Beroë ovata	9	5·2	10·2	17·7
	3	10·6	8·2	18·0
	1	32·2	6·4	20·4
	7	32·9	6·4	20·5
	4	38·3	5·5	18·5
Cestus veneris	3	40·8	6·2	21·3
	2	49·7	4·8	17·7
	3	61·7	4·7	18·6
	3	69·2	3·3	13·6
	1	115·5	2·8	13·6
	2	123·6	3·3	16·5

In three out of the four series of experiments there is a very distinct decrease in oxygen absorption per kg. with increasing weight of the animal, but in *Carmarina* the oxygen absorption per kg. ap-

[1] A simple calculation shows that figures given per unit weight can be reduced to arbitrary "surface" units by multiplication with $\sqrt[3]{\text{Weight}}$.

pears to be approximately constant. The exchange per unit surface is increasing in *Carmarina*, approximately constant in *Beroë*, but decreasing in *Rhizostoma* and *Cestus*.

Montuori [1913] has made a large number of determinations (242) on eighty different species of marine animals (fish, molluscs, Crustacea, worms, echinoderms and Cœlenterata). All the experiments were made at a constant temperature, but the animals were free to move about. Many of them were very quiet however. The results are extremely irregular, and, as in most cases very few experiments have been made on each species, valid conclusions cannot be arrived at with regard to these. On each of eleven species five or more determinations have been made. Seven of these series are too irregular to be of much value, while four are fairly regular. Of the seven, three (the crustacean *Pachygrapsus marmoratus*, the mollusc *Lithodomus lithofagus*, and the eel *Anguilla vulgaris*) show on the whole a *decrease* of the respiratory exchange per unit weight with decreasing size, three give results which appear to be independent of the size (*Ascidia mentula*, *Mugil cephalus*, *Torpedo ocellata*), and one only (*Uranoscopus scaber*) shows increasing metabolism with decreasing size. Of the four which give fairly regular results the three (*Beroë Forskåli*, *Holothuria impatiens*, *Sepia officinalis*) have a metabolism per unit weight which is independent of the size, while *Carcinus mœnas* alone shows an increase with decreasing size. The results obtained on the eight last-named species have been reproduced in Table XXVIII and figures for the metabolism per unit surface added.

If any general conclusion can be based on Montuori's results it must be, as Montuori himself thinks, that the metabolism is proportional to the weight and not to the surface, but it is certainly safer not to be emphatic on the point. It should be borne in mind that there is at present no valid reason for assuming a priori that the same rule should hold with regard to all cold-blooded animals.

The Theory of the "Surface Law".

Bergmann [1848], Regnault and Reiset, and especially Rubner [1883], have tried to bring the observed relation between the size and the respiratory exchange of warm-blooded animals into correlation with their heat loss. *Other things being equal*, the loss of heat is proportional to the surface of an animal, and, according to Rubner, the metabolism is simply a function of the conditions for loss of heat, while there is no such thing as a specific oxidative activity of the cell. This view and the theory of direct chemical heat regulation are to a

TABLE XXXVIII.—Oxygen Absorption per Unit Weight and Unit Surface in Different Animals.

No. in Montuori's Tables.	Name.	Weight, W., gr.	O_2 per kg. and h. c.c.	$O_2 \sqrt[3]{W.}$
57	Ascidia mentula . .	191	6·8	39·2
		85	2·9	12·7
		69	4·7	19·3
		35	4·2	13·7
		13	5·4	12·7
67	Mugil cephalus . .	100	100	465
		68	324	1320
		23	454	1310
		18	453	1190
		13	292	690
		12	465	1060
		11	307	680
		0·27	281	180
79	Torpedo ocellata . .	370	68	440
		100	41	190
		79	33	142
		75	89	376
		50·5	40	148
		22	45	126
80	Uranoscopus scaber .	137	40	206
		100	57	265
		13	167	392
		4	267	424
		2	117	147
3	Beroë Forskäli . .	7·7	98	193
		3·3	117	174
		2·9	126	180
		2·0	82	103
		0·7	128	114
22	Holothuria impatiens .	10·3	18·9	41·2
		4·0	19·1	30·3
		3·9	17·5	27·5
		1·3	24·8	27·1
		1·2	15·9	16·9
56	Sepia officinalis . .	65	268	1080
		64	195	780
		42	255	850
		31	268	840
		23	234	665
		21	156	430
		5·6	275	490
		5·3	309	540
31	Carcinus mœnas . .	47	68	246
		34·5	72	209
		14·0	82	198
		10·6	114	251
		7·0	100	182
		1·65	128	152

certain extent mutually interdependent, and it involves a serious difficulty when it must be admitted that the resting metabolism of a warm-blooded animal is not directly governed by the conditions for loss of heat. The objection has been met by Rubner by the assumption that the standard metabolism cannot undergo rapid changes, that the oxidative energy of the cells is adapted to the *usual* conditions regarding loss of heat and is altered very gradually with those conditions.

The limitation, "other things being equal," represents a very formidable further objection, because the other things in question are practically never even approximately equal. Between different dogs, for instance, the differences in the insulating properties of the fur are very large. If the metabolism was correlated with the heat loss dogs with a thick fur ought to have a lower metabolism per unit surface, but this is certainly not so. Hoesslin [1888] made the experiment to keep two exactly similar young dogs for a long time at very different temperatures. According to Rubner's theory differences in standard metabolism ought to develop, but they did not, whereas after some weeks the fur of each animal was changed in evident correlation with the different temperature conditions.

Hoesslin [1888], and more recently Zuntz [1906], have attempted to correlate the standard metabolism with the functional activity. Hoesslin especially has treated the whole problem theoretically at great length. He assumes that, when different animals are to compete with one another, their velocity of locomotion must be nearly the same. Natural selection will exterminate those which are slower. He attempts to show then by an elaborate calculation, the details of which I must confess myself unable to follow, that in animals of different size, if they be taken to move with the same maximum velocity, the corresponding maximum metabolism must be proportional to the cross section (or surface) of each, and he takes it for granted further that the standard (or minimum) metabolism is a constant fraction of the maximum attainable. This latter proposition is certainly arbitrary.

Following another line of argument Hoesslin points out that the bodily functions are essentially surface functions (the absorption of food for instance a function of the surface of the small intestine) and that they must therefore be proportional to the active surfaces of organs in animals of different size. When similarity of structure is to be preserved the active surfaces will, according to Hoesslin, be approximately proportional to the body surface of each animal. The truth of this proposition has been demonstrated in recent years for

certain organs by the researches of Dreyer and his collaborators [1912] who found that the blood volume, the sectional area of the aorta and of the trachea of animals of different size, are proportional to $W^{\frac{2}{3}}$, that is to the surface.[1] For such organs as the lungs or kidneys which are built up of elementary units (alveoli, Malpighian bodies) the total active surface would be proportional to the body surface if the number of elements were always the same and their linear dimensions proportional to those of the body. This is far from being the case however.

The arguments so far mentioned, Rubner's as well as Hoesslin's, are of a more or less teleological character, and do not consider the mechanism by which the metabolism must be supposed to be regulated. Hoesslin alone has touched upon this point. He assumes that the metabolism of a tissue depends upon and is proportional to the supply of oxygen, an assumption which, as shown on page 78, may be true with regard to the muscles. According to Hoesslin the circulation rate per unit weight and consequently the supply of oxygen must for anatomical reasons be proportional to $W^{\frac{2}{3}}$ (the body surface), and the regulation of the metabolism in accordance with the experimental results obtained on warm-blooded animals would follow from these premises.

Hoesslin's argumentation is certainly inconclusive though he has given much thought to the problem, which appears to the writer as being so important that it would well deserve a renewed treatment both experimental, as far as cold-blooded animals are concerned, and theoretical. Hoesslin has been careful to point out that if his deductions are correct they must apply with equal force to cold-blooded animals. It is obvious that measurements of the actual body surface or the use of elaborate formulas to obtain the surface from certain linear measurements can have a real significance only when Rubner's view of the conditions for loss of heat as the factor directly governing the metabolism is accepted. In the opinion of the writer the reasons against Rubner's view are very strong, and the line of inquiry initiated by Dreyer is much more likely ultimately to clear up the relationship between size and metabolism. The metabolism should not therefore be expressed per sq. m. or any other unit of surface but as a function of W^n. For warm-blooded animals n can be taken, at least provisionally as $\frac{2}{3}$.

[1] In the cold-blooded frogs and lizards, no proportionality exists between body surface and blood volume, which increases with the size even more rapidly than the weight, being proportional to $W^{1.2}$, as shown by Fry [1913].

Comparison between Different Species of Warm-blooded Animals.

For comparisons between different warm-blooded animals series of sufficiently reliable experiments made under truly standard conditions are not available, and the comparisons have to be made between experiments made by different experimenters using different methods, usually at different temperatures and with only scanty information about the state of the animals. Tables can be put together, therefore, which will satisfy almost any theory which could be put forward.

Tigerstedt [W.] has given the following table showing the 24-hour metabolism of fasting animals, to which I have added the last column:—

TABLE XXXIX.

		Temp. of Air during Experiment.	Usual Body Temperature.	Weight, W., kg.	Calories per kg. in 24 h., C.	$C\sqrt[3]{W}$.
	Man	16°	37·4	70·0	24·0	99
	Dog	16°	39·2	31·2	35·7	112
	,,	—	—	24·0	40·9	118
	,,	—	—	19·8	45·9	124
	,,	—	—	18·2	46·2	121
	,,	—	—	9·6	65·2	141
	,,	—	—	6·5	66·1	123
	,,	—	—	3·2	88·1	130
	Rabbit	16°	39·6	2·03	51·9	69
	Guinea-pig	16°	38·6	0·59	153·2	128
	,,	30°	—	0·223	128·2	77
	,,	30°	—	0·206	141·1	83
	Rat	16°	37·9	0·117	227	111
	Mouse	7°	—	0·013	639	150
Marsupials	Trichosurus	10°	36·5	2·16	79	102
Marsupials	Bettongia	10°	36	1·63	84	99
Marsupials	Dasyurus	10°	37·0	0·65	50	43
	Echidna	—	30	3·12	144	210
	,,	—	27	1·67	106	126
	Ornithorynchus	—	32	0·69	52	46
	Hen	—	41·4	1·513	67	77
	,,	—	—	0·921	93	90
	Sparrow	—	42	0·022	755	211

It should be remarked that while the figure for man is standard metabolism, the other results have been obtained on animals which were more or less quiet in the ordinary sense. This does not even apply to the mouse or to the small birds which are never really quiet when awake. When these things are taken into account the table shows that the respiratory exchange per unit weight falls regularly

with increasing size, while the exchange per unit surface shows only irregular variations without any marked tendency.

Loewy [Op.] has given another table of comparisons which, when reduced to calories per twenty-four hours, and after exclusion of the values for the ox and the sheep, which are not comparable with the rest, is as follows:—

TABLE XL.

	Weight, W., kg.	Calories per kg. in 24 hours, C.	$C\sqrt[3]{W}$.
Horse	450	27·6	212
Man	75	33·1	139
Dog	15	93·5	230
Cat	2·5	79·5	107
Rabbit	2	72·5	91
Hen	1	93·5	93·5

To conclude from this table that the respiratory exchange of different warm-blooded animals is approximately proportional to the surface area would be rash indeed.

The most reliable comparisons are undoubtedly those made by E. Voit [1901]. He compares first series of determinations made on each species in the Pettenkofer apparatus. The animals had fasted for one or more days[1] before the experiments and were quiet during the determinations. For each species the metabolism is carefully reduced to unit surface (square metre) by means of the complete formula given on p. 133 and the specific constant.

TABLE XLI.

	Number of Determinations.	Average Weight, kg.	Calories per kg. in 24 hours.	Calories per sq. m. in 24 hours.
Horse . . .	8	441	11·3	> 948
Pig . . .	2	128	19·1	1078
Man . . .	5	64·3	32·1	1042
Dog . . .	15	15·2	51·5	1039
Rabbit . . .	5	2·3	75·1	776
Goose . . .	6	3·5	66·7	1018
Hen . . .	2	2·0	71·0	1008

It must be admitted that the metabolism per square metre is fairly constant. Voit puts forward as an explanation of the low value found

[1] The experiments on the horse are an exception from this rule. They were made by Zuntz and Hagemann [1898] on horses during digestion, and a correction has been applied for the resulting increase in metabolism. This correction appears somewhat arbitrary.

for the rabbit that the percentage of organ nitrogen is lower in this animal than in the rest. This appears doubtful, however.

Voit points out that his comparisons are valid only for well-nourished animals after a fast which must not be unduly prolonged. Underfed animals have at once, and other animals after prolonged starvation (Table XXIX, p. 120), a considerably lower exchange in twenty-four hours. Voit ascribes this to differences in oxidative energy of the tissues, but it may easily be due to differences in muscular activity or tone.

In the comparisons between different warm-blooded animals no account has ever been taken of the differences in body temperature which are not quite negligible. I have given Tigerstedt's [W.] figures for the temperature of the animals mentioned in column 3 of Table XXXIX.

It is at present not possible to determine accurately the influence of these differences upon the standard metabolism, but to judge from the material available in Krarup's experiments (p. 94) and the curve given by Krogh (p. 94) for a young dog, it should be of the order 5 to 6 per cent. decrease in metabolism for each degree lowering of the body temperature.

Comparison between Warm-blooded and Cold-blooded and between different Cold-blooded Animals.

Very few investigations have been undertaken with the definite object of comparing the standard metabolism of different cold-blooded animals.

Cohnheim [1912] has compared forms which possess striped muscles (Crustacea) with such which do not (molluscs), but did not find any distinct difference when the results were calculated on the basis of the fresh weight. The experiments were not made under standard conditions.

Vernon [1896] has made an extensive and very valuable series of experiments on transparent pelagic animals, the oxygen absorption of which he compared with that of fishes and cephalopods. Though standard conditions were not maintained it is probable that the results, so far as the pelagic animals are concerned, have not been seriously affected by the activity. Vernon found that the respiratory activity of the lower pelagic animals (Cœlenterata, Tunicata, and Mollusca) is very small when compared by weight with that of higher animals, such as a teleost fish. Per kilogram and hour he found the following oxygen absorptions in deci-mg. at 16° as averages in most cases of a number of determinations:—

TABLE XLII.

		Average Weight, g.	O_2 per kg. and h., deci-mg.	Mean Percentage of Solid Constituents.	O_2 per 223 gr. Dry Tissue, g.
Protozoa	Collozoum inerme .	0·1	1113[1]	0·40	6·21[1]
Cœlenterata	Carmarina hastata .	34·0	87	0·38	0·51
	Rhizostoma pulmo .	83·8	103	0·53	0·43
	Beroë ovata . .	23·8	72	0·60	0·23
	Cestus veneris . .	76·7	37·5	0·24	0·35
Mollusca	Tethys leporina . .	160·7	165	1·20	0·31
	Pterotrachea coronata .	60·4	112	0·53	0·47
	Octopus vulgaris . .	7·1	1240	11·7	0·24
Tunicata	Salpa pinnata . .	3·2	116	0·26	0·99
	Salpa tilesii . .	84·4	27·5	0·43	0·14
Vertebrata	Amphioxus lanceolatus	0·24	511	12·8	0·09
	Heliasis chromis . .	10·4	1330	22·3	0·13
	Serranus scriba . .	4·1	1660	16·7	0·22
	Rana temporaria . .	30	1230	19·1	0·14

While the metabolism of the different vertebrates (*Amphioxus* excepted) and also of *Octopus* is of the same order of magnitude, viz. about 130 mg. oxygen = 0·43 Cal. per kg. and hour, the exchange of the pelagic animals is much lower, varying between 2·7 and 16·5 mg. = 0·009 and 0·055 Calories. The radiolarian *Callozoum* forms, however, a very striking exception, showing a respiratory activity of the same order as that of the fishes. Vernon found further that the composition of the tissues differs enormously in different animals, and that the transparent pelagic forms contain only from 0·4 to 1·2 per cent. of solids, exclusive of sea-water salts, while the higher animals contain from 11·7 per cent. (*Octopus*) to 22·3 per cent. (*Heliasis*). Even between the two fishes there is a very notable difference, *Serranus* having only 16·7 per cent. of solids. It is obvious therefore that a fair comparison cannot be instituted on the basis of the fresh weight, and Vernon has compared the values corresponding to 223 gr. dry substance (= 1 kg. fresh *Heliasis*). The resulting figures (Table XLII, column 6), though differing considerably and on the whole distinctly lower for the animals with a high percentage of solids than for the hyaline ones, are all of about the same order of magnitude.[2]

Though the dry weight is obviously a much better basis for com-

[1] One single determination.

[2] *Collozoum* again forms a very striking exception. The result obtained on these animals is so extraordinary, unless indeed they have been very active during the determination, that a confirmation must be awaited before it can be accepted.

parisons than the fresh, it is far from ideal, as the varying amounts of reserve material, skeletal and other inactive tissues, must influence the results unduly. The best basis would probably be the nitrogen present in active tissues (E. Voit's "Organstickstoff"), but the determination of this would in many cases entail very considerable difficulties and none have been made so far. Materials for a comprehensive and valid comparison are therefore absolutely wanting.

In the following table a series of determinations have been put together which can be considered as having been made under standard conditions at least as regards muscular movements and at a constant

TABLE XLIII.—STANDARD METABOLISM OF DIFFERENT ANIMALS PER UNIT WEIGHT AND PER UNIT "SURFACE" MEASURED AT 20°.

Animal.	Weight, kg., W.	Metabolism[1] per kg. and hour Cal.	Calories[1] per hour per unit "surface," Cal. $\sqrt[3]{W}$.	Authority.
Young dog . . .	950×10^{-3}	1·16	1·14	Krogh.
Frog	30×10^{-3}	0·34	0·106	,,
Decerebrate toad . .	34×10^{-3}	0·15	0·049	,,
Embryo of snake . .	500×10^{-6}	1·4	0·111	Bohr.[2]
Goldfish . . .	$9{\cdot}3 \times 10^{-3}$	0·53	0·111	Ege and Krogh.
Gnat (Culex) . .	8×10^{-6}	2·70	0·054	Ellinger.
Chrysalides of Tenebrio (At first	160×10^{-6}	1·35	0·087	Krogh.
Chrysalides of Tenebrio (Average	150×10^{-6}	0·81	0·043	,,
Chrysalides of flies .	—	1·2	—	Battelli and Stern.
,, ,, Ophyra (fly)	$7{\cdot}3 \times 10^{-6}$	1·5	0·029	Tangl.[3]
,, ,, Calliphora (fly)	70×10^{-6}	1·07	0·044	Weinland.[3]
,, ,, Bombyx .	$1{\cdot}05 \times 10^{-3}$	1·10	0·112	Farkas.[3]
,, ,, ,, .	—	0·6	—	Battelli and Stern.
Eggs of Bombyx . .	128×10^{-9}	8·3	0·042	Farkas.[4]
,, ,, Acilius (beetle)	$1{\cdot}5 \times 10^{-6}$	3·35	0·038	Krogh (unpubl. exp.).
,, ,, Arbacia (sea urchin) 6 hours after fertilization . .	285×10^{-12}	2·9	0·0019	Warburg.[5]

[1] The metabolism has been calculated from the O_2 absorption in most cases, 1 lit. oxygen = 4·8 Cal.

[2] Bohr's determinations were made at 15° and 27°. The interpolation to 20° is somewhat uncertain.

[3] Determinations were made of the energy content of fresh chrysalides and fresh imagines and the average loss of energy per day computed from these. The values which include the visible metamorphosis and the muscular movements accompanying it are probably rather high.

[4] The temperature varied from 13° to 24·5°. The figures are very uncertain therefore.

[5] The respiratory exchange has been determined by Warburg, per 28 mg. N, and he states that one million eggs contain 8·5 mg. N. I have assumed, in accordance with Meyerhof, that the eggs contain 3 per cent. N, and calculated the weight and the metabolism per kg. by means of these figures.

temperature, 20°. They show a wide divergence with regard to respiratory activity both when considered per kg. of body weight and when approximately reduced to "surface" units by multiplication with $\sqrt[3]{W}$. It is worthy of note that the metabolism of the single warm-blooded animal, the young dog, at low temperature is considerably larger than of the cold-blooded vertebrates. When considered per unit "surface" it is much greater than any other. As the metabolism of this dog did not at 37° differ materially from that of other dogs or of other warm-blooded animals when calculated per unit "surface," the result appears to indicate that the oxidative energy of the tissues is greater in the warm-blooded than in a cold-blooded organism.

While the metabolism per kilogram is on the whole increasing with decreasing size (*Arbacia* eggs excepted), the metabolism per unit "surface" decreases with the size though the variations are on the whole not very large.

In the final table a large number of determinations made at temperatures between 15° and 25° (at 20° whenever such were available) have been put together. They show the order of magnitude of the respiratory exchange of the animals in ordinary circumstances. That they cannot claim much confidence is evident enough from the wide differences found by different observers for the same species.

In reptiles, Amphibia, and fish, values of 0·2 to 0·5 Cal. per kilogram and hour are generally observed on quiet animals irrespective of size, and the figures for Crustacea and cephalopod molluscs are of the same order, but very young animals of all these groups may show much higher values, probably to a great extent on account of their muscular activity.

In insects the respiratory exchange is always high compared with that of other animals, but as all experiments have been made on a large number of insects at a time, the animals have probably always been very restless, and the figures do not represent anything approaching standard conditions.

In all the lower invertebrates the respiratory exchange is smaller and often much smaller than in the higher, but the proportion of active substances in their bodies is certainly smaller also, and it is possible that the differences per gr. "organ nitrogen" would not be very large.

In the protozoa the respiratory exchange is very considerable, and the more so the smaller the size. This may be due, however, to the constant activity of these animals.

TABLE XLIV.—METABOLISM OF COLD-BLOODED ANIMALS AT TEMPERATURES ABOUT 20°.

Name.	Weight, gr.	Temperature.	Calories per kg. and hour.	From determination of	Authority.
Reptiles.					
Lacerta agilis	0·8	17-20°	9·3	CO_2	Pott.
,, viridis?	21	23·4°	0·78	O_2	Regnault and Reiset.
,, viridis	110	25·3°	0·8	Cal.	Krehl and Soetbeer.
Uromastix	1250	25·3°	0·26	,,	,, ,, ,,
Alligator lucius	1380	25·3°	0·3	,,	,, ,, ,,
Cyclodes gigas	374	25·15°	0·48	CO_2	Martin.
Anguis fragilis	14	20°	0·19	,,	Vernon [1897].
Coluber natrix	3·8	(20°)	0·7	O_2	Bohr [1903] (interpo-
,, ,,	84	20°	0·43	Cal.	Hill. [lation).
Amphibia.					
Rana mugiens	600	25·3°	0·5	,,	Krehl and Soetbeer.
,, temporaria	40	20°	0·42	CO_2	Vernon [1897].
,, ,,	40	19-19·6°	0·4-2·6	O_2	Bohr [1899].
,, ,,	13·9	19-20°	1·06	CO_2	Pott.
,, ,,	1·26	19-20°	3·8	,,	,,
,, esculenta	40	20°	0·33	,,	Vernon [1897].
,, ,,	16-30	18-20°	0·4-2·05	O_2	Bohr [1899].
Frogs (fresh	16	20°	0·48	Cal.	Hill.
Frogs (1 month inanition	—	20°	0·30	,,	,,
Molge vulgaris	9	20°	0·58	CO_2	Vernon [1897].
Newts	—	20°	0·51	Cal.	Hill.
Fishes.					
Cyprinus carpio	12·2	19·8°	1·5	O_2 and CO_2	Knauthe.
,, ,,	105	18·0°	0·47	,,	,,
,, ,,	232	20·4°	0·65	,,	,,
,, ,,	504	18·6°	0·42	,,	,,
,, ,,	737	20·4°	0·45	,,	,,
,, ,,	1217	20·8°	0·35	,,	,,
,, tinca	8·4	20°	0·65	,,	Lindstedt (Extrapolation from 17°.
,, ,,	33	20°	0·48	,,	,,
,, ,,	184	20°	0·35	,,	,,
Esox lucius	72	18°	0·55	,,	,,
,, ,,	284	18°	0·41	,,	,,
,, ,,	680	15°	0·26	,,	,,
Salmo trutta	218	15°	1·06	,,	,,
Anguilla vulgaris	3	24-25°	0·25	O_2	Montuori.
,, ,,	17	24-25°	0·66	,,	,,
,, ,,	135	24-25°	0·88	,,	,,
Sargus Rondeletti	66	24-25°	1·76	,,	,,
Serranus scriba	4·1	20°	0·71	,,	Vernon [1896].
Heliasis chromis	10·4	20°	0·76	,,	,,
Sparus auratus	75	19°	0·82	,,	Jolyet and Regnard.
Cobitis fossilis	52	19-21·5°	0·24	,,	Baumert.
Amphioxus	0·24	20°	0·21	,,	Vernon [1896].
,,	0·18	24-25°	0·69	,,	Montuori.
Insects.					
Melolontha	1	20°	3·4	,,	Regnault and Reiset.
,,	—	20°	4·5	,,	Battelli and Stern.
Geotrupes	0·876	18-24°	2·1	,,	Slowtzoff.
Tenebrio larva (inanition)	0·099	24·8°	1·74	,,	M. Krogh.

TABLE XLIV.—METABOLISM OF COLD-BLOODED ANIMALS AT TEMPERATURE ABOUT 20°—*cont.*

Name.	Weight, gr.	Temperature.	Calories per kg. and hour.	From determination of	Authority.
Insects—cont.					
Tenebrio larva	0·1	18°	1·45	O_2	Thunberg.
Formica	0·01	20°	2·5	,,	Slowtzoff.
Apis mellifica	0·09	20°	82	,,	Parhon.
Musca	—	20°	24	,,	,,
,,	—	20°	15	,,	Battelli and Stern.
,, larva	—	20°	6·2	,,	,, ,, ,,
Bombyx larva	1·5	20°	3·5	,,	Regnault and Reiset.
Periplaneta orientalis	0·7	20°	1·3	CO_2	Vernon [1897].
Crustacea.					
Astacus fluviatilis	32	15°	0·14	O_2 and CO_2	Lindstedt.
Carcinus mænas	47	24-25°	0·32	O_2	Montuori.
,, ,,	56	16°	0·30	,,	Cohnheim.
Palæmon serratus	3·5	16°	0·50	,,	,,
,, squilla	39·5	19°	0·60	,,	Jolyet and Regnard.
Paguristes maculatus	14·6	24-25°	1·36	,,	Montuori.
Vermes.					
Lumbricus	0·41	19·2°	0·81	,,	Thunberg.
,,	0·44	19·7°	0·80	,,	,,
,,	1·02	19·2°	0·84	,,	,,
,,	1·3	20·5°	0·40	,,	,,
,,	0·167	19·4°	0·39	,,	Lesser.
,,	0·236	18·0°	0·26	,,	,,
,,	0·249	17·1°	0·28	,,	,,
,,	0·317	19·3°	0·30	,,	,,
,,	0·385	19·5°	0·28	,,	,,
,, terrestris	—	20·4°	0·65	,,	Konopacki.
,, communis	—	20-23°	0·97	,,	,,
Glycera siphonostoma	29	24-25°	0·07	,,	Montuori.
Sipunculus nudus	15-30	16°	0·15-0·33	,,	Cohnheim.
Cephalopoda.					
Octopus vulgaris	7·1	20°	0·55	,,	Vernon [1896].
,, ,,	35·5	24-25°	0·48	,,	Montuori.
,, ,,	280	24-25°	0·32	,,	,,
,, ,,	2310	15·5°	0·22	,,	Jolyet and Regnard.
Eledone moschata	6	24-25°	0·13	,,	Montuori.
,, ,,	12	16°	0·85	,,	Cohnheim.
Sepia officinalis	5·3	24-25°	1·48	,,	Montuori.
Gastropoda.					
Helix pomatia	4·7	20°	0·44	CO_2	Vernon [1897].
Limax agrestis	0·153	19·6°	2·25	O_2	Thunberg.
,, ,,	0·164	19·5°	1·15	,,	,,
,, ,,	0·25	19·5°	1·55	,,	,,
Tethys leporina	207	20°	0·07	,,	Vernon [1896].
Pterotrachea coronata	16	20°	0·05	,,	,, ,,
Pleurobranchea Meckeli	86	24-25°	0·17	,,	Montuori.
Aplysia limacina	215-915	16°	0·10-0·18	,,	Cohnheim.

TABLE XLIV.—METABOLISM OF COLD-BLOODED ANIMALS AT TEMPERATURE ABOUT 20°—*cont.*

Name.	Weight, gr.	Temperature.	Calories per kg. and hour.	From determination of	Authority.
Lamellibranchia.					
Mytilus edulis . .	25	14°	0·06	O_2	Jolyet and Regnard.
,, galloprovincialis	21·6	24-25°	0·085	,,	Montuori.
Tunicata.					
Ascidia mentula . .	69	24-25°	0·02	,,	,,
Salpa max. africana .	47	24-25°	0·11	,,	,,
Salpa tilesii . . .	85	20°	0·013	,,	Vernon [1896].
,, pinnata . . .	3·2	20°	0·057	,,	,, ,,
Echinoderma.					
Holothuria . . .	70-210	?	0·02	,,	Cohnheim.
,, stellata . .	17	24-25°	0·02	,,	Montuori.
,, impatiens .	10·3	24-25°	0·09	,,	,,
Ophioderma longicauda .	8	?	0·04	,,	Cohnheim.
,, ,, .	11·2	24-25°	0·15	,,	Montuori.
Strongylocentrotus lividus	33	24-25°	0·02	,,	,,
,, ,,	35·5	24-25°	0·13	,,	,,
Cœlenterata.					
Carmarina hastata . .	25	24-25°	0·01	,,	,,
,, ,, . .	30	20°	0·037	,,	Vernon [1896].
Cestus Veneris . .	24	24-25°	0·12	,,	Montuori.
,, ,, . .	70	20°	0·018	,,	Vernon [1896].
Protozoa.					
Collozoum inerme . .	0·1	16°	0·38	,,	,, ,,
Paramæcium . .	0·0002–0·001 mg.	20°	2·4	CO_2	Barrat.
Colpidium . . .	0·00015 mg.	17°	4·6	O_2	Wachendorf.

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CHAPTER I.

The Physiological Significance of the Gas Exchange.—Biocalorimetry.

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The Influence of Chemical Factors upon the Respiratory Exchange.

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